

Figure 134.6 An important technical point is to visualize the tip of the guide wire during the intervention and to position the guide wire in the main trunk of the superior mesenteric artery (curved black arrow) as opposed to distal jejunal branches (black straight arrow), which are prone to perforate resulting in a mesenteric hematoma (white straight arrow).

small 1- to 2-cm incision just above the antecubital crease is used to expose and repair the brachial artery.⁴⁴

Percutaneous access is established with a micropuncture set, which is exchanged to a 0.035-inch system. Full systemic heparinization (80 mg/kg) is administered prior to catheter manipulations. A 6- or 7-F 90-cm hydrophilic sheath is positioned in the descending thoracic aorta, and mesenteric catheterization is done with a 5-F MPA catheter. An SOS or VS1 catheter can be used if the procedure is performed from the femoral approach. The initial selective angiogram should demonstrate the area of stenosis and should document the distal runoff branches for comparison with postintervention views. The target lesion is initially crossed using a 0.035-inch soft angled glide wire, which is exchanged for the interventional wire of choice. The tip of the guide wire should be visualized and positioned within the main trunk of the SMA, rather than within small jejunal branches, which are prone to perforate or dissect (Fig. 134.6). Embolic protection may be useful in select patients with occlusions, long lesions (>30 mm length), severe calcification, thrombus, acute, or subacute symptoms. When utilized,

the author's preference is to use an exchange length working 0.014-inch filter wire (Spider RX, Medtronic Covidien, Plymouth, MN). If an over-the-wire 0.035-inch stent is selected, a two-wire technique can be used by combining a 0.014-inch filter wire with a 0.018-inch "buddy wire." Most recently, our practice has changed to covered stents (0.035-inch), based on a recent report that indicates superior patency rates compared with bare metal stents.⁴⁵ The stent is introduced via both wires for better support and to facilitate subsequent retrieval of the embolic protection device (Fig. 134.7). Predilatation is recommended only if there is a tight stenosis, occlusion, severe calcification, or to size stents. A balloon-expandable stent with diameters ranging from 5 to 8 mm is used in greater than 95% of cases, allowing precise deployment and greater radial force. The stent should cover slightly more than the entire length of the lesion and should extend 1 to 2 mm into the aortic lumen. Ideally the stent should be flared gently into the aorta to prevent missing the ostia and to facilitate re-catheterization if needed. Occasionally a self-expandable stent is used to treat narrowing in tortuous segments.

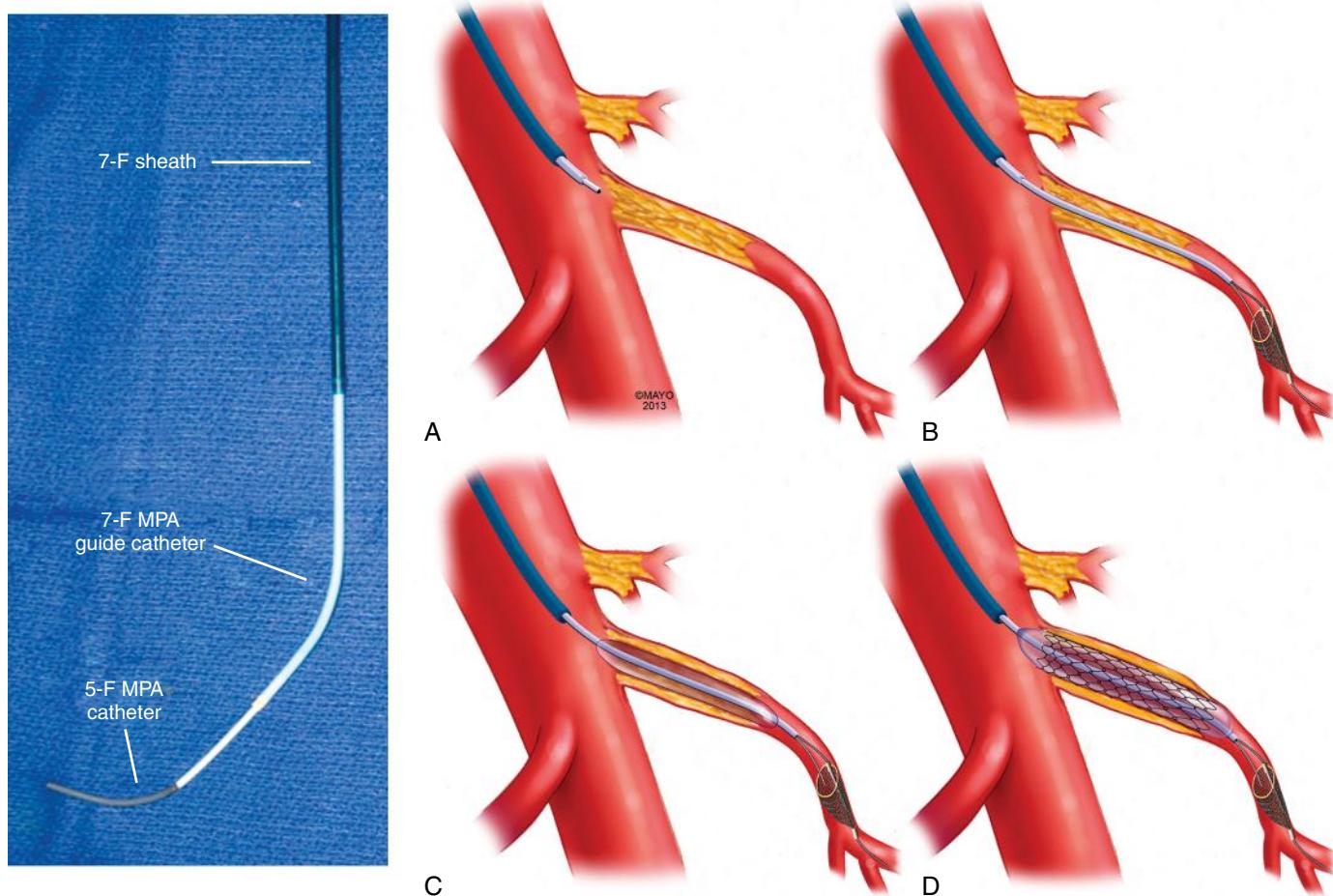


Figure 134.7 Technique of recanalization and primary stenting of a total superior mesenteric artery (SMA) occlusion. In these cases, a coaxial stiff support system is built, with combination of a 7-F 90-cm hydrophilic sheath, 7-F 100-cm MPA guide catheter, and 5-F 125-cm MPA catheter. The stump of the occluded SMA is engaged by the sheath-catheter combination (A); the lesion is crossed using a straight glide wire. After true lumen access is confirmed, a 0.014-inch filter wire and a 0.018-inch buddy wire are deployed into the SMA via 0.035-inch catheter (B); the lesion is predilated (C) and stented using a balloon-expandable stent (D).

Recanalization of Mesenteric Occlusions

Occlusions require a stiffer support system to cross the lesion and deliver the stent. A coaxial support system uses a 7-F sheath, 7-F MPA guide catheter, and 5-F MPA catheter (Fig. 134.8). Attempting difficult recanalization from the femoral approach adds time, contrast, catheter manipulations, and is fraught with failure and the brachial approach should be used if possible. Indeed, in patients with tortuous anatomy or calcified occlusions it may be necessary to establish through-and-through wire access from the brachial artery to the femoral artery in order to stabilize the sheath and increase the likelihood of successfully crossing the lesion. The tip of the MPA catheter engages the stump of the occluded SMA (see Fig. 134.8) whereas the support system allows the lesion to be crossed using a straight tip, hydrophilic, soft 0.035-inch glide wire. Occasionally, 0.018- or 0.014-inch guide wires are needed. It is important to avoid the subintimal plane because of risk of dissection or disruption, which is best achieved using straight tip guide wires. A Quick-Cross catheter (Spectranetics, Colorado Springs, CO) or an alternative support catheter, or even a small

coronary balloon, may be needed to cross a tight lesion. Once the lesion is crossed, access into the true lumen should be confirmed. Some authors recommend using an embolic protection device with a two-wire technique in cases of total occlusion but this technique is not fully supported by data.

Following deployment and flaring of the stent, the embolic protection device is retrieved with careful attention to avoid entrapment into the stent. The basket is examined for debris. A formal completion angiography should be obtained. The angiogram should provide a focal magnified view of the stent with the sheath in the aorta. Demonstration of the vessel origin and a panoramic view of the entire SMA and its branches to rule out embolization or perforation are critical. The stiff guide wire should be retracted, and nitroglycerin may be administered via the sheath to minimize spasm or kinks caused by the guide-wire tip.

Adjunctive Techniques

A number of adjunctive techniques can be used to optimize results in complex lesions, but the authors acknowledge that these techniques are anecdotal. The presence of acute and subacute

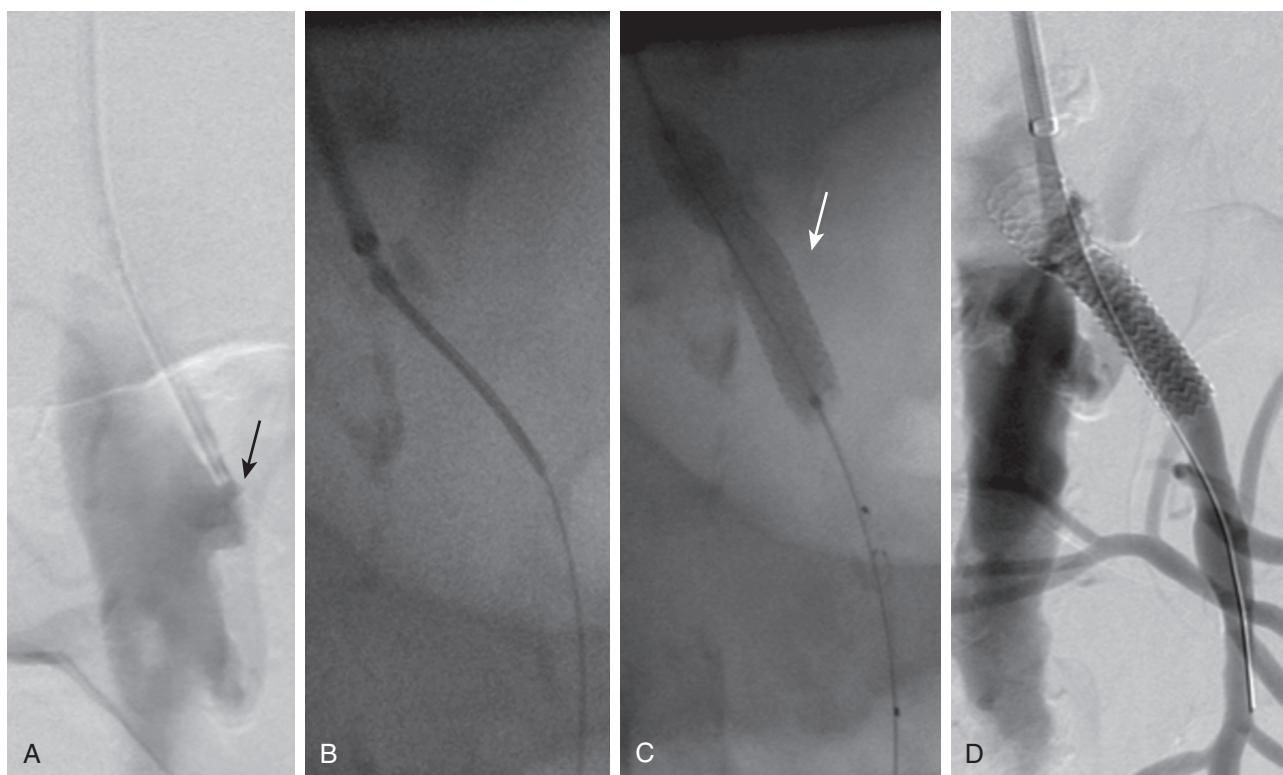


Figure 134.8 Recanalization of superior mesenteric artery (SMA) occlusion utilizing the technique described in Figure 134.7. After the stump is engaged by the catheter, guide catheter, and sheath (**A**, black arrow), the lesion was crossed (**B**) and stented using embolic protection (**C**). Note that the balloon is used to flare the proximal part of the stent (**C**, white arrow). Completion angiography shows a flared widely patent SMA stent (**D**).

symptoms suggests fresh thrombus or a complicated plaque. In these cases local administration of t-PA into the diseased segment 20 to 30 minutes prior to stent placement may improve technical success. For eccentric, calcified lesions, percutaneous atherectomy has been used selectively.⁴⁶ It is critical to have an appreciation of the limitations of this technique when applied as an off-label use in the mesenteric arteries.

Complications

The most common causes of death after mesenteric stenting are cardiac events, gastrointestinal bleeding, and bowel ischemia. The latter is typically associated with intraprocedural complications such as distal embolization, thrombosis, or dissection. Distal embolization occurs in 8% of patients treated by SMA stents without embolic protection, with higher rates among patients with subacute symptoms, SMA occlusion, long lesions (>30 mm), and severe calcification. The most commonly reported complications are access-related problems in 3% to 16%, renal insufficiency in 2% to 8%, acute bowel ischemia in 1% to 7%, gastrointestinal bleeding in 1% to 5%, cardiac events in 1% to 7%, and respiratory complications in 1% to 7%.^{15,16,43,47–58}

Post-Procedure Management

The post-procedure care after mesenteric interventions is comparable to that of other peripheral endovascular procedures.

All patients are admitted for observation overnight. Worsening abdominal pain after the procedure is unusual and warrants evaluation to rule out thrombosis, embolization, or a mesenteric hematoma from jejunal branch perforation (see Fig. 134.6). Patients are allowed to resume a regular diet within 6 to 8 hours. Antiplatelet therapy is typically started prior to the intervention with acetylsalicylic acid, and continued indefinitely thereafter. Clopidogrel is started the day of the intervention with a loading dose of 300 mg followed by a dose of 75 mg daily for 6 to 8 weeks as a dual antiplatelet agent and it is the author's practice to continue dual antiplatelets indefinitely if a covered stent is used. A duplex ultrasound scan prior to discharge or within the first few days after the procedure serves as a baseline for future comparison. Follow-up includes clinical examination and duplex ultrasound every 6 months during the first year and annually thereafter.

OPEN REVASCULARIZATION

Choice of Open Revascularization Procedure

A variety of open surgical techniques have been described to revascularize the mesenteric arteries. Selection involves the type of incision (transperitoneal vs. retroperitoneal), conduit (vein vs. prosthetic), graft configuration (antegrade vs. retrograde), source of inflow (aortic vs. iliac), and the number of vessels to be reconstructed (single vs. multiple).

The type of open reconstruction is selected based on the patient's anatomy and clinical risk.²³ Two-vessel reconstructions (CA and SMA) using a bifurcated polyester graft from the supraceliac aorta comprises more than 80% of open mesenteric reconstructions.^{15,23,59} This approach is selected in lower risk patients who are not candidates for endovascular treatment and have multi-vessel disease, with no evidence of significant supraceliac aortic calcification or thrombus. Elderly patients and those with cachexia or severe cardiac, pulmonary, and renal dysfunction are often not good candidates for supraceliac aortic-based procedures, and are best treated with retrograde grafts based in the infrarenal aorta or the iliac arteries. A hybrid approach using retrograde open mesenteric stent via midline laparotomy may be selected for patients with extensive aortoiliac disease and no good source of inflow.^{60,61} Trans-aortic endarterectomy is rarely indicated, but may be considered in patients who failed or are not candidates for endovascular therapy and have bacterial contamination or perforated bowel, previous abdominal irradiation, extensive abdominal wall hernias, or other hostile conditions.

Antegrade Mesenteric Bypass

The distal thoracic or supraceliac aorta is often spared from severe atherosclerotic disease. Bypass with antegrade graft configuration based in the supraceliac or lower thoracic aorta⁶² offers a potential hemodynamic advantage, while avoiding kinks that can occur with grafts placed in a retrograde fashion. The operation can be done through an 8th interspace thoracoabdominal or a midline incision, depending on the patient's body habitus and costal cartilage flare (Fig. 134.9) (see Ch. 55, Thoracic and Thoracoabdominal Vascular Exposure and Ch. 56, Abdominal Vascular Exposures).

For the thoracoabdominal approach, the patient is positioned in the lateral position with the left side up at an approximately 60-degree angle. Extend the right arm on an arm-board, being sure to leave room for an Omni or other self-retaining retractor post. The upper, left arm should be placed on another arm-board and padded to prevent neural injury. The bed should be flexed at the patient's flank to open up the area between the ribs and the anterior superior iliac spine. Position the legs so that the lower leg is straight and the upper leg is bent. Use two pillows as padding between legs. A beanbag can be inflated to keep the patient in place and use thick cloth tape over the hip to secure the patient on his/her side. Ideally the patient should be placed on a beanbag, however blanket rolls can be used anteriorly and posteriorly to further secure the patient. Be sure to allow access to prep from the spine posteriorly to the umbilicus anteriorly, and from the nipple line to the groins. All bony prominences and pressure points should be well padded to avoid injury. Use clippers to remove hair within the prep area. Prep from the axilla and nipple line to the upper thigh. Mark all previous incisions and use a Steri-Drape or Ioban (3M, St. Paul, MN) over the entire prepped area to secure the drapes. Once in position, check PVRs and/or distal pulses.

A thoracoabdominal incision at the 8th interspace will usually provide adequate exposure to the supraceliac aorta for the

inflow anastomosis, and a double lumen tube for deflation of the left lung is generally not necessary in these cases. The abdominal portion of the incision is not extended to the midline; rather, it is kept well lateral on the abdominal wall along the edge of the rectus. The advantage of this approach is that it allows the visceral contents to lie within the abdominal cavity thus decreasing evaporative fluid and heat losses. Divide the transversalis fascia and enter the retroperitoneal space down to but not violating Gerota's fascia. It is possible to stay entirely within a retroperitoneal plane, however if the peritoneum is violated the abdominal contents can be packed away with retractors or the peritoneum can be repaired with a running 3-0 running chromic suture. The aorta may be approached via an anterorenal (colloquially referred to as "leaving the kidney down") or retrorenal plane ("taking the kidney up"). Generally, for an aorto-SMA bypass, leaving the kidney down will allow the surgeon to dissect out the SMA to an area beyond the occlusion.

The renal artery should be cephalad to the renal vein, which will be draped over the aorta with the kidney down. Once this is identified it can be used as a landmark and dissected back to the aorta. Once the origin of the renal artery is identified, a right angle can be placed along the surface of the aorta and the overlying retroperitoneal tissue divided with electrocautery. It is imperative here to get on the aorta and stay on the aorta to avoid excessive bleeding from the retroperitoneal tissue. The aorta is exposed proximally and the median arcuate ligament and diaphragmatic crura are divided superiorly to expose the supraceliac aorta. Approximately 5 to 10 cm is dissected free in preparation for clamping.

The SMA is identified on the aorta and can be exposed anteriorly with the kidney down. There will be several lymphatic and small venous tributaries here that require meticulous ligation. The SMA and several jejunal branches are dissected free and carefully controlled with vessel loops. Excessive traction on these vessel loops can easily result in avulsion of small branches and should be avoided. In most cases, the SMA is dissected several centimeters beyond the lesion to a soft area to sew.

Patients are given systemic heparin (60–80 mg/kg), and the blood pressure is lowered to a systolic pressure of less than 100. Partial aortic cross clamping can be performed using a Satinsky or multipurpose clamp, or alternatively total aortic clamping with two cross-clamps affords better exposure for the proximal aortic-graft anastomosis. A straight or angled aortic clamp (Cherry supraceliac clamp) and a Wylie hypogastric clamp work well (see Fig. 134.9). Placed appropriately, occlusion of the lumbar vessels is achieved as well. A gentle slightly oblique or vertical aortotomy is made. A 14 × 7 mm knitted polyester graft is beveled in an oblique fashion with a short main body and anastomosed to the supraceliac aorta in an end-to-side fashion using running 4-0 Prolene suture. The aorta can be friable at this level and it is wise to tie the knots of the anastomosis over pledgets to prevent tearing. Aortic cross-clamp time rarely exceeds 20 minutes and most often ranges from 12 to 15 minutes. However, if bleeding is encountered from the anastomosis after the clamps are removed, consider reapplying the aortic clamps prior to placing repair stitches as suturing a

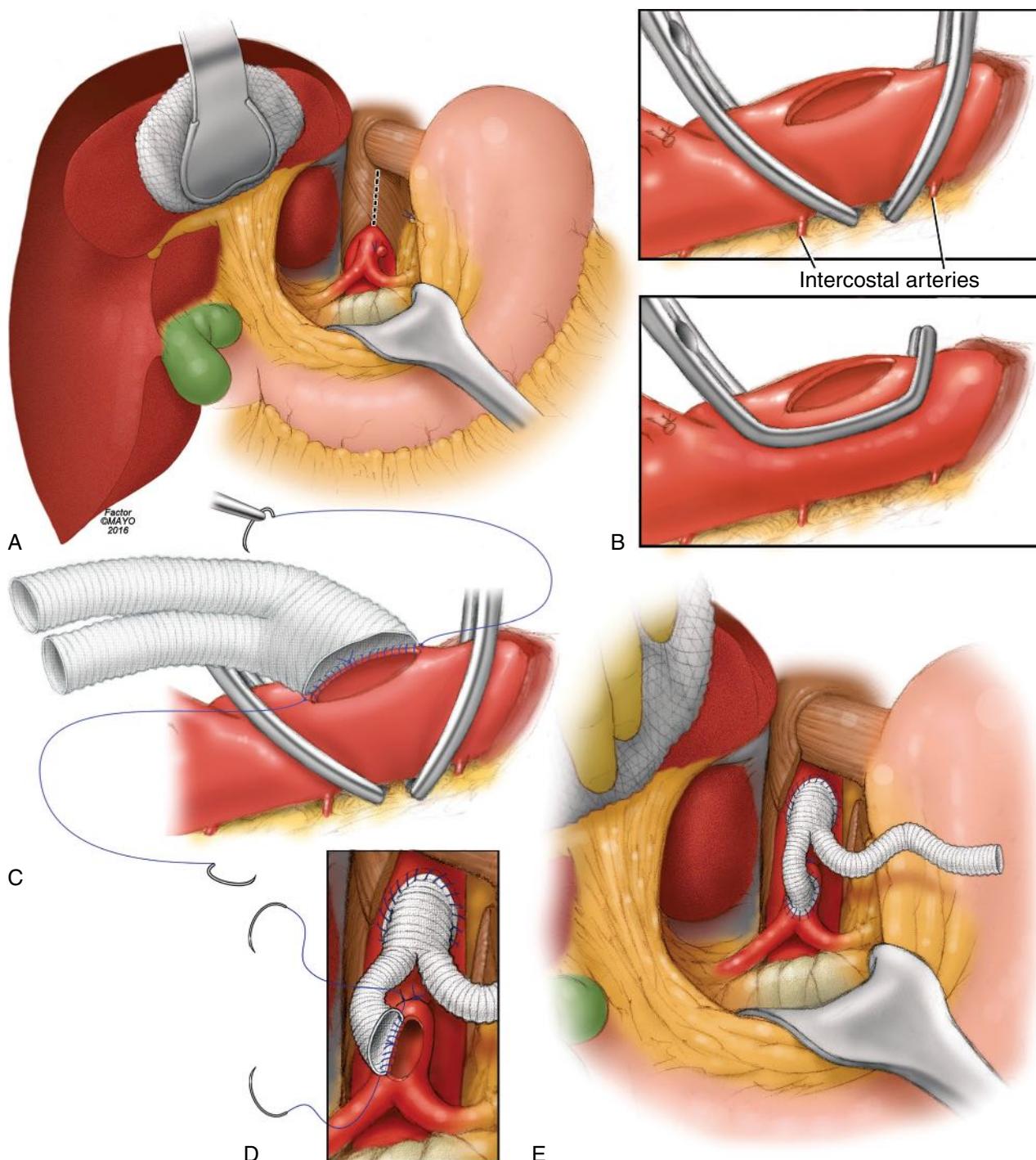


Figure 134.9 The anterior approach to the supraceliac aorta is exposed after division of the diaphragmatic crura (A). Following systemic heparin, the supraceliac is clamped using either two aortic clamps or a Satinsky clamp (B). A slightly oblique aortotomy is made for the proximal anastomosis of the bifurcated graft (C). Note that the graft is gently beveled and that the right graft limb is anastomosed end-to-side to the celiac axis or hepatic artery (D). The left limb of the graft is tunneled behind the pancreas (E).

fully pressurized aorta is a recipe for catastrophe. The risk of renal ischemia or embolization is low when patients are properly selected and have a relatively disease-free supraceliac aorta.

The left limb of the bifurcated graft is positioned slightly posterior and is fashioned in a C-curve toward the SMA. The anastomosis to the SMA is performed in an end-to-side fashion when the anastomosis is performed at the base of the mesentery below the pancreas. If the SMA is extensively diseased or

the patient has had prior stents, the lumen may require modest endarterectomy or removal of stent struts. Any endarterectomy should be done carefully, so as not to result in tear or an excessively thin arterial wall that cannot be reconstructed. In a few cases with very extensive plaque, the distal graft can be beveled into a long patch or anastomosed end-to-side into a bovine pericardium patch. It is important to relax retraction when cutting the graft limbs to length to avoid angulation or kinking.

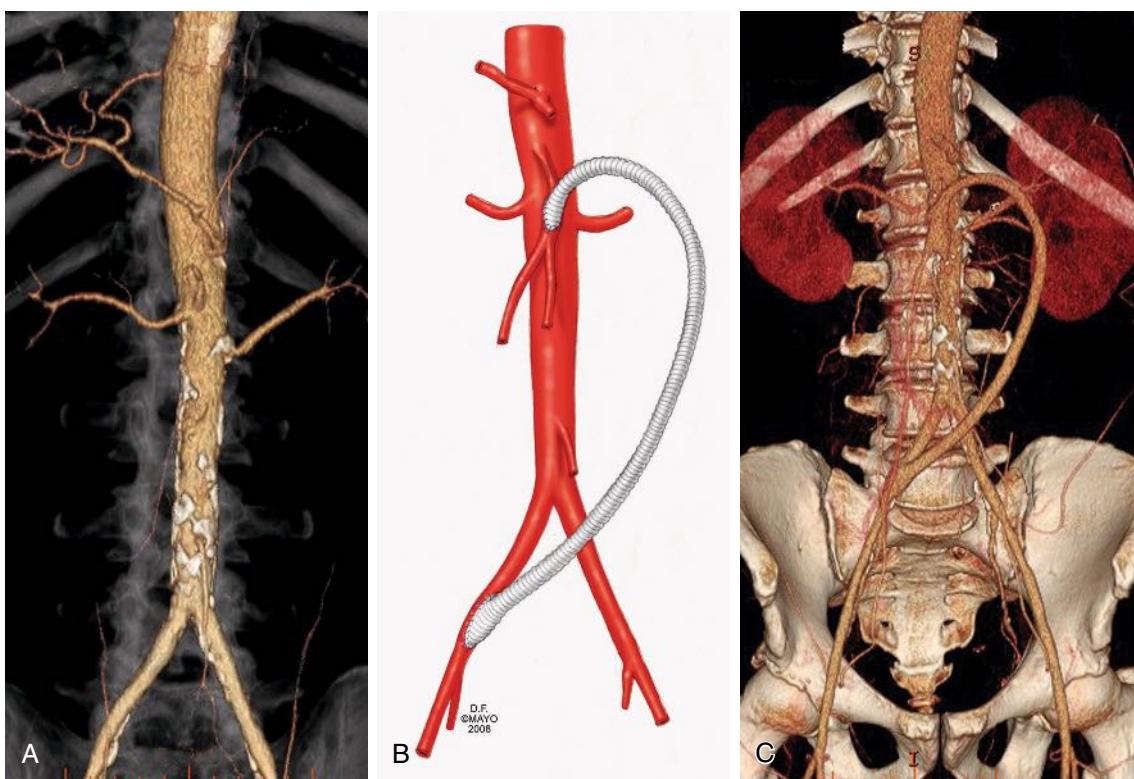


Figure 134.10 Computed tomography angiography (CTA) of a patient with vasculitis and occlusion of the superior mesenteric artery (A). The patient was treated by retrograde C-shaped iliac artery to superior mesenteric artery bypass (B). Follow-up CTA revealed widely patent bypass graft (C).

Next, the celiac axis anastomosis is performed in end-to-end fashion, or more frequently the anastomosis may be performed end-to-side to the common hepatic artery.

Retrograde Mesenteric Bypass

Sources of inflow for retrograde grafts are the infrarenal aorta, prior infrarenal aortic grafts, or the iliac arteries (Fig. 134.10). In general, only one artery (SMA) is bypassed if a retrograde graft is used. The infrarenal aorta may be replaced, if diseased, but concomitant aortic reconstruction increases operative mortality and should be avoided unless absolutely necessary.¹⁵ The proximal anastomosis is performed to the anterolateral wall of the aorta and can be done with either two cross-clamps or a partial occlusion clamp, depending on the aortic size and the presence of atherosclerosis or calcification within that segment. A 6-mm coronary punch can be used to remove a portion of the aortic wall. However, the common iliac artery as source of inflow should be selected whenever possible, thus avoiding an aortic cross-clamp.

The key to prevention of graft elongation, angulation, or kinking is to cut it to length, with the SMA in a nearly anatomic position. This is done by relaxing the retractors prior to cutting the graft and after the proximal or distal anastomosis is done. A large 8- or 10-mm graft should be used for a retrograde, straight aortomesenteric graft, and it is imperative to perform the distal anastomosis first and then push the mesentery close to the aorta and select the appropriate aortic site for the anastomosis. The author prefers a C-shaped graft when the iliac artery is the source of inflow. In these cases, the proximal

anastomosis may be done first to the iliac artery or distal aorta, followed by the distal anastomosis to the SMA. There are some patients who have extensive circumferential aortic calcification but soft common or external iliac arteries with normal perfusion, which can serve as good donor vessels. Either the right or left common iliac artery can be chosen for inflow, depending on the orientation of that artery to the normal anatomic position of the SMA. In general, the right iliac artery lays better if both vessels are suitable. Two-vessel reconstructions can also be performed with retrograde grafts by doing a side-to-side anastomosis to the SMA and an end-to-side anastomosis to the common hepatic artery. These grafts may be passed on top of or beneath the pancreas and curved in a C-fashion toward the hepatic artery.

Retrograde Open Mesenteric Stenting

A hybrid approach using retrograde open mesenteric stenting (ROMS) via midline laparotomy to expose the SMA (Fig. 134.11) has been reported by Milner and colleagues from the University of Pennsylvania and Dartmouth Group.^{60,63} This option is selected in patients with acute mesenteric ischemia due to *in situ* thrombosis when there is an indication for laparotomy. It is also well suited in patients with severe aortic and iliac calcifications when there is not a good source of inflow for bypass. The SMA is dissected below the pancreas as previously described. Several jejunal branches are controlled with Silastic vessel loops and occluded prior to manipulation to avoid distal embolization. Retrograde SMA access is established using a micropuncture set with 0.018-inch guide wire.

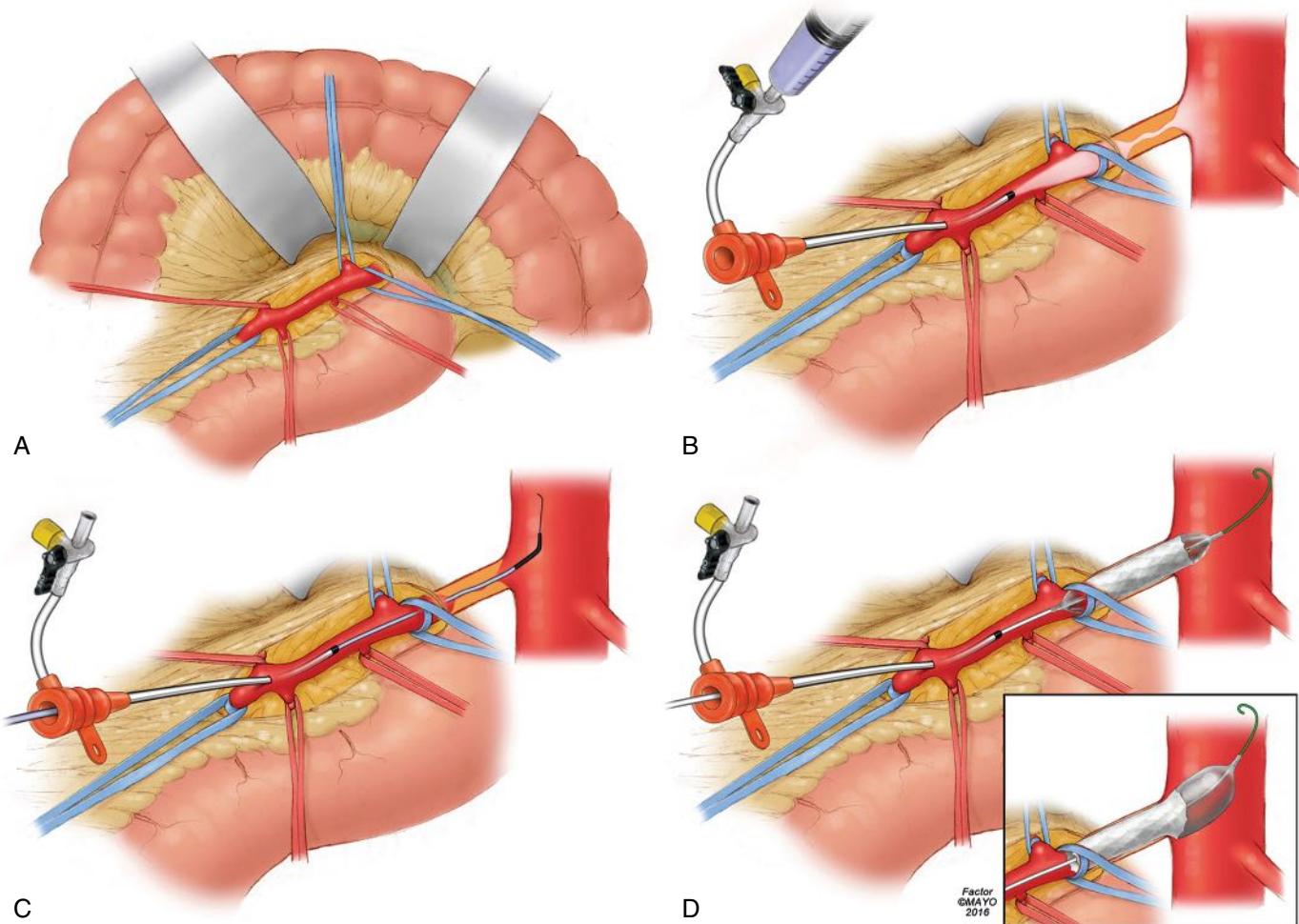


Figure 134.11 Technique of retrograde open mesenteric stenting requires open surgical exposure of the superior mesenteric artery (SMA) (A). Retrograde access is established using a 7-F sheath and catheter (B). After retrograde angiography, the occluded SMA is crossed using a glide wire (C). Stenting is performed using a covered stent or bare metal stent (D).

This is exchanged for a 0.035-inch guide-wire system, and a 6- to 7-F sheath is advanced to the SMA. Retrograde angiography is obtained and the SMA occlusion or stenosis is crossed, predilated, and stented with a balloon-expandable stent. Prior to restoring antegrade flow to the SMA, the sheath is flushed to prevent distal embolization. The puncture site may be closed with interrupted sutures or opened longitudinally and closed over a patch if severely diseased.

Transaortic Mesenteric Endarterectomy

Transaortic endarterectomy is performed using a full-length midline abdominal or subcostal incision or a thoracoabdominal incision for patients who have narrow costal flares or are truly obese. The aorta is exposed using medial visceral rotation with the left kidney remaining in its bed and dissection performed anterior to the renal vein. The left diaphragmatic crura is transected longitudinally, allowing exposure of the left anterior-lateral wall of the aorta and origins of the SMA and celiac axis (Fig. 134.12). The SMA is dissected over several centimeters. After administration of systemic heparin and induced diuresis, the supraceliac and infrarenal aorta are clamped. A longitudinal or trapdoor aortotomy is performed, starting at

the level of the renal arteries up to just above the celiac axis origin. Endarterectomy of the paravisceral aorta, the celiac, and SMA is performed, ending at the renal artery orifices. In the rare patient in whom there is symptomatic renal artery stenosis, the endarterectomy should include the renal artery ostia as well. The aortotomy is closed longitudinally and rarely requires a patch. Endarterectomy of the celiac artery usually has an endpoint at its bifurcation, whereas SMA disease may extend beyond the limits of the ostial endarterectomy. This requires a separate transverse or longitudinal SMA arteriotomy after flow is restored through the distal aorta and celiac artery. If a longitudinal arteriotomy is done, this can be repaired with a patch.

Intraoperative Duplex Ultrasound Monitoring

Technical imperfections may be a cause of early graft failure after mesenteric revascularization. We have routinely performed intraoperative duplex ultrasound (IOUS) surveillance in all patients who undergo open mesenteric or renal reconstructions. The author has found technical defects in 15% of the reconstructions. Minor defects (7%) are typically left untreated and include arterial abnormalities with normal velocities such as small kinks, mild residual stenosis, and small intimal flaps.

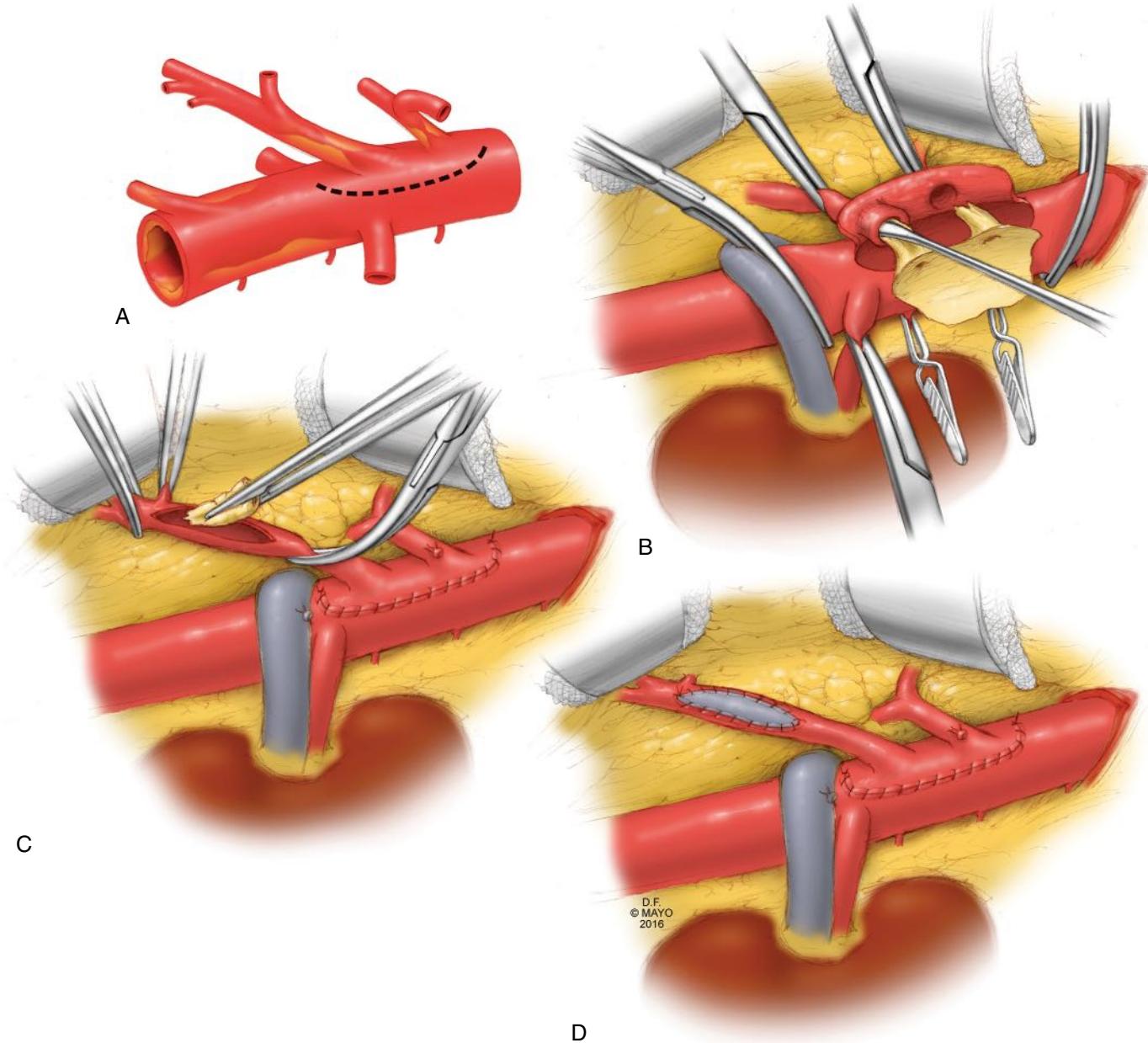


Figure 134.12 Technique of transaortic mesenteric endarterectomy using medial visceral rotation and a trapdoor aortotomy (A). The endarterectomy includes the origins of the celiac axis and superior mesenteric artery (B). The aortotomy is closed and the end point of the superior mesenteric artery is revised if needed (C). This is closed using vein patch angioplasty (D).

Major defects (9%) consist of hemodynamically significant arterial abnormalities such as significant stenosis, kinks, thrombus, and large intimal flaps. These require prompt immediate revision. Intraoperative ultrasound assessment is particularly important in visceral endarterectomies where the endpoint of the plaque removed is not directly visualized.

Complications

Complication rates after open mesenteric revascularization average 20% to 40%.^{4,64–69} Pulmonary (15%), gastrointestinal (14%), cardiac (10%), and renal (4%) complications are the most frequent. Patients with severe malnutrition require

perioperative nutritional support. Prolonged ileus occurs in 8%.¹⁵ Meticulous wound closure is important, particularly in the patient with malnutrition or severe ascites, due to risk of wound-related complications (4%–8%).^{14,62,67,69–71} Early graft thrombosis is uncommon (<2%) and indicates a technical problem (e.g., kink, intimal flap, dissection, thrombus), poor runoff, or hypercoagulable state.¹⁵ If not recognized, early graft thrombosis may be a lethal complication.

Postoperative Management

Patients undergoing open mesenteric reconstruction are admitted for 1 to 3 days to a monitored bed or intensive care unit.

The average length of hospital stay is 12 days.¹⁵ Patients with severe ischemia typically experience major fluid shifts and have a high volume requirement over the first 48 hours because of the loss of autoregulation of the mesenteric arterioles and the systemic inflammatory response. Persistent hypotension, tachycardia, leukocytosis, reduction in urinary output with elevated bladder pressures, or increase in abdominal pain may indicate graft occlusion, ischemic bowel, or abdominal compartment syndrome. CT, abdominal re-exploration, or both are needed to exclude these problems.

Return of oral intake varies, but many patients develop prolonged postoperative ileus and may need enteral or parenteral nutritional support. If not already started preoperatively, total parenteral nutrition is started early after the operation once fluid requirements diminish if an ileus is anticipated in the malnourished patient. The “food fear” many patients have preoperatively does not resolve quickly after the operation, as it is often a “learned behavior.” Furthermore, absorptive capacity of the gut changes, and patients often experience diarrhea over the first few postoperative weeks. Postoperative medical therapy includes ongoing recommendations for smoking cessation, antiplatelet, and cholesterol-lowering agents. Imaging surveillance is recommended using duplex ultrasound, which is obtained every 6 months during the first year and annually thereafter.

RESULTS

Despite the lack of prospective randomized comparisons between open surgery and endovascular treatment, mesenteric angioplasty and stenting have been widely adopted in most centers, resulting in a decline in the number of open surgical reconstructions. Endovascular revascularization has been associated with decreased morbidity, length of stay, and convalescence time, but similar mortality compared with open repair.^{15,72} Mesenteric bypass offers improved patency, with lower rates of reinterventions and better freedom from recurrent symptoms.^{4,15,16,48,72–80} While creating the practice guideline for CMI, the SVS writing group performed a systematic review of almost 19,000 patients and found that there was no significant difference in 30-day mortality or 3-year survival between patients treated with the open or endovascular approach but open repair showed a significant decrease in the 3-year rate of recurrence.³⁷

Morbidity and Mortality

Based on a review of single-center reports and a systematic review, endovascular revascularization has been associated with decreased morbidity, length of stay, and convalescence time (Tables 134.1 and 134.2).⁷² Morbidity and length of stay averages 11% and 3 days with endovascular, compared with 33% and 14 days with open surgery.^{37,72} Mortality rates are similar, with average 30-day mortality of 6% (0%–15%) for open and 5% (0%–21%) for endovascular revascularization.^{37,72} Open

surgical bypass can be performed with low mortality in good risk patients operated on in referral centers.^{16,76} At the Massachusetts General Hospital, the 30-day mortality after open repair was 2.0% and 3.2% after endovascular revascularization.¹⁶ This is similar to results from the Mayo Clinic and when they stratified patients by operative risk the mortality was 1% for low-risk and 6.7% for high-risk patients treated by open bypass, with the highest mortality rate (8.9%) in those patients who had a concomitant aortic reconstruction.¹⁵ Nonetheless, these operations can carry a high mortality in the community, reaching 20% in the state of New York and 13% in the United States.^{4,76}

Symptom Relief

Both methods of revascularization are highly effective in patients who have the correct diagnosis of CMI. In a systematic review, symptom improvement averaged 88% with endovascular and 93% with open revascularization.⁷² Single-center reports indicate symptom improvement approaches 90% in patients treated by stents.^{15,16} Angioplasty alone may be associated with lower rates of technical success (78%) compared with stenting (>95%) and should be used infrequently.⁷⁶ Symptom improvement is usually noted immediately after revascularization, but it is not uncommon for patients to experience modest bloating and worsening diarrhea in the early postoperative period, and may persist as chronic diarrhea in a small group of patients. The presence of persistent abdominal pain after adequate revascularization may suggest another diagnosis.

Restenosis, Symptom Recurrence, and Reintervention

Most single-center reports and a systematic review indicate that open reconstructions are more durable (Table 134.2).^{14,16,37,48,58,66,68,77,79,81–86} Bypass is associated with lower rates of restenosis, better patency, and higher freedom from recurrent symptoms or reinterventions compared with mesenteric angioplasty and stenting. Primary patency of open bypass averaged 89% at 5 years in a recent review of the pooled literature (57%–92%), with freedom from reinterventions of 93%.⁷⁶ Ryer and colleagues indicated that open bypass has been increasingly performed in patients with more comorbidities and worse anatomy. Despite these adverse characteristics, open surgery had excellent primary patency of 76% at 5 years.⁶⁸ In the systematic review of van Petersen and associates,⁷² endovascular treatment was associated with more restenosis (37% vs. 15%), symptom recurrences (30% vs. 13%), and reinterventions (20% vs. 9%). Primary patency was lower for mesenteric stenting (51% vs. 86%), with similar secondary patency rates (83% vs. 87%).

Endovascular treatment has been plagued by high rates of restenosis, affecting as much as 20% to 66% of the patients, not matching the excellent patency rates reported for open reconstructions (see Table 134.1).^{15,16,43,47–58,79,80,82,86–90}

TABLE 134.1

Results of Contemporary Reports of Angioplasty and Stenting for Treatment of Chronic Mesenteric Ischemia

Author (Year)	N	Vessels	Stented Vessels (%)	Technical Success (%)	Mortality (%)	Morbidity (%)	Recurrence (%)	Reintervention (%)	Primary Patency (%)	Follow-up (Months)
Bare Metal Stents										
Kasirajan (2001)	28	32	82	100	11	18	34	—	73 at 3 years	24
Matsumoto (2002)	33	47	32	88	0	13	15	15	—	20
van Wanroij (2004)	27	33	94	93	0	11	—	19	81 at 19 months	19
Landis (2005)	29	63	27	97	7	10	45	37	70	28
Silva (2006)	59	79	100	96	2	—	17	17	71	38
Biebl (2007)	23	40	96	—	0	4	26	22	—	10
Atkins (2007)	31	42	87	100	3.2	13	23	16	58	15
Sarac (2008)	65	87	100	—	8	31	—	31	65	12
Lee (2008)	31	41	—	98	14	6	44	10	69 at 7 years	32
Dias (2010)	43	49	100	98	0	23	12	33	—	43
Oderich (2009)	83	105	72	95	2.4	18	31	31	41 at 5 years	36
Fioole (2010)	51	60	100	93	0	4	25	22	86	25
Peck (2010)	49	66	89	100	2	16	29	29	64 at 3 years	37
Schoch (2011)	107	116	78	100	0	—	42	42	67	16
Turba (2012)	166	221	74	92	3	10	17	19	67	34
AbuRahma (2013)	83	105	100	97	2	2	35	30	19	31
Grilli (2014)*	47	41	100	87	2	7	17	17	78 at 24 moths	19.1
Sundermeyer (2014)	27	27	74	100	0	0	22	22	50 at 24 months	16
Barret (2015)	43	—	77	95	0	19	37	37	—	63
Zacharias (2016)	116	143	—	—	5.2	—	23	23	74 at 36 months	37
Covered Stents										
Schoch (2011)	14	14	100	100	0	—	—	0	100	16
Oderich (2012)	42	42	100	98	0	12	10	10	92 at 3 years	19
Total	1197	1453	84	96	3	12	27	23		25

*Considering only occluded SMA. One case used a covered stent and others, a bare metal stent.

Contemporary reports of primary stenting indicate that restenosis occurs in 40% of patients and that half of these require reinterventions.³⁹ The average 3-year primary patency rate for bare metal stents is 52% (range, 30%–81%), calculated from pooled literature.⁷⁶ The secondary patency rate is better than 90%, as evidenced by reports of mesenteric reinterventions.^{39,76} Oderich and associates compared covered versus bare metal stents in 225 patients treated for CMI and showed that all stents had a 92% ± 6% primary and 100% secondary patency rates at 3 years, rivaling the results of open bypass.⁴⁵ Covered stents outperformed bare metal stents, with less restenosis, symptom recurrences, reinterventions, and better patency rates. These observations held true both in primary interventions for native artery lesions and in reinterventions

for in-stent or native artery restenosis after endovascular procedure. Independent predictors of restenosis were use of bare metal stents, cigarette smoking, advanced age, and female gender.⁴⁵

Patient Survival

Poor prognostic indicators for long-term patient survival after mesenteric revascularization include advanced age and presence of severe cardiac, pulmonary, or renal disease.^{15,91} The type of revascularization has not been shown to affect survival, but comparative analysis is limited by selection bias, favoring open bypass for good risk and endovascular revascularization for higher risk patients. The SVS writing group's meta-analysis

TABLE 134.2

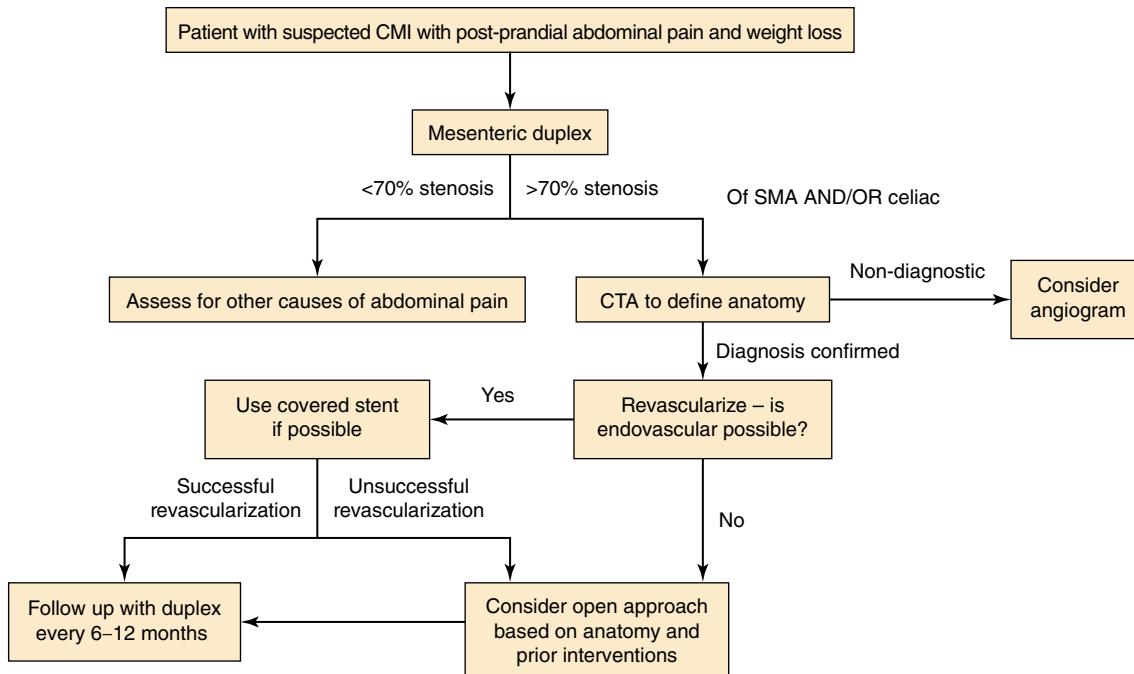
Results of Contemporary Reports of Open Surgical Revascularization for Treatment of Chronic Mesenteric Ischemia

Author (Year)	N	Vessels	Mortality (%)	Morbidity (%)	Recurrence (%)	Reintervention (%)	Primary Patency (%)	Follow-up (Months)
Leke (2002)	17	25	6	41	0	0	100 at 34 months	34
Cho (2002)	25	41	4	—	32	20	57 at 5 years	64
Brown (2005)	33	51	9	30	9	7	100 at 6 months	34
Sivamurthy (2006)	46	66	15	46	32	12	83 at 6 months	9
Biebl (2007)	26	48	8	42	11	8	—	25
Kruger (2007)	39	67	2.5	12	5	3	92 at 5 years	39
Atkins (2007)	49	88	2	4	22	22	90	42
Mell (2008)	80	120	3.8	26	11	11	90	46
Oderich (2009)	146	265	2.7	36	6	5	88 at 5 years	36
Low risk	101	—	0.9	37	6	6	94 at 5 years	—
High risk	45	—	6.7	38	11	11	90 at 5 years	—
Concomitant aortic reconstruction	23	—	8.4	—	—	—	—	—
Rawat (2010)	52	75	13	32	15	13	81	41
Ryer (2011)	116	203	2.5	50	14	16	86 at 5 years	43
Lejay (2015)	86	123	3.5	13.9	—	—	—	83
Complete revascularization	46	—	—	—	—	—	84 at 10 years	—
Incomplete revascularization	40	—	—	—	—	—	88 at 10 years	—
Barret (2015)	11	—	0	64	27	27	—	59
Zacharias (2016)	45	72	11	—	—	—	91 at 3 years	37
Total	1026	1244	6	34	14	12		38

of 19,000 patients showed no difference in 3-year survival between open and endovascular repair.³⁷ In a single center study, Tallarita and associates reported long-term survival in a cohort of 343 patients treated for CMI, with nearly identical 5-year survival rates using propensity matched scores for patients treated by open (57%) or endovascular (60%) revascularization.⁹¹ Five-year patient survival averaged $71\% \pm 4\%$ for low-risk, $49\% \pm 6\%$ for intermediate-risk, and $38\% \pm 7\%$ for high-risk patients. Freedom from mesenteric-related death was $91\% \pm 2\%$ after open and $93\% \pm 4\%$ after endovascular revascularization at 5 years. Independent predictors of any cause mortality were age greater than 80 years (OR 3.3, CI 1.03–1.06,

$P = < 0.001$), chronic kidney disease stage IV or V (OR 5.5, CI 1.4–16.6, $P < 0.01$), diabetes (OR 1.7, CI 1.2–2.6, $P < 0.01$), and home oxygen therapy (OR 3.7, CI 1.2–9.1, $P < 0.001$). Chronic kidney disease stage IV or V (OR 3.4, CI 3.3–345, $P = 0.003$) and diabetes (OR 4.2, CI 1.7–10.5, $P = 0.005$) were independently associated with mesenteric-related death. In that study, the most common causes of late death were cardiac events, followed by cancer, respiratory complications, and mesenteric-related complications. The combined rate of early and late mesenteric-related death was 8% for patients treated by open and 6% for those who underwent endovascular revascularization.

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

Foley MI, Moneta GL, Abou-Zamzam Jr AM, et al. Revascularization of the superior mesenteric artery alone for treatment of intestinal ischemia. *J Vasc Surg*. 2000;32(1):37–47.

Large single-center experience with single-vessel retrograde revascularization based on the iliac artery.

Huber TS, Bjorck M, Chandra A, et al. Chronic mesenteric ischemia: Clinical practice guidelines from the Society for Vascular Surgery. *J Vasc Surg*. 2021;73:87S–115S.

Society for Vascular Surgery practice guidelines that includes meta-analysis of 19,000 CMI patients treated with open and endovascular repair.

Kasirajan K, O'Hara PJ, Gray BH, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. *J Vasc Surg*. 2001;31(1):63–71.

Oderich GS, Erdoes L, LeSar C, et al. SS14. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. *J Vasc Surg*. 2012;55(6):23S.

Contemporary nonrandomized study evaluating use of bare metal stents versus covered stents to treat chronic mesenteric ischemia. The study showed that covered stents were associated with improved patency, freedom from recurrence, and reinterventions.

Thomas JH, Blake K, Pierce GE, et al. The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg*. 1998;27(5):840–844.

This natural history study followed patients with mesenteric artery disease, including a subset of patients with severe stenosis or occlusion of all three mesenteric arteries.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Goodman GH. Angina abdominis. *Am J Med Sci.* 1918;155(4):524–528.
2. Mitchell EL, Moneta GL. Mesenteric duplex scanning. *Perspect Vasc Surg Endovasc Ther.* 2006;18(2):175–183.
3. Shaw RS, Maynard 3rd EP. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption; a report of two cases successfully treated by thromboendarterectomy. *N Engl J Med.* 1958;258(18):874–878.
4. Schermerhorn ML, Giles KA, Hamdan AD, et al. Mesenteric revascularization: management and outcomes in the United States, 1988–2006. *J Vasc Surg.* 2009;50(2):341–348.e1.
5. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. *World J Gastroenterol.* 2008;14(48):7309–7320.
6. Fara JW. Postprandial mesenteric ischemia. In: Shepherd AP, Granger DN, eds. *Physiology of the Intestinal Circulation.* New York: Raven Press; 1984.
7. Gallavan RH, Chou CC. Possible mechanisms for the initiation and maintenance of postprandial intestinal hyperemia. *Am J Physiol.* 1985;249(3):G301–308.
8. Poole JW, Sammartano RJ, Boley SJ. Hemodynamic basis of the pain of chronic mesenteric ischemia. *Am J Surg.* 1987;153(2):171–176.
9. Mikkelsen WP. Intestinal angina: its surgical significance. *Am J Surg.* 1957;94(2):262–267; discussion, 267–269.
10. Carrick RP, Borge MA, Labropoulos N, Rodriguez H. Chronic mesenteric ischemia resulting from isolated lesions of the superior mesenteric artery—a case report. *Angiology.* 2005;56(6):785–788.
11. Park WM, Głowiczki P, Cherry Jr KJ, et al. Contemporary management of acute mesenteric ischemia: Factors associated with survival. *J Vasc Surg.* 2002;35(3):445–452.
12. Ryer EJ, Kalra M, Oderich GS, et al. Revascularization for acute mesenteric ischemia. *J Vasc Surg.* 2012;55(6):1682–1689.
13. Wilson DB, Mostafavi K, Craven TE, et al. Clinical course of mesenteric artery stenosis in elderly Americans. *Arch Intern Med.* 2006;166(19):2095–2100.
14. Thomas JH, Blake K, Pierce GE, et al. The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg.* 1998;27(5):840–844.
15. Oderich GS, Bower TC, Sullivan TM, et al. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. *J Vasc Surg.* 2009;49(6):1472–1479.e3.
16. Atkins MD, Kwolek CJ, LaMuraglia GM, et al. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. *J Vasc Surg.* 2007;45(6):1162–1171.
17. van Noord D, Mensink PB, de Knecht RJ, et al. Serum markers and intestinal mucosal injury in chronic gastrointestinal ischemia. *Dig Dis Sci.* 2011;56(2):506–512.
18. Pecoraro F, Ranicic Z, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. *Ann Vasc Surg.* 2013;27(1):113–122.
19. Reed NR, Kalra M, Bower TC, et al. Efficacy of combined renal and mesenteric revascularization. *J Vasc Surg.* 2012;55(2):406–412.
20. Moneta GL, Lee RW, Yeager RA, et al. Mesenteric duplex scanning: a blinded prospective study. *J Vasc Surg.* 1993;17(1):79–84; discussion 85–86.
21. Bowersox JC, Zwolak RM, Walsh DB, et al. Duplex ultrasonography in the diagnosis of celiac and mesenteric artery occlusive disease. *J Vasc Surg.* 1991;14(6):780–786; discussion 786–788.
22. Zwolak RM, Fillinger MF, Walsh DB, et al. Mesenteric and celiac duplex scanning: a validation study. *J Vasc Surg.* 1998;27(6):1078–1087; discussion 1088.
23. Oderich GS, Głowiczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? *Semin Vasc Surg.* 2010;23(1):36–46.
24. Wildermuth S, Leschka S, Alkadhi H, Marinsek B. Multislice CT in the pre- and postinterventional evaluation of mesenteric perfusion. *Eur Radiol.* 2005;15(6):1203–1210.
25. Baden JG, Racy DJ, Grist TM. Contrast-enhanced three-dimensional magnetic resonance angiography of the mesenteric vasculature. *J Magn Reson Imaging.* 1999;10(3):369–375.
26. Hagspiel KD, Leung DA, Angle JF, et al. MR angiography of the mesenteric vasculature. *Radiol Clin North Am.* 2002;40(4):867–886.
27. Dalman RL, Li KC, Moon WK, et al. Diminished postprandial hyperemia in patients with aortic and mesenteric arterial occlusive disease. Quantification by magnetic resonance flow imaging. *Circulation.* 1996;94(suppl 9):II206–II210.
28. Li KC, Dalman RL, Wright GA. In vivo flow-independent T2 measurements of superior mesenteric vein blood in diagnosis of chronic mesenteric ischemia: a preliminary evaluation. *Acad Radiol.* 1999;6(9):530–534.
29. Boley SJ, Brandt LJ, Veith FJ, et al. A new provocative test for chronic mesenteric ischemia. *Am J Gastroenterol.* 1991;86(7):888–891.
30. Otte JA, Oostveen E, Mensink PB, et al. Triggering for submaximal exercise level in gastric exercise tonometry: serial lactate, heart rate, or respiratory quotient? *Dig Dis Sci.* 2007;52(8):1771–1775.
31. Sana A, Vergouwe Y, van Noord D, et al. Radiological imaging and gastrointestinal tonometry add value in diagnosis of chronic gastrointestinal ischemia. *Clin Gastroenterol Hepatol.* 2011;9(3):234–241.
32. Van Noord D, Sana A, Benaron DA, et al. Endoscopic visible light spectroscopy: a new, minimally invasive technique to diagnose chronic GI ischemia. *Gastrointest Endosc.* 2011;73(2):291–298.
33. Ubbink R, Van Dijk LJK, Van Noord D, et al. Evaluation of endoscopic visible light spectroscopy: Comparison with microvascular oxygen tension measurements in a porcine model. *J Transl Med.* 2019;17:65.
34. Rheudasil JM, Stewart MT, Schellack JV, et al. Surgical treatment of chronic mesenteric arterial insufficiency. *J Vasc Surg.* 1988;8(4):495–500.
35. Mueller C, Borriello R, Perlov-Antzis L. Parenteral nutrition support of a patient with chronic mesenteric artery occlusive disease. *Nutr Clin Pract.* 1993;8(2):73–77.
36. Baxter JP, Fayers PM, Bozzetti F, et al. An international study of the quality of life of adult patients treated with home parenteral nutrition. *Clin Nutr.* 2019;38:1788–1796.
37. Huber TS, Björck M, Chandra A, et al. Chronic mesenteric ischemia: Clinical practice guidelines from the Society for Vascular Surgery. *J Vasc Surg.* 2021;73:87S–115S.
38. Malgor RD, Oderich GS, McKusick MA, et al. Results of single- and two-vessel mesenteric artery stents for chronic mesenteric ischemia. *Ann Vasc Surg.* 2010;24(8):1094–1101.
39. Tallarita T, Oderich GS, Macedo TA, et al. Reinterventions for stent restenosis in patients treated for atherosclerotic mesenteric artery disease. *J Vasc Surg.* 2011;54(5):1422–1429.e1.
40. Oderich GS, Tallarita T, Głowiczki P, et al. Mesenteric artery complications during angioplasty and stent placement for atherosclerotic chronic mesenteric ischemia. *J Vasc Surg.* 2012;55(4):1063–1071.
41. Oderich GS, Macedo TA, Malgor RD, et al. RR26. Natural history of mesenteric artery stent restenoses and clinical and anatomic predictors for re-intervention in patients with chronic mesenteric ischemia. *J Vasc Surg.* 2009;49(5):e1–e2. Supplement.
42. Hannawi B, Lam WW, Younis GA. Pressure wire used to measure gradient in chronic mesenteric ischemia. *Tex Heart Inst J.* 2012;39(5):739–743.
43. Silva JA, White CJ, Collins TJ, et al. Endovascular therapy for chronic mesenteric ischemia. *J Am Coll Cardiol.* 2006;47(5):944–950.
44. Kret MR, Dalman RL, Kalish J, Mell M. Arterial cutdown reduces complications after brachial access for peripheral vascular intervention. *J Vasc Surg.* 2016;64(1):149–154.
45. Oderich GS, Erdoes L, LeSar C, et al. SS14. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. *J Vasc Surg.* 2012;55(6):23S.
46. Manunga JM, Oderich GS. Orbital atherectomy as an adjunct to debulk difficult calcified lesions prior to mesenteric artery stenting. *J Endovasc Ther.* 2012;19(4):489–494.
47. van Wanroij JL, van Petersen AS, Huisman AB, et al. Endovascular treatment of chronic splanchnic syndrome. *Eur J Vasc Endovasc Surg.* 2004;28(2):193–200.

48. Biebl M, Oldenburg WA, Paz-Fumagalli R, et al. Surgical and interventional visceral revascularization for the treatment of chronic mesenteric ischemia—when to prefer which? *World J Surg.* 2007;31(3):562–568.
49. Sarac TP, Altinel O, Kashyap V, et al. Endovascular treatment of stenotic and occluded visceral arteries for chronic mesenteric ischemia. *J Vasc Surg.* 2008;47(3):485–491.
50. Lee RW, Bakken AM, Palchik E, et al. Long-term outcomes of endoluminal therapy for chronic atherosclerotic occlusive mesenteric disease. *Ann Vasc Surg.* 2008;22(4):541–546.
51. Dias NV, Acosta S, Resch T, et al. Mid-term outcome of endovascular revascularization for chronic mesenteric ischaemia. *Br J Surg.* 2010;97(2):195–201.
52. Fioole B, van de Rest HJ, Meijer JR, et al. Percutaneous transluminal angioplasty and stenting as first-choice treatment in patients with chronic mesenteric ischemia. *J Vasc Surg.* 2010;51(2):386–391.
53. Peck MA, Conrad MF, Kwolek CJ, et al. Intermediate-term outcomes of endovascular treatment for symptomatic chronic mesenteric ischemia. *J Vasc Surg.* 2010;51(1):140–147.e1–2.
54. Schoch DM, LeSar CJ, Joels CS, et al. Management of chronic mesenteric vascular insufficiency: an endovascular approach. *J Am Coll Surg.* 2011;212(4):668–675; discussion 675–677.
55. Turba UC, Saad WE, Arslan B, et al. Chronic mesenteric ischaemia: 28-year experience of endovascular treatment. *Eur Radiol.* 2012;22(6):1372–1384.
56. AbuRahma AF, Campbell JE, Stone PA, et al. Perioperative and late clinical outcomes of percutaneous transluminal stentings of the celiac and superior mesenteric arteries over the past decade. *J Vasc Surg.* 2013;57(4):1052–1061.
57. Grilli CJ, Fedele CR, Tahir OM, et al. Recanalization of chronic total occlusions of the superior mesenteric artery in patients with chronic mesenteric ischemia: technical and clinical outcomes. *J Vasc Interv Radiol.* 2014;25(10):1515–1522.
58. Barret M, Martineau C, Rahmi G, et al. Chronic mesenteric ischemia: a rare cause of chronic abdominal pain. *Am J Med.* 2015;128(12):1363.e1–8.
59. Park WM, Cherry Jr KJ, Chua HK, et al. Current results of open revascularization for chronic mesenteric ischemia: a standard for comparison. *J Vasc Surg.* 2002;35(5):853–859.
60. Milner R, Woo EY, Carpenter JP. Superior mesenteric artery angioplasty and stenting via a retrograde approach in a patient with bowel ischemia—a case report. *Vasc Endovascular Surg.* 2004;38(1):89–91.
61. Pisimisis GT, Oderich GS. Technique of hybrid retrograde superior mesenteric artery stent placement for acute-on-chronic mesenteric ischemia. *Ann Vasc Surg.* 2011;25(1):132.e7–11.
62. Farber MA, Carlin RE, Marston WA, et al. Distal thoracic aorta as inflow for the treatment of chronic mesenteric ischemia. *J Vasc Surg.* 2001;33(2):281–287; discussion 287–288.
63. Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg.* 2007;45(2):269–275.
64. Kihara TK, Blebea J, Anderson KM, et al. Risk factors and outcomes following revascularization for chronic mesenteric ischemia. *Ann Vasc Surg.* 1999;13(1):37–44.
65. Foley MI, Moneta GL, Abou-Zamzam Jr AM, et al. Revascularization of the superior mesenteric artery alone for treatment of intestinal ischemia. *J Vasc Surg.* 2000;32(1):37–47.
66. Cho JS, Carr JA, Jacobsen G, et al. Long-term outcome after mesenteric artery reconstruction: a 37-year experience. *J Vasc Surg.* 2002;35(3):453–460.
67. Jimenez JG, Huber TS, Ozaki CK, et al. Durability of antegrade synthetic aortomesenteric bypass for chronic mesenteric ischemia. *J Vasc Surg.* 2002;35(6):1078–1084.
68. Ryer EJ, Oderich GS, Bower TC, et al. Differences in anatomy and outcomes in patients treated with open mesenteric revascularization before and after the endovascular era. *J Vasc Surg.* 2011;53(6):1611–1618.e2.
69. Davenport DL, Shivazad A, Endean ED. Short-term outcomes for open revascularization of chronic mesenteric ischemia. *Ann Vasc Surg.* 2012;26(4):447–453.
70. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: initial experience. *Radiology.* 2003;229(1):91–98.
71. Oderich GS, Panneton JM, Macedo TA, et al. Intraoperative duplex ultrasound of visceral revascularizations: optimizing technical success and outcome. *J Vasc Surg.* 2003;38(4):684–691.
72. van Petersen AS, Kolkman JJ, Beuk RJ, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. *J Vasc Surg.* 2010;51(5):1309–1316.
73. Assar AN, Abilez OJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. *J Cardiovasc Surg (Torino).* 2009;50(4):509–514.
74. Gupta PK, Horan SM, Turaga KK, et al. Chronic mesenteric ischemia: endovascular versus open revascularization. *J Endovasc Ther.* 2010;17(4):540–549.
75. Indes JE, Giacovelli JK, Muhs BE, et al. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. *J Endovasc Ther.* 2009;16(5):624–630.
76. Oderich GS, Malgor RD, Ricotta 2nd JJ. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. *Ann Vasc Surg.* 2009;23(5):700–712.
77. Rawat N, Gibbons CP. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. *Ann Vasc Surg.* 2010;24(7):935–945.
78. Rose SC, Quigley TM, Raker EJ. Revascularization for chronic mesenteric ischemia: comparison of operative arterial bypass grafting and percutaneous transluminal angioplasty. *J Vasc Interv Radiol.* 1995;6(3):339–349.
79. Sivamurthy N, Rhodes JM, Lee D, et al. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. *J Am Coll Surg.* 2006;202(6):859–867.
80. Zerbib P, Lebuffe G, Sergent-Baudson G, et al. Endovascular versus open revascularization for chronic mesenteric ischemia: a comparative study. *Langenbecks Arch Surg.* 2008;393(6):865–870.
81. Leke MA, Hood DB, Rowe VL, et al. Technical consideration in the management of chronic mesenteric ischemia. *Am Surg.* 2002;68(12):1088–1092.
82. Brown DJ, Schermerhorn ML, Powell RJ, et al. Mesenteric stenting for chronic mesenteric ischemia. *J Vasc Surg.* 2005;42(2):268–274.
83. Kruger AJ, Walker PJ, Foster WJ, et al. Open surgery for atherosclerotic chronic mesenteric ischemia. *J Vasc Surg.* 2007;46(5):941–945.
84. Mell MW, Acher CW, Hoch JR, et al. Outcomes after endarterectomy for chronic mesenteric ischemia. *J Vasc Surg.* 2008;48(5):1132–1138.
85. Lejay A, Georg Y, Tartaglia E, et al. Chronic mesenteric ischemia: 20 year experience of open surgical treatment. *Eur J Vasc Endovasc Surg.* 2015;49(5):587–592.
86. Zacharias N, Eghbalieh SD, Chang BB, et al. Chronic mesenteric ischemia outcome analysis and predictors of endovascular failure. *J Vasc Surg.* 2016;63(6):1582–1587.
87. Davies RS, Wall ML, Silverman SH, et al. Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. *Vasc Endovascular Surg.* 2009;43(2):157–164.
88. Landis MS, Rajan DK, Simons ME, et al. Percutaneous management of chronic mesenteric ischemia: outcomes after intervention. *J Vasc Interv Radiol.* 2005;16(10):1319–1325.
89. Matsumoto AH, Angle JF, Spinoza DJ, et al. Percutaneous transluminal angioplasty and stenting in the treatment of chronic mesenteric ischemia: results and longterm followup. *J Am Coll Surg.* 2002;194(suppl 1):S22–S31.
90. Sundermeyer A, Zapenko A, Moysidis T, et al. Endovascular treatment of chronic mesenteric ischemia. *Interv Med Appl Sci.* 2014;6(3):118–124.
91. Tallarita T, Oderich GS, Głowiczki P, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia using propensity score-matched comparison. *J Vasc Surg.* 2013;57(3):747–755; discussion 754–755.

Mesenteric Arterial Dissection

MATTHEW J. DOUGHERTY, DOUGLAS A. TROUTMAN,
and KEITH D. CALLIGARO

INTRODUCTION 1779

INCIDENCE 1779

ETIOLOGY 1779

CLINICAL PRESENTATION 1780

DIAGNOSIS 1780

CLASSIFICATION SYSTEMS 1781

TREATMENT 1781

Asymptomatic Patients 1781

Symptomatic Patients 1782

Surgical Treatment 1784

Endovascular Treatment 1784

Thrombolysis 1784

Embolization 1784

Stenting 1785

OTHER CONSIDERATIONS 1786

Segmental Arterial Mediolyisis 1786

SURVEILLANCE 1786

REMODELING 1787

SUMMARY 1787

CHAPTER ALGORITHM 1787

INTRODUCTION

Spontaneous isolated arterial dissection within the splanchnic circulation without associated aortic dissection or associated connective tissue disorder is a rare entity, but is being reported with increasing frequency. This most likely reflects improved imaging modalities, particularly abdominal computed tomography (CT), and increasing awareness of this condition rather than an increasing prevalence. Spontaneous isolated superior mesenteric artery dissection (SISMAD) was first reported by Bauersfeld in 1947.¹ Due to the low prevalence of spontaneous isolated visceral artery dissection and the variety of clinical presentations, there is a lack of consensus regarding treatment guidelines.^{2–4} The goal of this chapter is to review the current literature on visceral dissection and help establish the best contemporary treatment guidelines.

INCIDENCE

The superior mesenteric artery (SMA) is the most common visceral artery affected, followed by the celiac artery.^{5,6} In 1959, Ford reported an incidence of 0.06% SISMAD from a cohort of 6666 autopsies.⁷ Prior to 2001, only 46 cases of SISMAD were reported. As of 2016, that number has increased to more than 622 cases.^{2,8} There is a lower incidence of spontaneous

isolated celiac artery dissection (SICAD).⁹ There are even fewer reports of concomitant SISMAD and SICAD. Garrett et al. reviewed the literature through 2008 and reported 13 concomitant spontaneous isolated visceral artery dissections (SIVADs).⁴ Spontaneous isolated dissection of the splenic, hepatic, middle colic, and inferior mesenteric arteries have also been reported.^{10–13} Sixty-seven percent to 88% of isolated splanchnic artery dissection have been observed in males.^{2,4,10,14–16} Typically, patients present in the fifth to sixth decade of life.^{2,4,17,18} Sixty percent to 70% of patients with an aortic dissection present with hypertension; in contrast, only 30% to 40% of patients with isolated splanchnic dissections present with hypertension^{2,4,14,19,20} (see Ch. 83, Aortic Dissection: Epidemiology, Pathophysiology, Clinical Presentation, and Medical and Surgical Management). Although isolated splanchnic dissections have been reported on all continents, the majority of cases have been reported in Korea, China, and Japan, suggesting a genetic predisposition.⁴

ETIOLOGY

There are multiple theories on the etiology of isolated splanchnic artery dissections and the cause may vary between different visceral vessels. Proposed etiologies of SIVAD include connective tissue diseases (Marfan syndrome, Ehlers–Danlos

syndrome, Loeys–Diest syndrome), cystic medial necrosis, segmental arteriole mediolysis, Behçet disease, and fibromuscular dysplasia^{2,4,21–24} (see Ch. 141, Aneurysms Caused by Connective Tissue Abnormalities). However, the majority of patients with SIVAD do not have any of these arteriopathies. Tobacco use, atherosclerosis, alcohol abuse, obesity, heavy weight lifting, and pregnancy have also been suggested as risk factors for SIVAD.^{7,19,25–27}

In the majority of SISMADs, the dissection originates 1 to 3 cm from the SMA ostium.^{2,4,6,28–32} At this position, the SMA transitions from a fixed retropancreatic position with an acute turn into a mobile mesenteric root. Hyperdynamic forces occurring at this transition point most likely result in this zone's becoming the origin for most SISMADs.¹⁴ Park et al. conducted flow dynamic studies using computational fluid dynamic models that showed greater shear stress on the anterior convex portion of the SMA just distal to the ostium. These authors suggested that the etiology of SISMAD is more likely due to elevated shear stress at this location in the SMA rather than an underlying connective tissue disease or uncontrolled hypertension.¹⁹ Solies et al. also suggested high shear stress as the etiology of SISMAD due to the 1- to 3-cm origin of SISMAD.^{33,34} This theory is analogous to Type II aortic dissections originating at the ligamentum arteriosum due to luminal stress at the transition from a fixed to an unfixed point. Another proposed hypothesis is development of primary hemorrhage in the media due to a rupture of the vasa vasorum, which then leads to dissection.¹⁰ Jia et al. have linked chromosome locus 5q13–14, which is associated with familial ascending aortic aneurysms and dissections, with SISMAD.³⁵

There is no clear etiology for SICAD.^{9,36–38} In theory, the median arcuate ligament may represent a fixed transition point for the origin of celiac dissection. However, DiMusto et al. did not find any evidence of SICAD originating from the median arcuate ligament in their reported series of 19 SICAD.⁵

There are several case reports describing the histologic findings of SIVAD. Common features include fragmentation of elastic fibers, loss of smooth muscle cells, myxoid degeneration, and atheromatous changes. No definitive correlation to arteritis, cystic medial necrosis, or other arteriopathies was identified.^{2,14,19} It appears that only a minority of SIVAD cases are associated with other arteriopathies.

The majority of current published literature on SIVADs comes from east Asian countries. Corrected for population, Korea appears to have the highest number of reports per capita, followed by Japan and then China.^{2,19} This suggests, but does not prove, a higher prevalence of SIVAD in Asian populations.

CLINICAL PRESENTATION

The presentation of SIVAD varies greatly, and may include bowel ischemia, aneurysmal formation with or without rupture, or as an incidental finding on imaging. With modern CT and computed tomography angiography (CTA), a larger number of incidental SIVADs have been identified. In some series, as many as one-third of SIVADs are found incidentally.^{31,39} Symptomatic SIVAD presents with abdominal pain in 90%

of cases. Pain is described as severe and tearing in the midepigastric area with occasional radiation to the back. Other potential SIVAD symptoms may include nausea, emesis, melena, and diarrhea.

Abdominal pain out of proportion to physical findings suggests the diagnosis of mesenteric ischemia, which may be a clue to the diagnosis of SIVAD. Without the presence of bowel ischemia, abdominal pain is believed to originate from the visceral nerve plexus due to inflammation from the arterial dissection. It has been suggested that increased length of a SISMAD causes more periarterial inflammation and more severe pain.^{14,40,41} Persistent abdominal pain that does not resolve is more likely due to mesenteric ischemia rather than inflammation of neural tissue²⁰ (see Ch. 133, Acute Mesenteric Ischemia: Epidemiology, Pathophysiology, Clinical Evaluation, and Management). Patients with SIVAD have a wide variety of clinical presentations and, thus, multiple treatment algorithms have been proposed, which creates diagnostic and therapeutic management challenges for the clinician.

DIAGNOSIS

There are no specific laboratory tests for SIVAD; however, elevated lactate levels correlate with end organ malperfusion. In patients with SIVAD without mesenteric ischemia, leukocytosis as well as elevated C-reactive protein and/or erythrocyte sedimentation rate may be present.²

Prior to 1975, all SIVAD cases were diagnosed by autopsy. The first case of SISMAD was reported in 1947. This patient had a SISMAD originating 2 cm from the SMA ostium that led to bowel infarction and death.¹ The first documented survivor after treatment of SISMAD was reported in 1992, wherein angiography demonstrated the lesion after laparotomy for ischemic bowel.⁴² Digital subtraction angiography (DSA) supplanted conventional arteriography by minimizing contrast exposure and providing improved definition of distal mesenteric branch vessels compared to other imaging modalities. However, DSA is a more invasive test with limited ability to identify end-organ malperfusion when compared with contrast-enhanced CT.¹⁰

CTA and contrast-enhanced CT are now used to diagnose more than 95% of contemporary cases of SIVAD. Less commonly used are duplex ultrasonography (DU), DSA, and magnetic resonance angiography (MRA), respectively.² Although DU is a reliable, inexpensive, and noninvasive modality for diagnosis and surveillance of mesenteric vascular disease, it may have low diagnostic sensitivity. Subhas et al. reported that DU only identified 56% of SISMADs.¹⁰ An intimal flap may be difficult to visualize sonographically and acute thrombosis of the false lumen may hinder discrimination of the false channel. Bowel gas and obesity also render DU studies difficult to perform successfully even with experienced technologists. MRA may demonstrate similar evidence of disease, but is both less efficient and less commonly available in the acute setting compared to CT.

Contrasted-enhanced CT is capable of identifying dissection flaps, false lumens, reentry tears, thrombus, intramural

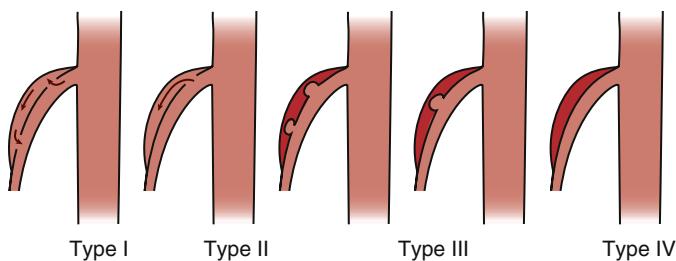


Figure 135.1 Spontaneous isolated superior mesenteric artery dissection classification system proposed by Sakamoto et al.: *Type I*, patent false lumen with both entry and reentry; *Type II*, a “cul de sac”-shaped false lumen without reentry; *Type III*, thrombosed false lumen with ulcer defect; and *Type IV*, a completely thrombosed false lumen without ulcer. (From Sakamoto I, Ogawa Y, Sueyoshi E, et al. Imaging appearances and management of isolated spontaneous dissection of the superior mesenteric artery. *Eur J Radiol*. 2007;64:103–110.)

hematomas, aneurysm formation, and rupture of splanchnic arteries. When visualization of the dissection itself is limited, increased attenuation of the mesenteric fat may suggest the diagnosis.^{10,43,44} CT not only identifies the SIVAD, but also demonstrates the characteristics of the dissection such as its origin, length, and concomitant lesions.³² CT is also able to identify other markers of end-organ malperfusion. CTA should now be considered the gold standard for diagnosis of SIVAD.¹⁰

CLASSIFICATION SYSTEMS

A number of classification systems have been developed for SISMAD. The goals of a classification system are to assist with risk assessment and determination of the best treatment algorithm for different types, extent, and characteristics of SISMADs. In 2007, Sakamoto et al. reported the first classification system for SISMAD. This group characterized SMA dissections based on CT appearance: Type I, patent false lumen with both entry and reentry; Type II, a “cul de sac”-shaped false lumen without reentry; Type III, thrombosed false lumen with ulcer defect; and Type IV, a completely thrombosed false lumen without ulcer (Fig. 135.1). In Sakamoto’s series, all Type I SISMAD were treated successfully with conservative measures such as anticoagulation and medical management. In patients with Type II SISMAD, the true lumen may be compromised by false lumen compression. They recommended that these patients be followed very closely for signs of mesenteric ischemia. Type III SISMADs had the highest rate of intervention in contrast to Type IV SISMADs that did not require any intervention. Although this series only included 12 patients, it was the first classification system that attempted to determine best treatment using image classification.⁴⁵ A criticism of this system is the exclusion of patients with thrombotic occlusion.⁴⁶

Yun et al. reported a classification system with three types of SISMADs. Type I, patent true and false lumen revealing entry and reentry sites; Type IIa, patent true lumen but no reentry of the patent false lumen; Type IIb, patent true lumen but no reentry of thrombosed false lumen; and Type III, dissection with occlusion of SMA (Fig. 135.2). This classification system was based on a clinical series of 32 patients. The authors were able to correlate pain severity with length of dissection, but

could not predict outcome or recommend treatment guidelines based on the classification system due to small sample size. Four of the 32 patients underwent intervention (one endovascular and three open surgeries) for persistent pain due to bowel ischemia, but the type of SISMADs in these patients was not described.⁴⁰ Notably, due to the simplicity of Yun’s classification system, it has become the most commonly used.

Zerbib et al. described a more complex classification system by adding more categories to Sakamoto’s scheme. Type V is aneurysmal dissection with stenosis of the distal segment of the SMA. Type Va is total thrombosis of SMA and Type VIb shows partial SMA thrombosis. These authors compared outcomes of reported cases in the literature using their classification system. Their results showed that Types II and III lesions required more interventions in contrast to Types I and IV. Unfortunately, they were unable to predict clinical outcome based on this classification system.⁴⁷

Luan and Li described a classification system based on the location and extent of the SMA dissection rather than luminal patency. These authors suggest four types of dissection. Type A is described as a dissection at the curve of the SMA and extending proximally to the SMA ostium. Type B is described as a dissection limited to the curve of the SMA. Type C is described as extending from the curve of the SMA distally, but not involving the ileocolic or distal ileal artery. Type D is described as extending toward the ileocolic and/or ileal artery (Fig. 135.3). In this series, patients with Type B dissection were symptomatic less often in contrast to patients with Type D dissection, who presented with more severe pain. Unfortunately, management strategies are difficult to assess due to a sample size of only 20 patients. Type B patients were more likely to have successful treatment with conservative treatment compared with Type C and D patients.³²

Other classification systems have been proposed, but unfortunately have not added to improvement of clinical management strategies.³⁰ Dissections of other visceral vessels have not been included in these systems. There is lack of wide acceptance of any one algorithm at this point in time.

TREATMENT

Management of SISMAD or other visceral vessel dissection depends on the clinical circumstances including morphology of the dissection, resultant symptoms, and the patient’s clinical course. Little can be stated with authority at this time due to the low prevalence of reported SISMAD cases in the English medical literature worldwide and fewer cases including vessels other than the SMA. The majority of these cases have been reported within the last 2 decades, a time period with major advances in diagnostic imaging and therapeutic interventions.

Asymptomatic Patients

Technical improvements in multi-helical CT in the last decade, as well as increasing frequency of the use of CT in evaluating patients with various conditions, have led to an increase in the reported incidence of SIVAD. As a result, SIVAD has

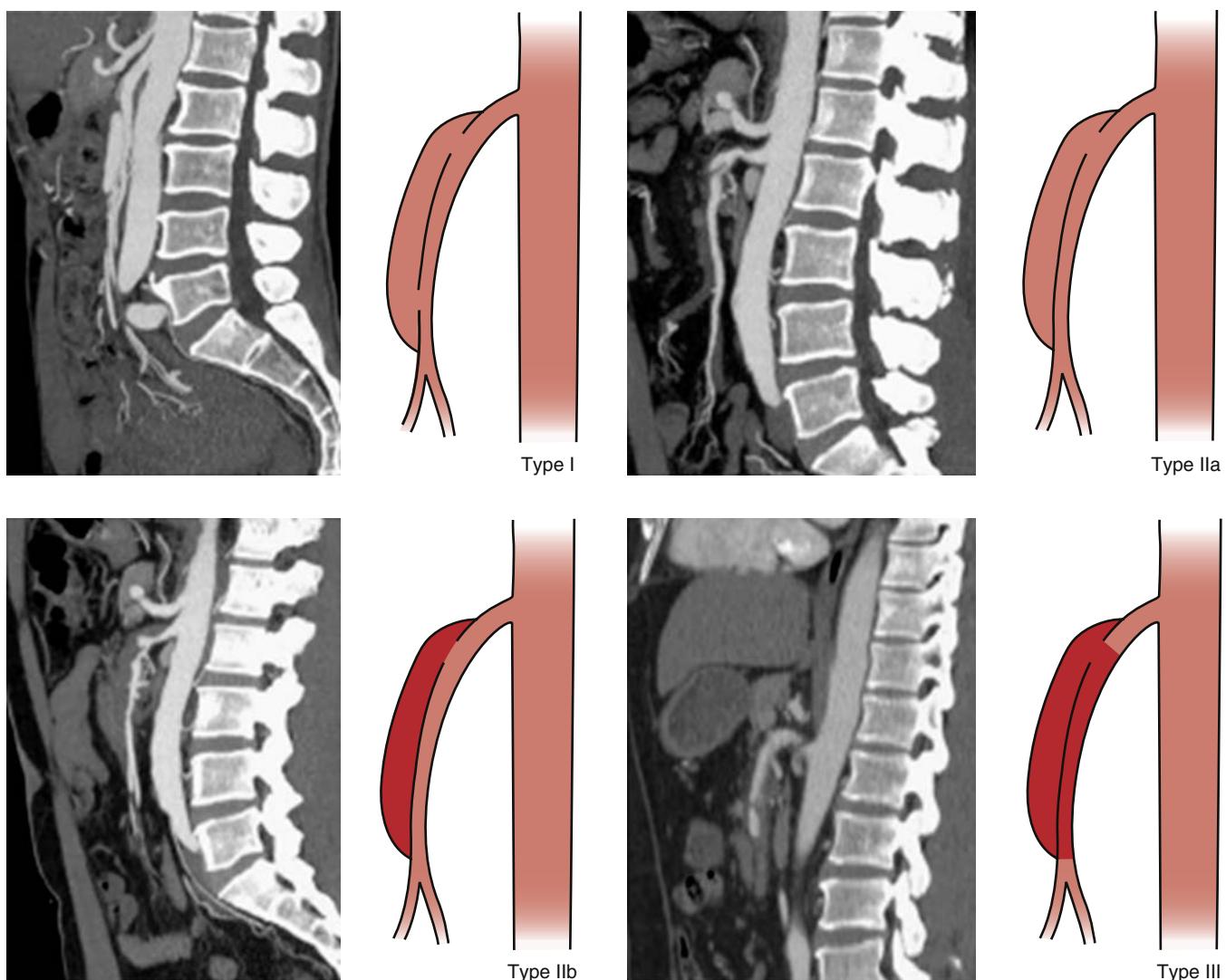


Figure 135.2 Yun et al. classification system for spontaneous isolated superior mesenteric artery dissection: *Type I*, patent true and false lumen revealing entry and reentry sites; *Type IIa*, patent true lumen but no reentry of the patent false lumen; *Type IIb*, patent true lumen but no reentry of thrombosed false lumen; and *Type III*, dissection with occlusion of superior mesenteric artery. (From Yun WS, Kim YW, Park KB, et al. Clinical and angiographic follow-up of spontaneous isolated superior mesenteric artery dissection. *Eur J Vasc Endovasc Surg.* 2009; 37(5):572–577.)

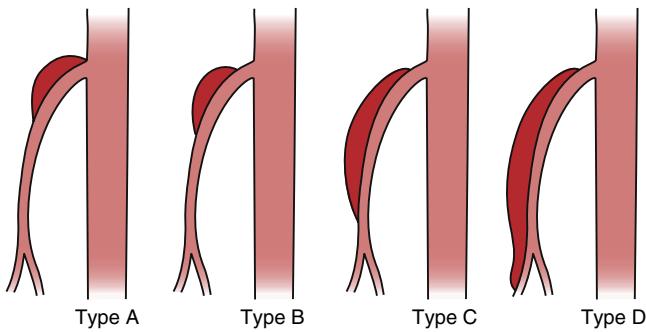


Figure 135.3 Classification system by Laun et al.: *Type A* dissection at the curve of the superior mesenteric artery (SMA) and extending proximally to the SMA ostium; *Type B* dissection limited to the curve of the SMA; *Type C* extending from the curve of the SMA distally, but not involving the ileocolic or distal ileal artery; *Type D* extending toward the ileocolic and/or ileal artery. (From Luan JY, Li X. Computed tomography imaging features and classification of isolated dissection of the superior mesenteric artery. *Eur J Vasc Endovasc Surg.* 2013;46(2):232–235.)

been observed in a number of asymptomatic patients. There is consensus that these patients should be managed medically.^{7,20,40,48–53} However, the role of antiplatelet agents and anticoagulants is not well defined in either asymptomatic or symptomatic patients.

Symptomatic Patients

As previously noted, a minority of patients that present with acute symptoms of SIVAD have vessel perforation and/or hemorrhage. Most patients report abdominal pain. The pain may be due to the dissection itself or to visceral malperfusion with end-organ ischemia.

Most would agree that an incidental finding of a SIVAD without significant aneurysmal dilation or symptoms does not require intervention. However, there is controversy regarding

management of patients presenting with symptoms of abdominal pain. The variability of collateral networks to maintain intestinal perfusion creates unpredictability regarding the persistence or resolution of ischemic symptoms.

Initial treatment is typically bowel rest and observation, particularly for patients with normal serum lactate level and lack of leukocytosis. Patients with persistent pain may be treated with parenteral nutrition to reduced visceral “demand ischemia,” and continue until pain is resolved and the SIVAD is stable on imaging. Recruitment of collateral flow pathways or resolution of dynamic obstruction with dissection stabilization may explain resolution of ischemic pain. Pain secondary to the inflammatory process created by the dissection itself may persist for days. The role of anticoagulation is not well defined. Most authors have utilized at least short-term anticoagulation, but the benefit of this treatment has been questioned in recent reports.^{5,40,54}

It is possible for patients with SIVAD, who present with abdominal pain and without bleeding, to be managed medically. Ambo et al. was the first to report this treatment approach in

1994.^{54,55} Park et al. reported a series of 46 SIVAD patients with CTA surveillance for a mean of 23 months.¹⁴ These authors observed remodeling and improvement of the dissection in a majority of patients (Fig. 135.4). More importantly, none of these patients developed extension of the dissection, bowel ischemia, or arterial rupture. However, in a different series by Li et al., 3 of 24 patients initially managed conservatively developed progression, including one patient with a fatal bowel infarction.³⁰ Overall, a majority of patients with SIVAD reported in the last two decades have undergone successful medical management.^{20,30,56–58} There is a small number of patients with SICAD that have also undergone successful medical management.^{5,36,52,59,60} In patients whose symptoms resolved with conservative management involving gradual return to enteric nutrition, radiographic follow-up is recommended.⁸ There is no well-defined role for long-term anticoagulation or antiplatelet therapy.⁶¹ A majority of patients treated expectantly in recent reports have not been treated with oral anticoagulation, and some authors do not utilize antiplatelet therapy in patients who do not undergo intervention.^{40,46}

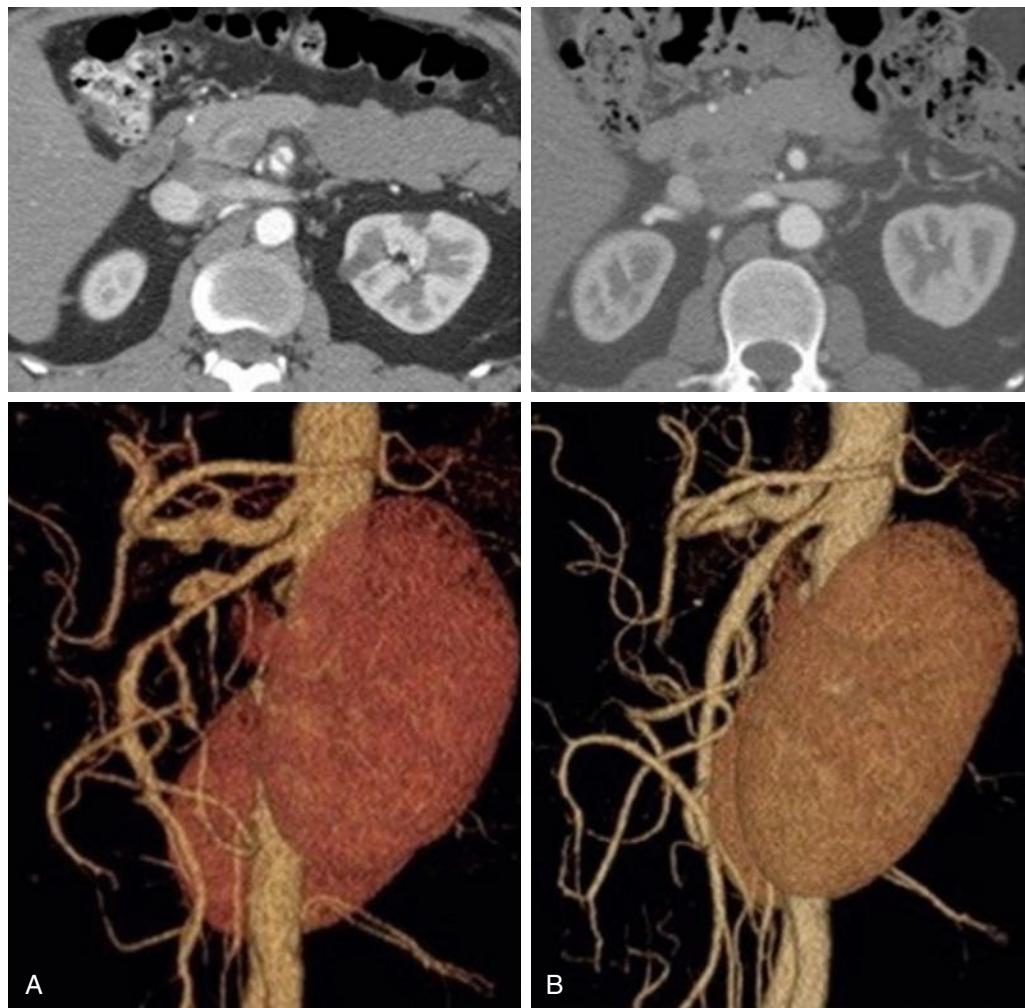


Figure 135.4 Computed tomography angiography demonstrating remodeling of spontaneous isolated superior mesenteric artery dissection before (A) and after (B) without intervention. (From Park YJ, Park KB, Kim DI, et al. Natural history of spontaneous isolated superior mesenteric artery dissection derived from follow-up after conservative treatment. *J Vasc Surg*. 2011;54:1727–1733.)

Surgical Treatment

A majority of early publications regarding treatment of SIVAD, mostly SISMAD, reported surgical treatment. The first documented successful surgery for SIVAD was reported in 1992. This patient was diagnosed with SISMAD via arteriography after laparotomy for mesenteric ischemia. The patient underwent a right gastroepiploic-to-SMA bypass.⁴² In most patients presenting with intra-abdominal hemorrhage or advanced bowel ischemia, open surgery remains the preferred option. Aside from resecting necrotic bowel when necessary, direct treatment of the arterial dissection can be accomplished by direct arterial repair. When operating for bleeding, ligation alone is appropriate if collateral flow appears sufficient.⁶² When bowel is threatened, surgery may include aorto-visceral bypass, extra-anatomic bypass (with gastroepiploic or hepatic artery inflow for SMA dissection), and intimectomy/fenestration often

combined with vein patch repair. Autogenous graft material, most commonly the greater saphenous vein, has been utilized in most reports.⁴²

Endovascular Treatment

Thrombolysis

Thromolytic therapy has rarely been employed in the setting of visceral vessel thromboembolism. There are few reports of its utilization in the setting of SIVAD, usually in combination with stenting. Mixed results have been observed.^{63–65}

Embolization

Occasionally patients present with aneurysm formation or vessel perforation by the false channel as the primary concern. Endovascular coil embolization has been utilized in this setting (Fig. 135.5).^{30,65,66}

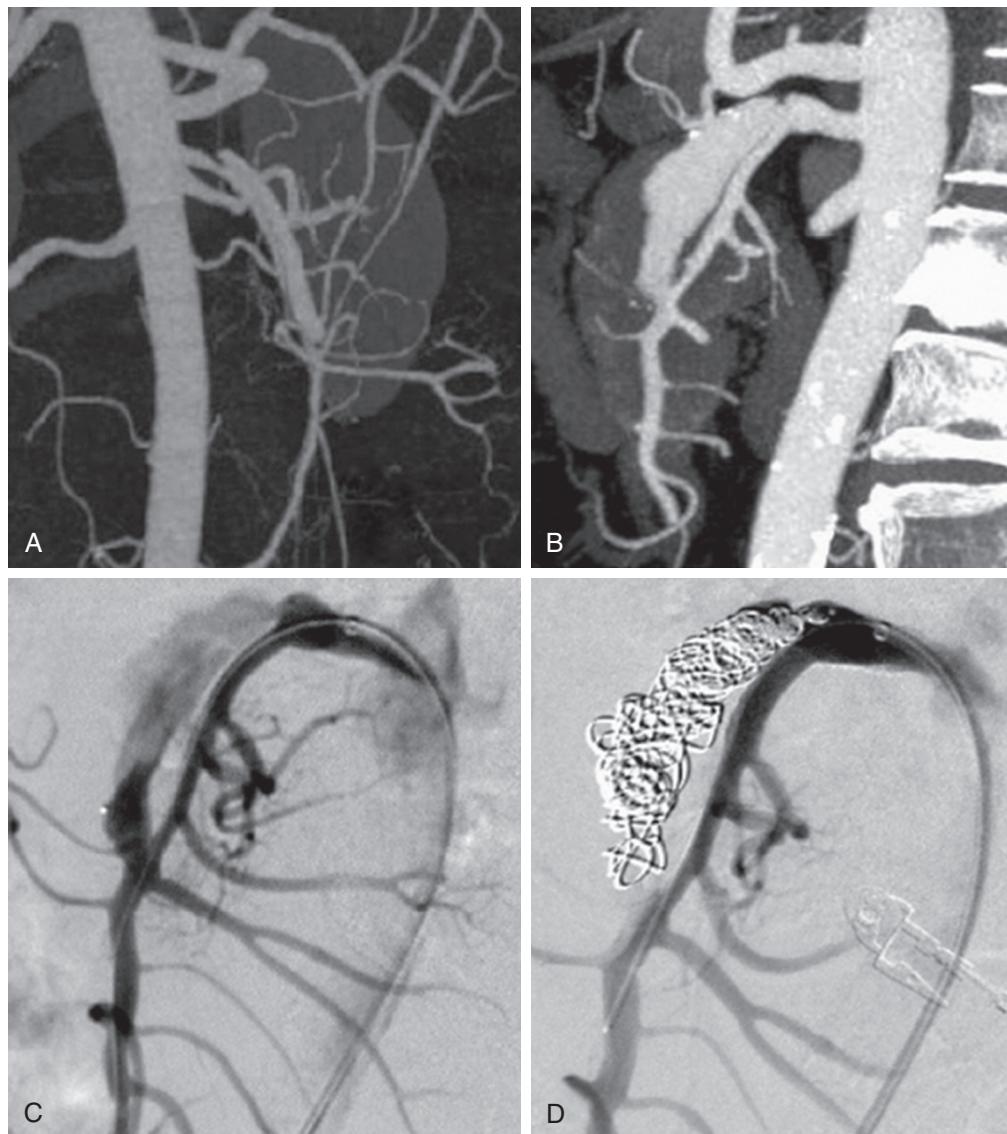


Figure 135.5 Imaging of superior mesenteric artery dissection (A), with pseudoaneurysm (B), treated with coil embolization of false lumen and pseudoaneurysm (C and D). (From Ozaki T, Kimura M, Yoshimura N, et al. Endovascular treatment of spontaneous isolated dissecting aneurysm of the superior mesenteric artery using stent-assisted coil embolization. *Cardiovasc Interv Radiol*. 2006;29:435–437.)

Stenting

The first report of endovascular stenting to treat a SISMAD was published in 2000 by Leung et al.⁶⁷ Cumulative experience with stenting in the published English literature totals only a few dozen cases; thus it is difficult to make broad conclusions regarding indications, technique, and efficacy.^{31,68} The majority of patients treated with stents had ongoing abdominal pain as the primary indication for treatment.^{69,70} Many theorize that the symptom of pain is more commonly due to the dissection itself with an inflammatory response to the vessel injury rather than from mesenteric malperfusion and ischemia. A disadvantage of endovascular treatment compared to surgery is the inability to inspect the bowel for evidence of ischemia or necrosis. Accordingly, almost all patients treated with endovascular stents had variable symptoms of abdominal pain, rather than advanced ischemia or bowel necrosis.

The goal of endovascular treatment is elimination of stenosis caused by false lumen encroachment, as well as stabilization

of vessel integrity to avoid late degeneration and aneurysm formation. According to the limited available natural history data, aneurysm formation appears to be a relatively rare occurrence; thus stenting should be primarily used for the former indication. Persistent pain is considered an indication for intervention in several series, analogous to the treatment of aortic dissection. Some authors have noted that patients having intervention with stenting have had an accelerated return to normal dietary intake and hospital discharge.^{28,71} Others advocate a more selective application of stenting. Min et al. suggest that SMA stenosis of greater than 80% or dilation to more than 2 cm are indications for primary stenting (Fig. 135.6).²⁸ However, other authors have observed radiographic improvement in the degree of stenosis with conservative management in the large majority of patients.^{58,64}

Visceral vessel stenting via transfemoral artery access has been reported most commonly. However, left brachial artery access provides significant advantage because it allows antegrade

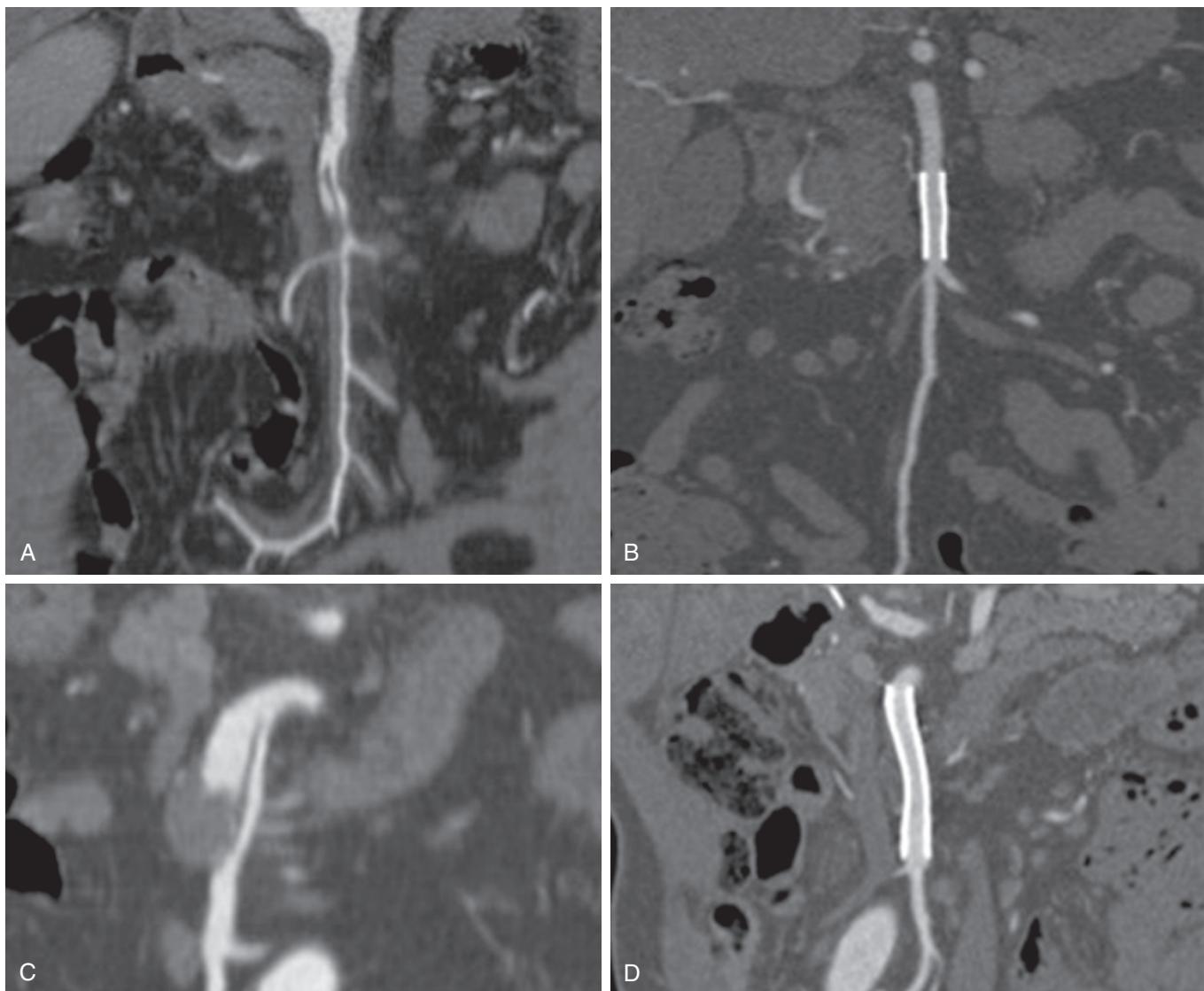


Figure 135.6 Superior mesenteric artery dissection (A and C), successfully treated with endovascular stenting (B and D). (From Min SI, Yoon KC, Min SK, et al. Current strategy for the treatment of symptomatic spontaneous isolated dissection of superior mesenteric artery. *J Vasc Surg*. 2011;54:461–466.)

tracking of the acutely angulated proximal vessel, particularly the SMA. Caution must be taken to gain wire access to the true lumen, which may be challenging.⁷² As the entry point for SMA dissection is rarely ostial, self-expanding stents are preferred over the balloon-expandable design for most lesions. Nitinol bare metal stents have been utilized in most reports.⁷³

Covered stents may have occasional utility, particularly when excluding aneurysmal vessels.^{74–76} However, in most situations, preservation of flow to the remaining patent SMA branches is the priority and bare stents are preferred. Most authors have utilized stents long enough to treat the entire length of the dissection rather than only the entry tear. Multiple stents have been reported in about one third of patients.⁷⁷ One group has reported on the successful use of flow-diverting stents for patients with aneurysmal dilatation of the SMA false lumen associated with dissection.⁷⁸

They achieved complete false lumen thrombosis with aneurysm shrinkage over time, while preserving patent SMA branches in the true lumen (Fig. 135.7).

Published long-term results with stenting are limited, but few failures have been reported to date.^{30,79–82} Intermediate-term patency appears to be high and late recurrent dissection or arterial degeneration appears to be very low. Most authors recommend long-term antiplatelet therapy as adjunctive therapy.

In comparison with medical management, the majority of the current literature available on endovascular management of SIVAD pertains to lesions of the SMA. However, there are a few reports of successful surgical and endovascular management of SICAD. Similar to SISMAD, recognizing which branch of the celiac artery has the dissection is more challenging than the technical aspects of the treatment^{5,36,60} (see Chapter Algorithm).

OTHER CONSIDERATIONS

Segmental Arterial Mediolyisis

Segmental arterial mediolyisis (SAM) has recently gained recognition as a distinct pathologic entity. Although dissections may occur with this noninflammatory arteriopathy, aneurysms are more common and multiple lesions in various vessels are often present at the time of diagnosis (Fig. 135.8). Renal and visceral vessels are at highest risk for SAM, often with multiple areas of aneurysmal dilation and dissections. Intraabdominal hemorrhage is more common than thrombotic or ischemic complications. Open surgical treatment has often been utilized on an emergent basis; however, endovascular management with coil embolization and stenting has played an increasing role in more recent reports.^{21,22,83}

SURVEILLANCE

There is no consensus on surveillance of patients with SIVAD; however, most clinicians suggest some type of routine follow-up.^{10,14,84} CTA is the surveillance study of choice; however, DU may also be used. The rationale for surveillance is the potential for SIVAD to form a splanchnic aneurysm.⁸⁵ The true incidence of aneurysm formation is unknown, but this has been reported.⁶⁸ Imaging at 1 month post initial SIVAD, every 6 months for the first year, then annual surveillance has been proposed. This is a reasonable approach until the natural history of this disease entity is better defined.^{4,14}

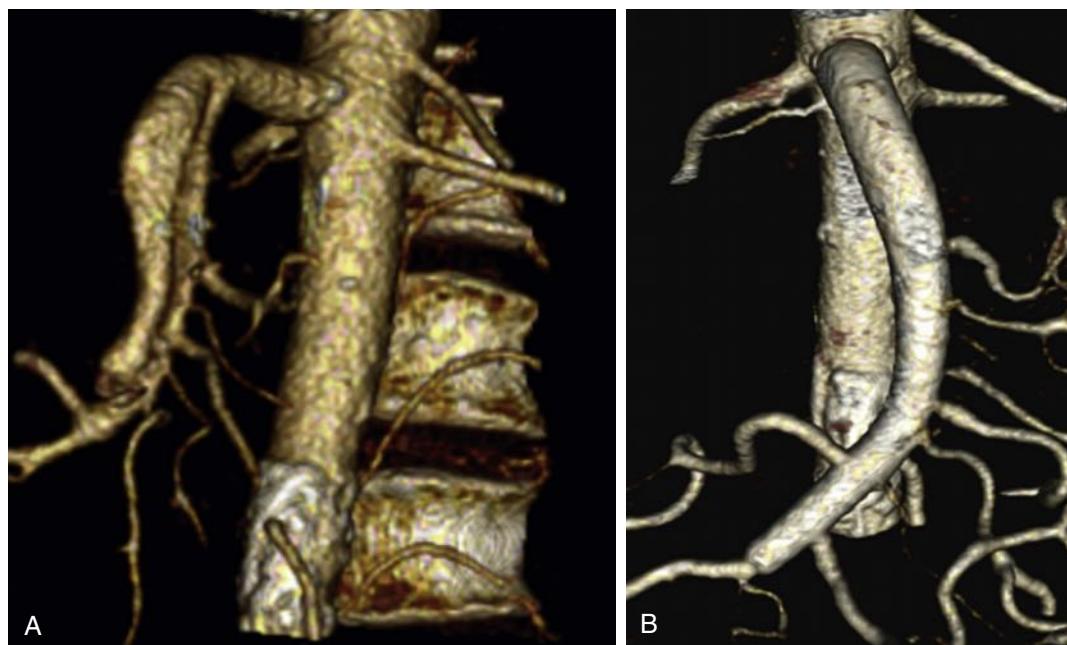


Figure 135.7 SMA dissection with (A) aneurysmal dilatation of the false lumen, and (B) 6-month follow-up following flow-diverting stent placement with SMA and side branch patency, obliteration of the false lumen and aneurysmal shrinkage. (From: Baldino G, Mortola P, Cambiaso M, et al. Endovascular treatment with flow-diverting stents of symptomatic superior mesenteric artery after dissection aneurysm. *J Vasc Surg Cases Innov Tech*. 2017;3:30.)



Figure 135.8 Segmental arterial mediolysis affecting the superior mesenteric artery in a patient presenting with rupture – distal superior mesenteric artery specimen opened, revealing dissection. (From Tameo MN, Dougherty MJ, Calligaro KD. Spontaneous dissection with rupture of the superior mesenteric artery from segmental arterial mediolysis. *J Vasc Surg.* 2011;53:1107–1112.)

REMODELING

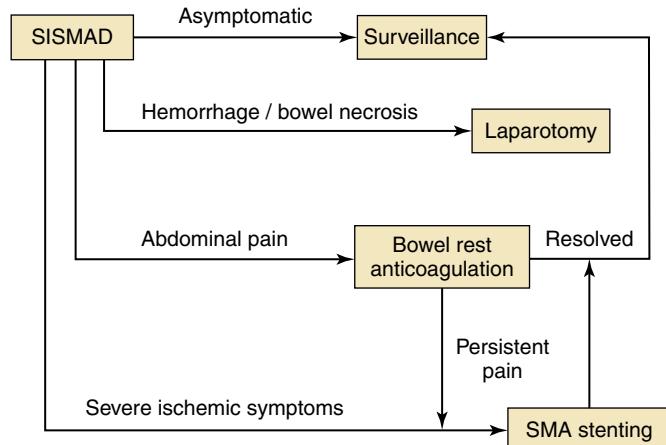
Surveillance of SIVAD has shown that more arteries remodel than form aneurysms. Park et al. showed that 41% of SISMAD treated medically had improvement on surveillance CTA and 15% of patients had complete remodeling of the SMA. Positive predictors for complete remodeling included type II lesions from the Yun classification system. These are SISMADs that had a single tear and no reentry tear. This leads to false lumen thrombosis and more complete remodeling of the SMA. It is unclear if remodeling leads to better clinical outcomes, but there is no report to date of late morbidity in a patient whose dissection was described as improving.¹⁴

SUMMARY

Isolated visceral artery dissections are rare, but have been increasingly recognized with advanced imaging techniques in recent years. No single etiologic factor has been identified, but a higher prevalence is observed in the east Asian population. Although bowel ischemia and hemorrhage can complicate these

SIVADs, the majority can be managed medically. Endovascular treatment has played a growing role in management of symptomatic lesions with high procedural and intermediate-term success. Radiographic surveillance is recommended in patients regardless of initial treatment.

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

- Garrett HE. Options for treatment of spontaneous mesenteric artery dissection. *J Vasc Surg.* 2014;59(5):1433–1439.
Great review article on spontaneous mesenteric artery dissection.
 - Gobble RM, Brill ER, Rockman CB, et al. Endovascular treatment of spontaneous dissections of the superior mesenteric artery. *J Vasc Surg.* 2009;50(6):1326–1332.
Study from the U.S. advocating stenting for symptomatic SISMADs.
 - Luan JY, Guan X, Li X, et al. Isolated superior mesenteric artery dissection in China. *J Vasc Surg.* 2016;63(2):530–536.
A large retrospective review of SISMADs.
 - Park YJ, Park KB, Kim DI, et al. Natural history of spontaneous isolated superior mesenteric artery dissection derived from follow-up after conservative treatment. *J Vasc Surg.* 2011;54(6):1727–1733.
A good paper for looking at the natural history of SISMADs.
 - Tameo MN, Dougherty MJ, Calligaro KD. Spontaneous dissection with rupture of the superior mesenteric artery from segmental arterial mediolysis. *J Vasc Surg.* 2011;53(4):1107–1112.
Detailed discussion about segmental arterial mediolysis.
- A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Bauersfeld SR. Dissecting aneurysm of the aorta; a presentation of 15 cases and a review of the recent literature. *Ann Intern Med.* 1947;26(6):873–889.
2. Luan JY, Guan X, Li X, et al. Isolated superior mesenteric artery dissection in China. *J Vasc Surg.* 2016;63(2):530–536.
3. Jean C, Marois M, Brochu P. Primary dissecting aneurysm of the superior mesenteric artery. *Can Med Assoc J.* 1961;85:942–943.
4. Garrett HE. Options for treatment of spontaneous mesenteric artery dissection. *J Vasc Surg.* 2014;59(5):1433–1439.
5. DiMasto PD, Oberdoerster MM, Criado E. Isolated celiac artery dissection. *J Vasc Surg.* 2015;61(4):972–976.
6. Luan JY, Li X, Li TR, et al. Vasodilator and endovascular therapy for isolated superior mesenteric artery dissection. *J Vasc Surg.* 2013;57(6):1612–1620.
7. Foord AG, Lewis RD. Primary dissecting aneurysms of peripheral and pulmonary arteries: dissecting hemorrhage of media. *Arch Pathol.* 1959;68:553–577.
8. Jia Z, Zhao J, Jiang G. Regarding “Management strategy for spontaneous isolated dissection of the superior mesenteric artery based on morphologic classification.” *J Vasc Surg.* 2014;59(3):876–877.
9. Sun J, Li DL, Wu ZH, et al. Morphologic findings and management strategy of spontaneous isolated dissection of the celiac artery. *J Vasc Surg.* 2016;64(2):389–394.
10. Subhas G, Gupta A, Nawalany M, et al. Spontaneous isolated superior mesenteric artery dissection: a case report and literature review with management algorithm. *Ann Vasc Surg.* 2009;23(6):788–798.
11. Moussa T, Nawfal G, Assi T, et al. Isolated celiac and splenic artery dissection: a case report and review of the literature. *Case Rep Vasc Med.* 2015;2015:194079.
12. Mei Z, Bao J, Jing Z, et al. Spontaneous isolated inferior mesenteric artery dissection. *Abdom Imaging.* 2011;36(5):578–581.
13. Higashiyama H, Ishii M, Fujimoto K, et al. Dissecting aneurysm of the hepatic artery caused by an isolated spontaneous celiac trunk dissection. *Ann Vasc Surg.* 2014;28(5):1316.e7–13.
14. Park YJ, Park KB, Kim DI, et al. Natural history of spontaneous isolated superior mesenteric artery dissection derived from follow-up after conservative treatment. *J Vasc Surg.* 2011;54(6):1727–1733.
15. Kang TL, Teich DL, McGillicuddy DC. Isolated, spontaneous superior mesenteric and celiac artery dissection: case report and review of literature. *J Emerg Med.* 2011;40(2):e21–e25.
16. Morris JT, Guerrero J, Sage JG, et al. Three isolated superior mesenteric artery dissections: update of previous case reports, diagnostics, and treatment options. *J Vasc Surg.* 2008;47(3):649–653.
17. Takayama T, Miyata T, Shirakawa M, et al. Isolated spontaneous dissection of the splanchnic arteries. *J Vasc Surg.* 2008;48(2):329–333.
18. Chen ZL, Zhang XC, Pan GR, et al. Clinical features and therapeutic options for isolated visceral artery dissection. *Ann Vasc Surg.* 2016;30:227–235.
19. Park YJ, Park CW, Park KB, et al. Inference from clinical and fluid dynamic studies about underlying cause of spontaneous isolated superior mesenteric artery dissection. *J Vasc Surg.* 2011;53(1):80–86.
20. Kim HK, Jung HK, Cho J, et al. Clinical and radiologic course of symptomatic spontaneous isolated dissection of the superior mesenteric artery treated with conservative management. *J Vasc Surg.* 2014;59(2):465–472.
21. Tameo MN, Dougherty MJ, Calligaro KD. Spontaneous dissection with rupture of the superior mesenteric artery from segmental arterial mediolysis. *J Vasc Surg.* 2011;53(4):1107–1112.
22. Hashimoto T, Deguchi J, Endo H, et al. Successful treatment tailored to each splanchnic arterial lesion due to segmental arterial mediolysis (SAM): report of a case. *J Vasc Surg.* 2008;48(5):1338–1341.
23. Poylin V, Hile C, Campbell D. Medical management of spontaneous celiac artery dissection: case report and literature review. *Vasc Endovascular Surg.* 2008;42(1):62–64.
24. Nat A, George T, Mak G, et al. Celiac artery disease and fatal rupture of a hepatic artery aneurysm in the Ehlers-Danlos syndrome. *Proc (Bayl Univ Med Cent).* 2014;27(2):116–117.
25. Sartelet H, Fedaoui-Delalou D, Capovilla M, et al. Fatal hemorrhage due to an isolated dissection of the superior mesenteric artery. *Intensive Care Med.* 2003;29(3):505–506.
26. Yasuhara H, Shigematsu H, Muto T. Self-limited spontaneous dissection of the main trunk of the superior mesenteric artery. *J Vasc Surg.* 1998;27(4):776–779.
27. Riles TS, Lin JC. Celiac artery dissection from heavy weight lifting. *J Vasc Surg.* 2011;53(6):1714–1715.
28. Min SI, Yoon KC, Min SK, et al. Current strategy for the treatment of symptomatic spontaneous isolated dissection of superior mesenteric artery. *J Vasc Surg.* 2011;54(2):461–466.
29. Dong Z, Fu W, Chen B, et al. Treatment of symptomatic isolated dissection of superior mesenteric artery. *J Vasc Surg.* 2013;57(2 suppl):69S–76S.
30. Li DL, He YY, Alkalei AM, et al. Management strategy for spontaneous isolated dissection of the superior mesenteric artery based on morphologic classification. *J Vasc Surg.* 2014;59(1):165–172.
31. Gobble RM, Brill ER, Rockman CB, et al. Endovascular treatment of spontaneous dissections of the superior mesenteric artery. *J Vasc Surg.* 2009;50(6):1326–1332.
32. Luan JY, Li X. Computed tomography imaging features and classification of isolated dissection of the superior mesenteric artery. *Eur J Vasc Endovasc Surg.* 2013;46(2):232–235.
33. Solis MM, Ranval TJ, McFarland DR, et al. Surgical treatment of superior mesenteric artery dissecting aneurysm and simultaneous celiac artery compression. *Ann Vasc Surg.* 1993;7(5):457–462.
34. Jung SC, Lee W, Park EA, et al. Spontaneous dissection of the splanchnic arteries: CT findings, treatment, and outcome. *AJR Am J Roentgenol.* 2013;200(1):219–225.
35. Jia Z, Zhang X, Wang W, et al. Spontaneous isolated superior mesenteric artery dissection: genetic heterogeneity of chromosome locus 5q13-14 in 2 male familial cases. *Ann Vasc Surg.* 2015;29(5):1019.e1–5.
36. Neychev V, Krol E, Dietzsch A. Unusual presentation and treatment of spontaneous celiac artery dissection. *J Vasc Surg.* 2013;58(2):491–495.
37. Chaillou P, Moussu P, Noel SF, et al. Spontaneous dissection of the celiac artery. *Ann Vasc Surg.* 1997;11(4):413–415.
38. Matsuo R, Ohta Y, Ohya Y, et al. Isolated dissection of the celiac artery – a case report. *Angiology.* 2000;51(7):603–607.
39. Ko SH, Hye R, Frankel DA. Management of spontaneous isolated visceral artery dissection. *Ann Vasc Surg.* 2015;29(3):470–474.
40. Yun WS, Kim YW, Park KB, et al. Clinical and angiographic follow-up of spontaneous isolated superior mesenteric artery dissection. *Eur J Vasc Endovasc Surg.* 2009;37(5):572–577.
41. Bair MJ, Lin IT, Chen HL. Superior mesenteric artery dissection. *Intern Med.* 2010;49(2):195–196.
42. Vignati PV, Welch JP, Ellison L, et al. Acute mesenteric ischemia caused by isolated superior mesenteric artery dissection. *J Vasc Surg.* 1992;16(1):109–112.
43. Takeda H, Matsunaga N, Sakamoto I, et al. Spontaneous dissection of the celiac and hepatic arteries treated by transcatheter embolization. *AJR Am J Roentgenol.* 1995;165(5):1288–1289.
44. Matsushima K. Spontaneous isolated dissection of the superior mesenteric artery. *J Am Coll Surg.* 2006;203(6):970–971.
45. Sakamoto I, Ogawa Y, Sueyoshi E, et al. Imaging appearances and management of isolated spontaneous dissection of the superior mesenteric artery. *Eur J Radiol.* 2007;64(1):103–110.
46. Jia Z, Zhao J, Jiang G. Commentary regarding “computed tomography imaging features and classification of isolated dissection of the superior mesenteric artery.” *Eur J Vasc Endovasc Surg.* 2014;47(1):108.
47. Zerbib P, Perot C, Lambert M, et al. Management of isolated spontaneous dissection of superior mesenteric artery. *Langenbecks Arch Surg.* 2010;395(4):437–443.

48. Cho YP, Ko GY, Kim HK, et al. Conservative management of symptomatic spontaneous isolated dissection of the superior mesenteric artery. *Br J Surg.* 2009;96:720–723.
49. Okamura K, Morizumi S, Kawata M, et al. Conservative therapy as a primary treatment for spontaneous isolated dissection of the superior mesenteric artery. *Ann Vasc Surg.* 2014;28:1939–1945.
50. Zhang X, Sun Y, Chen Z, et al. Therapeutic regimen options for isolated superior mesenteric artery dissection. *Vasc Endovascular Surg.* 2012;46(3):277–282.
51. Cho BS, Lee MS, Lee MK, et al. Treatment guidelines for isolated dissection of the superior mesenteric artery based on follow-up CT findings. *Eur J Vasc Endovasc Surg.* 2011;41(6):780–785.
52. Woolard JD, Ammar AD. Spontaneous dissection of the celiac artery: a case report. *J Vasc Surg.* 2007;45(6):1256–1258.
53. Alcantara S, Yang CK, Sasson J, et al. The evidence for nonoperative management of visceral artery dissections: a single-center experience. *Ann Vasc Surg.* 2015;29(1):103–108.
54. Morgan CE, Mansukhani NA, Eskandari MK, et al. Ten-year review of isolated spontaneous mesenteric arterial dissections. *J Vasc Surg.* 2018;67(4):1134–1142.
55. Ambo T, Noguchi Y, Iwasaki H. An isolated dissecting aneurysm of the superior mesenteric artery: report of a case. *Surg Today.* 1994;24:933–936.
56. Okamura K, Morizumi S, Kawata M, et al. Conservative therapy as a primary treatment for spontaneous isolated dissection of the superior mesenteric artery. *Ann Vasc Surg.* 2014;28:1939–1945.
57. Cho YP, Ko GY, Kim HK, et al. Conservative management of symptomatic spontaneous isolated dissection of the superior mesenteric artery. *Br J Surg.* 2009;96(7):720–723.
58. Choi JY, Kwon OJ. Approaches to the management of spontaneous isolated visceral artery dissection. *Ann Vasc Surg.* 2013;27(6):750–757.
59. Oh S, Cho YP, Kim JH, et al. Symptomatic spontaneous celiac artery dissection treated by conservative management: serial imaging findings. *Abdom Imaging.* 2011;36(1):79–82.
60. Obon-Dent M, Shabaneh B, Dougherty KG, et al. Spontaneous celiac artery dissection case report and literature review. *Tex Heart Inst J.* 2012;39(5):703–706.
61. Tian F, Li S, Wang K, et al. Comment on management of spontaneous isolated visceral artery dissection. *Ann Vasc Surg.* 2015;29(7):1482.
62. Nordanstig J, Gerdes H, Kocys E. Spontaneous isolated dissection of the celiac trunk with rupture of the proximal splenic artery: a case report. *Eur J Vasc Endovasc Surg.* 2009;37(2):194–197.
63. Hwang CK, Wang JY, Chaikoff EL. Spontaneous dissection of the superior mesenteric artery. *Ann Vasc Surg.* 2010;24:254.e1–254.e5.
64. Kim JH, Roh BS, Lee YH, et al. Isolated spontaneous dissection of the superior mesenteric artery: percutaneous stent placement in two patients. *Korean J Radiol.* 2004;5(2):134–138.
65. Langer S, Kobarg I, Puls R, et al. Acute mesenteric ischemia caused by spontaneous isolated dissection of the superior mesenteric artery: treatment by intra-arterial thrombolysis and percutaneous stent placement. *Eur J Radiol Extra.* 2007;69–72.
66. Batt M, Baque J. Successful percutaneous embolization of a symptomatic celiac artery dissection with aneurysmal dilation with detachable vascular plugs. *J Vasc Surg.* 2011;54(6):1812–1815.
67. Leung DA, Schneider E, Kubik-Huch R, et al. Acute mesenteric ischemia caused by spontaneous isolated dissection of the superior mesenteric artery: treatment by percutaneous stent placement. *Eur Radiol.* 2000;10(12):1916–1919.
68. Takach TJ, Madjarov JM, Holleman JH, et al. Spontaneous splanchnic dissection: application and timing of therapeutic options. *J Vasc Surg.* 2009;50(3):557–563.
69. Casella IB, Bosch MA, Sousa WO. Isolated spontaneous dissection of the superior mesenteric artery treated by percutaneous stent placement: case report. *J Vasc Surg.* 2008;47(1):197–200.
70. Yoon YW, Choi D, Cho SY, et al. Successful treatment of isolated spontaneous superior mesenteric artery dissection with stent placement. *Cardiovasc Interv Radiol.* 2003;26(5):475–478.
71. Pang P, Jiang Z, Huang M, et al. Value of endovascular stent placement for symptomatic spontaneous isolated superior mesenteric artery dissection. *Eur J Radiol.* 2013;3:490–496.
72. Dong Z, Ning J, Fu W, et al. Failures and lessons in the endovascular treatment of symptomatic isolated dissection of the superior mesenteric artery. *Ann Vasc Surg.* 2016;31:152–162.
73. Nomura Y, Yamaguchi M, Kitagawa A, et al. Hybrid management of ruptured isolated superior mesenteric artery dissecting aneurysm. *J Vasc Surg.* 2011;54(6):1808–1811.
74. Chu SY, Hsu MY, Chen CM, et al. Endovascular repair of spontaneous isolated dissection of the superior mesenteric artery. *Clin Radiol.* 2012;67(1):32–37.
75. Larson RA, Solomon J, Carpenter JP. Stent graft repair of visceral artery aneurysms. *Vasc Surg.* 2002;36(6):1260–1263.
76. Atkins BZ, Ryan JM, Gray JL. Treatment of a celiac artery aneurysm with endovascular stent grafting – a case report. *Vasc Endovascular Surg.* 2003;37(5):367–373.
77. Li N, Lu QS, Zhou J, et al. Endovascular stent placement for treatment of spontaneous isolated dissection of the superior mesenteric artery. *Ann Vasc Surg.* 2014;28(2):445–451.
78. Baldino G, Mortola P, Cambiaso M, et al. Endovascular treatment with flow-diverting stents of symptomatic superior mesenteric artery after dissection aneurysm. *J Vasc Surg Cases Innov Tech.* 2017;3:30.
79. Ly PH, Zhang XC, Wang LF, et al. Management of isolated superior mesenteric artery dissection. *World J Gastroenterol.* 2014;20(45):17179–17184.
80. Lim EH, Jung SW, Lee SH, et al. Endovascular management for isolated spontaneous dissection of the superior mesenteric artery: report of two cases and literature review. *J Vasc Interv Radiol.* 2011;22(8):1206–1211.
81. Lu PH, Zhang XC, Wang LF, Shi HB. Percutaneous endovascular reconstruction with bare stent implantation for isolated superior mesenteric artery dissection. *Vasc Endovascular Surg.* 2014;48:406–411.
82. Li Z, Ding H, Shan Z, et al. Initial and middle-term outcome of treatment for spontaneous isolated dissection of superior mesenteric artery. *Medicine (Baltimore).* 2015;94:e2058.
83. Peng KX, et al. Natural history and management outcomes of segmental arterial mediolysis. *J Vasc Surg.* 2019;70(6):1877–1886.
84. Amabile P, Ouässi M, Cohen S, et al. Conservative treatment of spontaneous and isolated dissection of mesenteric arteries. *Ann Vasc Surg.* 2009;23(6):738–744.
85. Ahn HY, Cho BS, Mun YS, et al. Treatment results for spontaneous isolated superior mesenteric artery dissection according to our previous guidelines and collective literature review. *Ann Vasc Surg.* 2014;28(7):1595–1601.

Median Arcuate Ligament Syndrome: Pathophysiology, Diagnosis, and Management

BENJAMIN R. BITEMAN and FREDRICK BRODY

INTRODUCTION	1788
ANATOMY	1788
PATHOPHYSIOLOGY	1789
DIAGNOSIS	1789
History and Physical Examination	1789
Radiologic Studies	1790
MANAGEMENT	1791
Laparoscopic Technique	1792
Results	1792

CLINICAL CHALLENGES: CASE STUDIES	1794
Case 1	1794
Case 2	1795
Case 3	1795
Case 4	1796
Lessons Learned	1796
CONCLUSION	1797
CHAPTER ALGORITHM	1797

INTRODUCTION

“Compression of the celiac artery by the median arcuate ligament is well-documented.”¹ Stanley and Fry published this statement in 1971 after reviewing “provocative xylose absorption tests” in ten female and five male patients over a 3.5-year period. After transecting the median arcuate ligament in these 15 patients, they concluded that intestinal ischemia was the underlying disorder in median arcuate ligament syndrome (MALS). However, 45 years later, MALS continues to be difficult to qualify, quantify, and diagnose. MALS (also known as celiac artery compression syndrome and Dunbar syndrome) is an anatomic and clinical illness resulting from extrinsic compression on the celiac axis. Clinical manifestations include postprandial and exercise-induced epigastric abdominal pain, nausea, vomiting, weight loss, and “food fear,” or fear of pain triggered by eating. Lipshutz² offered the first anatomic description of the celiac artery in 1917, and Harjola performed the first surgical release in 1963.³ In 1967 Dunbar et al.⁴ reported a larger case series in which operative division of the MAL resulted in clinical improvement in 13 of 15 patients. Anatomically, up to 24% of the population may have MAL compression; however, less than 1% of these patients are symptomatic.⁵ Over the last several years, the theoretical etiology

of MALS has shifted from a vascular disease to a neurogenic illness with compression of the surrounding celiac plexus and ganglion. Presently, patient selection remains critically important in order to obtain optimal clinical outcomes following treatment.⁶

ANATOMY

Embryologically, the diaphragm is derived from the septum transversum and descends from the neck toward the celiac axis between weeks 9 and 12 and ultimately forms the MAL. Typically the diaphragmatic crura arise from the anterior aspect of L1 to L4 and project cephalad to join the anterior longitudinal ligament of the spine overlying the celiac axis. The MAL is composed of the fibrous edge of the diaphragmatic crura that crosses the aorta at the level of the celiac artery. These fibers splay over the aorta and extend laterally toward the suspensory ligament of the fourth portion of the duodenum (Fig. 136.1). In the majority of the population, the ligament does not encroach on the celiac artery and causes no compression (Fig. 136.2). As noted previously, as much as 10% to 24% of the population may have MAL compression without symptoms.⁵ The celiac nerve plexus branches across the abdominal aorta between vertebral levels T11 to L1.

PATOPHYSIOLOGY

Multiple theories exist regarding the pathophysiology of the epigastric pain associated with MALS. One theory hypothesizes that increased blood demand through a compressed celiac artery leads to foregut ischemia and pain. However, collateral blood flow between the mesenteric vessels often compensates for either subtotal or intermittent occlusion of the celiac artery,

especially in the patient age group presenting with MALS. Also, studies performed using gastric exercise tonometry document that mucosal oxygen delivery does not correlate with celiac artery compression or clinical symptoms.⁷ Similar findings exist with gastric perfusion studies.⁸ In addition, MAL compression is not associated with gastric necrosis or even gastric ischemia on endoscopic evaluation.⁶ Another theory states that midgut ischemia induces abdominal pain through a vascular steal syndrome. In theory, blood flow from the superior mesenteric artery may be diverted through collaterals to compensate for inefficient delivery through a stenotic celiac artery, and this mechanism results in small bowel ischemia and pain. This mechanism would be difficult to document with retrograde flow studies. Others suggest that the epigastric pain is caused by overstimulation of the celiac plexus with subsequent splanchnic vasoconstriction and ischemia (Fig. 136.3).⁹ Some authors favor a neurogenic hypothesis for symptoms of MALS. Histologic analysis of the celiac plexus shows that the nerves consist of pain fibers and inhibitory motor fibers to the stomach. Thus, entrapment of the ganglion by the MAL may alter gastric myoelectrical activity and impair antral motility,¹⁰ and induce pain.¹¹ Since the underlying pathophysiology of MALS is unknown, the diagnosis of MALS is difficult. Consequently, to enhance the benefit of patient selection and surgical intervention, the diagnosis of MALS needs to be reliable and accurate.

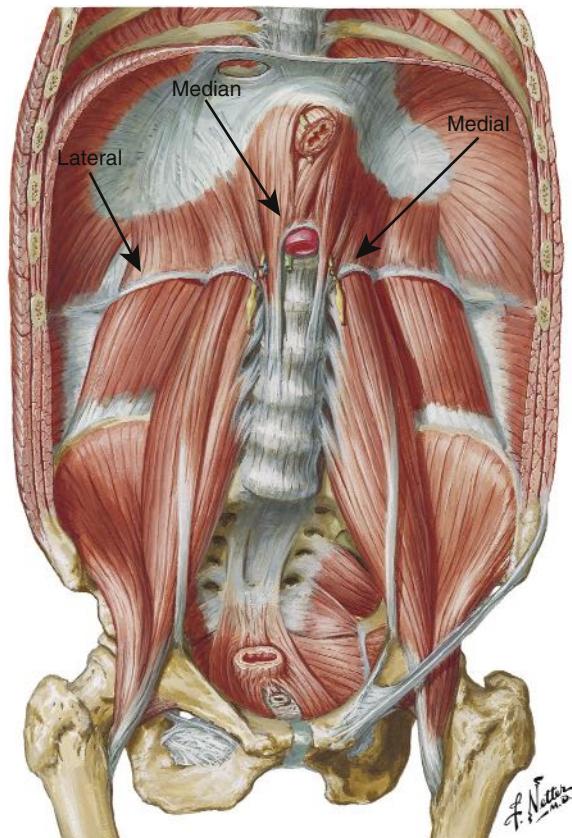


Figure 136.1 Artistic rendering of the retroperitoneal musculature and diaphragm. Arrows depicting the median, medial, and lateral arcuate ligaments. (February 28, 2018. Used with permission of Elsevier. All rights reserved.)

DIAGNOSIS

History and Physical Examination

The goal of surgical intervention begins with accurately identifying patients with symptomatic MALS and those patients who would benefit from surgery. Initially the workup includes consultation with a vascular and general surgeon for a detailed history and physical examination. Overall, history and physical examination often prove nondiagnostic or equivocal. The history may yield previous surgical interventions, including cholecystectomy and/or diagnostic laparoscopy. The most common

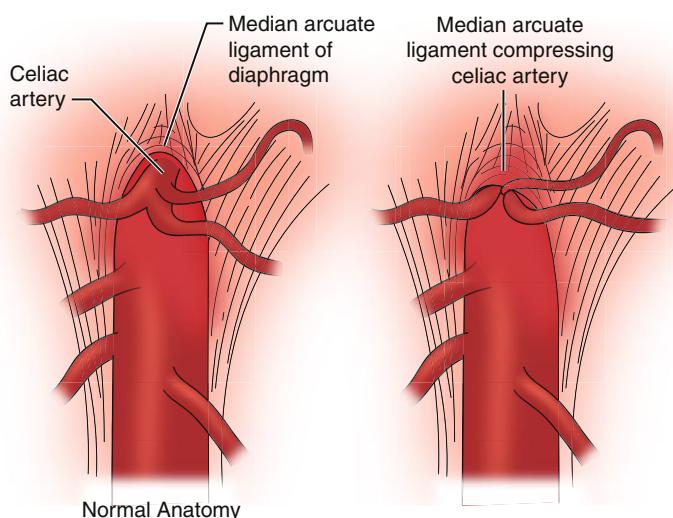


Figure 136.2 Artistic rendering of the proposed pathophysiology of celiac artery compression in those patients with median arcuate ligament syndrome.

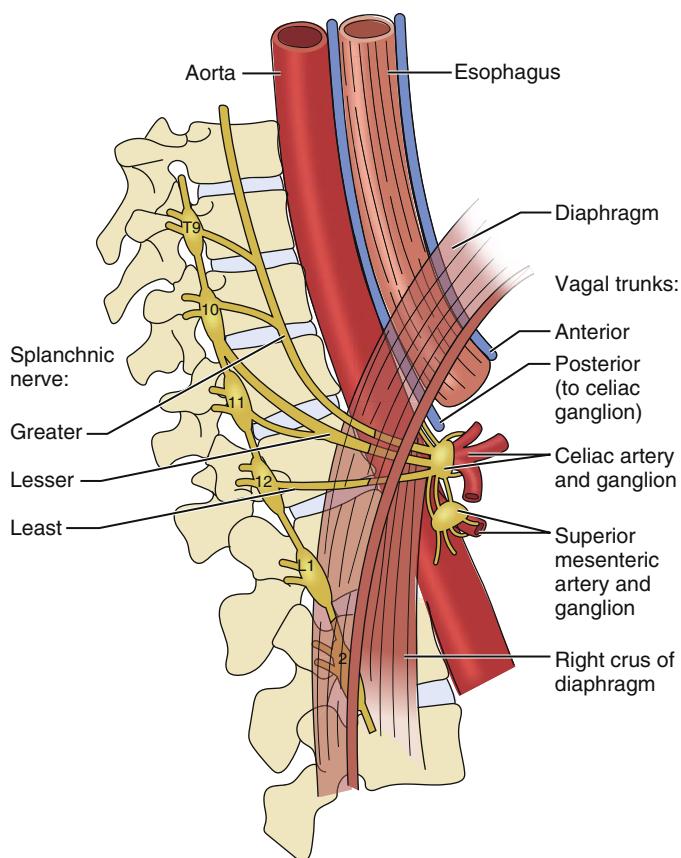


Figure 136.3 Artistic rendering of a sagittal view of the median arcuate ligament and proposed neural networks entering and exiting the celiac ganglion and plexus. Compression of the celiac axis by the median arcuate ligament simultaneously can cause compression of the celiac ganglion.

BOX 136.1

Signs and Symptoms of Median Arcuate Ligament Syndrome

More Common

Second to sixth decade of life
Female:Male 3:1
Postprandial abdominal pain
Nausea
Vomiting
Unintentional weight loss
Exercise-induced pain

Less Common

Autonomic dysfunction
Fibromyalgia
Postural
Orthostatic tachycardia syndrome

presenting symptom is abdominal pain, and an overwhelming majority of symptoms are classified as postprandial. Other symptoms include weight loss, bloating, nausea, vomiting, and exercise-induced pain (Box 136.1). Recently, patients with autonomic neuropathy, including postural orthostatic tachycardia syndrome (POTS), have been diagnosed with MALS.¹² Physical examination typically reveals a thin, flat, nontender abdomen. Despite the suspected underlying pathology, an abdominal bruit is usually not detected with auscultation.

There is a female predilection at 2:1 to 3:1, and typical ages range in the fourth and fifth decade. Some recent literature challenges the classic age range and shifts the disease onset to the second and third decades.¹³ However, some patients complain of years of symptoms which results in a delayed diagnosis.

Often patients have had multiple evaluations regarding their abdominal symptoms. Many patients face an inherent bias from their physicians following an initial negative workup, and many of these patients frequently carry a “psychiatric” or noncompliant diagnosis. Anecdotally, fibromyalgia, autonomic dysfunction, and pain medication-seeking behavior may be included in these patients’ charts. Most patients have already had an extensive gastrointestinal workup including gallbladder ultrasounds, ERCP, esophagogastroduodenoscopy, colonoscopy, enteric motility studies, computed tomography (CT), and magnetic resonance imaging (MRI). In one series, 54% of patients had undergone at least one prior abdominal procedure, including cholecystectomy, exploratory laparoscopy/laparotomy, and/or biliary and pancreatic sphincterotomy.¹⁴

Radiologic Studies

During the 1960s and 1970s, lateral aortography was the most reliable and objective means of documenting the presence and extent of celiac artery compression. Using inspiratory and expiratory images, this invasive test was considered pathognomonic for MALS. Today, CT angiography (CTA) and magnetic resonance arteriography (MRA) have emerged as the two most common diagnostic studies for MALS. CTA and MRA can evaluate the structural elements of the celiac artery, the MAL, and the surrounding viscera, in addition to providing aortic and celiac branch anatomy. CTA and MRA may also identify concomitant abdominal disease such as a co-existing neoplasm, mesenteric thromboses, or atherosclerosis. CTA (Fig. 136.4) and MRA provide information about the relationship of the celiac artery with the diaphragm and help visualize the compressed artery from various angles. Although they are not dynamic, CTA is now fast enough to be performed with inspiration and expiration cycles.

At some institutions, MALS is now diagnosed initially with transabdominal duplex ultrasound scanning of the celiac artery. Several studies have demonstrated varying degrees of compression of the celiac artery during the respiratory cycle. Normally the distance between the celiac artery and MAL increases during inspiration and decreases with expiration.¹⁵ During expiration, the aorta moves in a cephalad direction and may subject the celiac artery and its surrounding celiac plexus to compression by the MAL. During inspiration, the celiac artery moves away from the MAL as the aorta moves caudally.¹⁵ These distinct anatomic findings during normal breathing induce dynamic celiac artery velocities during inspiration and expiration. However, diagnostic ultrasound is technician-dependent and requires a high degree of expertise to reliably assess the mesenteric vessels.

Ultrasound scanning is performed during inspiration and expiration using 3.5 to 5.0 MHz probes with linear array or convex sector probes. Arterial inflow is based on B-mode and

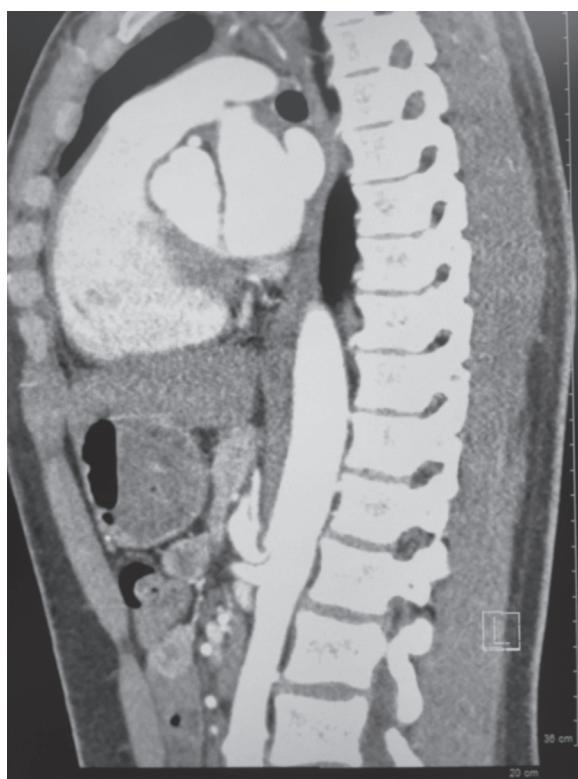


Figure 136.4 Sagittal view from a computed tomography angiography depicting celiac stenosis and poststenotic dilation due to median arcuate ligament compression.

the peak systolic velocity (PSV). Ultrasound measurements focus on the proximal portion of the celiac artery just distal to the ostia. According to criteria published by Moneta et al.,¹⁶ a PSV greater than 200 cm/s, no flow, or retrograde common hepatic arterial flow during inspiration or expiration were consistent with a significant (>70%) stenosis of the celiac artery (Fig. 136.5). Turbulent flow with elevated peak systolic velocities on expiration, which normalize or decrease with inspiration and standing erect, are suggestive of MALS (see Fig. 136.5). The ultrasound findings should document a peak expiratory velocity of greater than 200 cm/s to entertain a diagnosis of MALS and should be greater than resting and inspiratory velocities. Peak expiratory velocities of greater than 500 cm/s have been reported.¹³ Other ultrasound findings associated with MALS include abnormal origins of the celiac and superior mesenteric arteries, poststenotic bulbar dilation, and reverse flow in the hepatic artery.¹⁷ Gruber et al. were able to correlate a diagnosis of MALS with celiac artery end diastolic velocity of 350 cm/s or greater, a 210% change in pulse volume amplitude with inspiration and expiration, and a celiac artery deflection angle of 50 degrees. These findings by Gruber showed a sensitivity of 83% and specificity of 100% compared with angiographic evidence of MALS.¹⁸ The theory that elevated celiac artery velocities is a marker for celiac artery compression spawned measurement of the velocities with inspiration and expiration both preoperative and postoperatively. Brody et al. published a predictive model in 2018 showing that both age and baseline celiac artery expiratory velocities as measured on dynamic

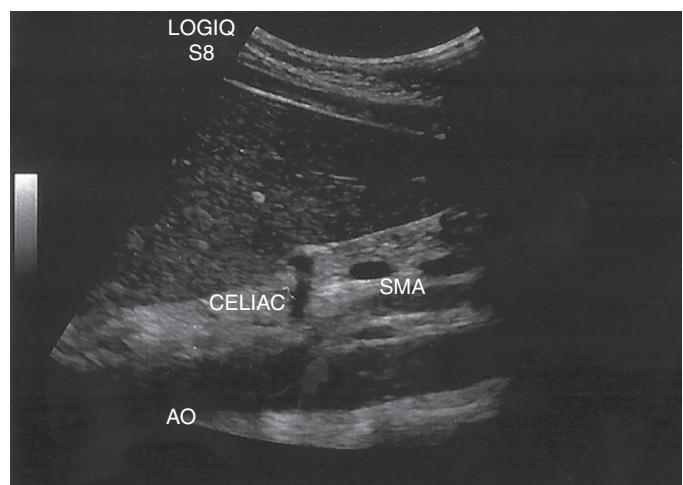


Figure 136.5 Doppler ultrasound image representation of normal findings and positioning during dynamic studies for median arcuate ligament syndrome.

ultrasound were significant independent predictors of good surgical outcome.^{19,20} A combination of ultrasound, CTA, and MRA usually provides enough information, coupled with the patient's symptoms, to confirm or exclude a diagnosis of MALS (see Fig. 136.4).¹³

Aortic angiography or CTA may reveal an asymmetric focal narrowing of the proximal celiac axis with poststenotic dilation. Narrowing is accentuated on expiration and relieved on inspiration. Increased collateral vessels in the celiac artery distribution may be evident and is indicative of significant stenosis.

Gastric exercise tonometry has been used as well to diagnose MALS. This test uses arterial blood gases and nasogastric fluid with a standardized protocol to measure arterial and gastric carbon dioxide levels before, during, and after 10 minutes of submaximal exercise. After acid suppression with a proton pump inhibitor or H2 blocker, baseline measurements of gastric PCO₂ and arterial blood gases are obtained. Following a 10-minute bicycle test and a 20-minute recovery period, blood gases and gastric PCO₂ are measured during peak exercise and recovery. A positive pathologic test consists of (1) a gastric–arterial PCO₂ gradient greater than 0.8 kPa after exercise, (2) an increase in gastric PCO₂ from baseline to peak exercise, and (3) an arterial lactate level less than 8 mmol/L.⁷

MANAGEMENT

Percutaneous celiac ganglion block has been used for decades to control intractable pain from intraabdominal cancer or chronic pancreatitis.¹⁴ In a series of 36 patients from the Mayo Clinic, preoperative celiac ganglion block was successfully performed on nine patients diagnosed with MALS, and all nine improved after surgery.⁸ Theoretically, a visceral block could be used as a preoperative diagnostic and potentially therapeutic test. However, there is limited data to support this algorithm.

Endovascular treatment alone does not benefit patients with MAL compression of the celiac axis. Matsumoto et al. reported immediate failure after performing five percutaneous

transluminal angioplasty (PTA) procedures for symptomatic visceral artery stenosis, secondary to extrinsic compression by the MAL or occult malignancy.²¹ In 2002 Matsumoto also described patients who immediately failed PTA in the setting of mesenteric ischemia but had immediate relief of symptoms after surgical release of the MAL.²² It is not uncommon to find patients with celiac artery stenosis who have had PTA attempted and subsequently required open or laparoscopic release of the MAL. Due to the angulation and compression of the celiac artery, PTA in patients with MALS may be associated with fractured stents and stent migration into various visceral arteries. Although data is limited to case reports, PTA alone is not successful without removal of the extrinsic compression of the MAL. PTA or stenting are now relatively contraindicated in the setting of MALS, as the extrinsic compression of the ligament would only obstruct or crush the stent and result in early restenosis.²² Some recent suggestions have been made for the adjuvant use of celiac angioplasty after robotic release if symptoms return after surgery. This may offer an additional step in algorithmic treatment of MALS.²³ However, purely endovascular treatment of MALS is not recommended.¹⁴

Currently most surgeons agree that laparoscopic, with or without robotic assistance, division of the MAL and the associated celiac ganglion tissue are critical for a successful treatment.¹³ In addition to sympathetic pain fibers, the celiac ganglion contains inhibitory sympathetic motor fibers, which modulate the intrinsic neural circuit of the stomach.²⁴ As noted earlier, decompressing or dividing the neural fibers would therefore decrease pain and improve gastric motility.^{10,13}

Laparoscopic Technique

A laparoscopic MAL release typically uses a standard five-port laparoscopic technique with the patient in the supine position (Fig. 136.6). The midline port is placed slightly more cephalad to visualize the aorta and celiac artery over the pancreatic body during the dissection. The ultrasonic scalpel is used to enter the lesser sac after the liver is retracted cephalad. A window is created to circumferentially expose the left gastric artery and coronary vein. With gentle retraction, the artery and vein are retracted from left to right to obtain an optimal view of the left and right borders of the aorta as it approaches the origin of the celiac artery. An extensive dissection of the common hepatic, left gastric, and splenic arteries is performed.¹ Typically the dissection extends 4 cm distal to the celiac artery bifurcation in order to divide all the neurovascular bundles surrounding the three associate vessels. The crural and MAL fibers are then divided

- ▶ from the overlying aorta using the hook cautery (Video 136.1). The aortic dissection extends 5 cm proximal to the origin of the celiac artery to ensure a complete division of the celiac plexus (Video 136.2; Video 136.3; Figs. 136.7–136.9). The dissection
- ▶ extends to the prevertebral fascia on the right of the aorta and to the suspensory ligament of the fourth portion of the duodenum on the left. All ganglionic fibers are divided with the electrocautery or ultrasonic scalpel (see Ch. 64, Laparoscopic and Robotic Aortic Surgery).

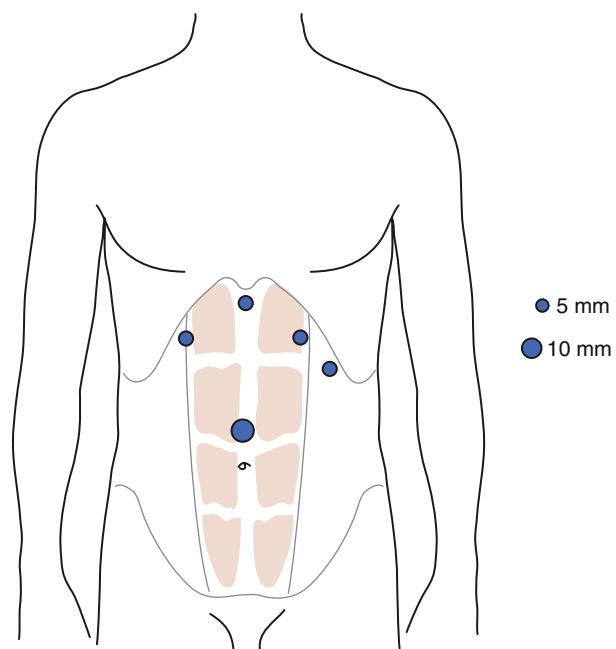


Figure 136.6 Port placement.

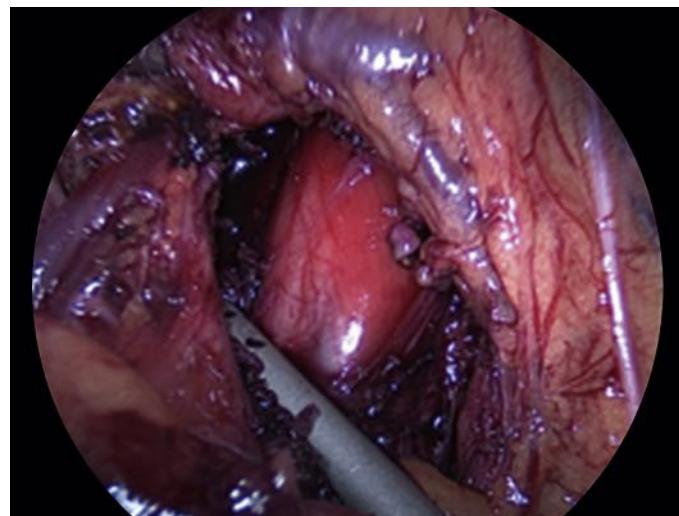


Figure 136.7 Midline view following aortic dissection during median arcuate ligament release. The released celiac origin can be appreciated as it branches from the aorta.

Results

Prior to laparoscopic release, open surgical treatment of MALS was described by several authors. Harjola³ and Dunbar et al.⁴ performed a midline laparotomy with decompression or division of the MAL and the associated celiac plexus. Reilly reported 51 patients with 9 years of follow-up (1964–1980) who underwent a combination of decompression alone, decompression with graduated celiac artery dilation through a celiac or splenic arteriotomy, or decompression with reconstruction and bypass of the stenotic arterial segments.²⁵ Of those 16 patients who underwent MAL decompression alone, 9 (56%) achieved symptom relief. Of 35 patients who underwent decompression and reconstruction, 27 (77%) achieved symptom relief. Ten

Video 136.1 Celiac Trifurcation Dissection.

Video 136.2 Plexus Dissection.

Video 136.3 Aortic Dissection.

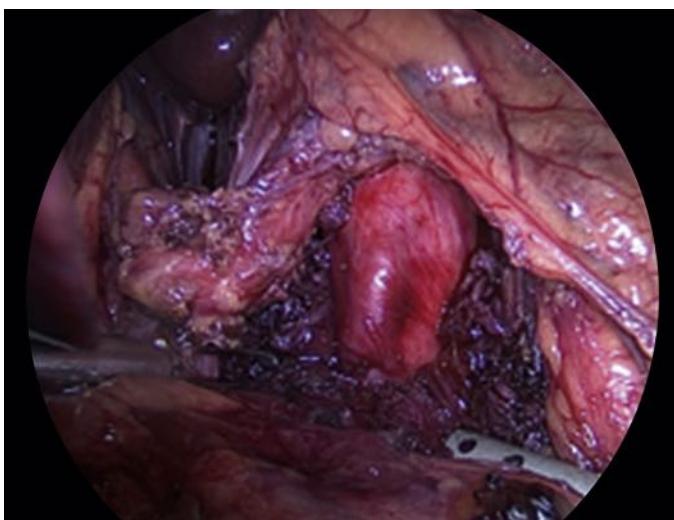


Figure 136.8 Further imaging showing release of median arcuate ligament and decompression of the celiac plexus.

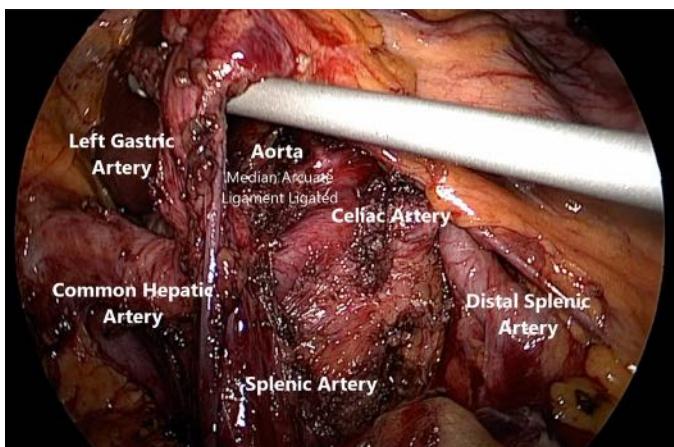


Figure 136.9 Completed dissection of the celiac axis with exposure of vasculature and neural lysis completed.

(40%) of 25 patients who received postoperative arteriograms remained symptomatic, and seven of those patients (70%) showed persistent celiac stenosis. In 2009, Grottemeyer et al. reported a case series of 18 patients, with three patients lost to follow-up, who underwent open decompression, and 11 of which (73%) had good resolution of their symptoms. However, five of the 11 patients (45%) required additional interventions on the celiac trunk prior to pain resolution.²⁶ Major postoperative complications following the open approach included a thrombosed bypass graft (2%), cerebrovascular accidents (1.4%), gastroesophageal reflux disease (1%), pancreatitis (1%), hemothorax (0.3%), and splenic infarction (0.3%).^{27,28} Based on these small series, it is clear that nearly 30% of patients will continue to be symptomatic despite surgery, and should be counseled regarding that risk preoperatively.

Several series have demonstrated successful laparoscopic treatment of MALS. In a single center report of data from 1999 to 2009 including 14 patients, 10 patients underwent a laparoscopic MAL release and two patients were converted to a laparotomy for bleeding from either the celiac or left gastric

artery. An additional four open MAL divisions were included. Median follow-up was 14 months, and 38% of the laparoscopic group and 50% of the open group had persistent pain at last follow-up.²⁹ The authors concluded that late recurrence was frequent but seemed to be milder than the initial clinical presentation. Laparoscopy was associated with a shorter hospital stay and decreased time to feeding. The authors also concluded that optimal patient selection, as a predictor of clinical response, remains a challenge.

A retrospective review was published in 2012, which encompassed 20 studies; 13 studies reported open MAL division and seven studies reported laparoscopic MAL division. Nearly 25% of patients in the open series underwent concomitant arterial reconstruction. Of those in the laparoscopic group, 9% underwent celiac artery angioplasty and stenting after laparoscopic division of MAL. Follow-up in the open group extended as far as 229 months, and laparoscopic follow-up extended to 44 months. Laparoscopic conversion to a laparotomy was 9.1%. Intraoperative complications included visceral bleeding, pneumothorax, aortic bleeding, and phrenic artery laceration. These complications occurred at a rate of less than 4%. The authors documented immediate postoperative symptom relief in 85% of patients, with a recurrence rate of 6.8% in the open group and 5.7% in the laparoscopic group.²⁸

In 2013, El-Hayek et al.²⁹ reviewed their treatment of 15 patients from 2007 to 2012, including one procedure performed with robotic assistance. They reviewed postoperative celiac velocities in 12 of the 15 patients. Ten patients showed a statistically significant decrease in celiac artery velocity. Of note, two patients showed celiac occlusion, but all but one patient reported the resolution of preoperative pain.³⁰

Recently the two largest laparoscopic series to date have been published. Weber et al. reported on 39 patients, of whom 70% reported symptom relief following laparoscopic treatment of MALS despite persistent celiac artery stenosis on postoperative duplex ultrasound. In the same study, all patients who did not have postoperative symptom improvement had normal celiac artery velocities after surgery.⁶ Brody reported that 33/38 patients had complete resolution of preoperative pain at follow-up, ranging from 6 months to 3 years.¹³ In this study, a short form (SF) 36-question survey was used pre- and postoperatively in addition to pre- and postoperative dynamic Doppler ultrasound. The reported postoperative complications from this study included pancreatitis and dehydration.¹³ Based on this experience, Brody and his group recommend a predictive formula utilizing SF-36 questionnaire values and celiac artery ultrasound values to identify patients for operative success.¹³ Such a formula may enhance preoperative patient counseling regarding symptom improvement. This series also reported several patients that required supplemental nutrition through enteric tubes or total parenteral nutrition before surgery. Following the laparoscopic MAL release, oral nutrition was restored in all patients, and two patients on TPN were transitioned to intermittent fluids on a weekly basis.¹³ There appears to be a scale of improvement based on symptom resolution that does not directly correlate with ultrasound velocity or other imaging changes.



Figure 136.10 Robotic ligation of celiac nerve ganglion overlying the origin of the celiac artery.

With the adoption of the robotic platform, a few cases have been reported using a robotic-assisted laparoscopic MAL release. In 2013, Do et al. reviewed 16 patients, four of which were completed with robotic assistance. The only significant difference was a shorter operative time for laparoscopy (101.7 min vs. 148.8 min).²³ Thus far, no clear advantage for a robotic-assisted MAL release has been demonstrated (Fig. 136.10).

Van Peterson et al.³⁰ reported their experience using an endoscopic retroperitoneal approach to divide the MAL in 46 patients. Complications included a 2% conversion rate to a laparotomy and a pneumothorax in 4% of patients. Overall, 78% (36/46) of patients had postoperative angiography confirming normal vessel anatomy. Six of the remaining 10 patients underwent endovascular treatment; five patients had a successful dilation with resolution of the celiac artery stenosis. Symptoms were based on three responses: free of symptoms, improved, or persistent symptoms. In this group, 41/46 (89%) patients reported improvement of symptoms and 65% reported resolution of symptoms with surgical intervention. The authors did not mention whether persistent symptom complaints resulted in endovascular intervention. But no patient who reported persistent symptoms received endovascular intervention. This further supports the theory that MALS is a neurogenic disease, and the vascular abnormalities are only a physiologic marker for ligamentous compression on the artery and nerve plexus. Their median follow-up of 20 months suggests comparable results to open procedures available at that time.³¹

Based on a literature review and institutional experience, Kim et al. recently proposed an algorithm for diagnostic evaluation and intervention in patients with MAL syndrome.³² As previously mentioned, patients begin with a workup for abdominal pain, including right upper quadrant ultrasound, abdominal CT, upper endoscopy, and/or HIDA scan. Abnormal findings on these studies result in appropriate treatment for the diagnosed pathology. Normal findings in these studies lead to

a duplex ultrasound of the celiac artery. Findings suggestive of MALS or equivocal ultrasound findings may be supplemented with CTA or MRA of the abdomen, or angiography of the celiac artery with pressure gradient measurements for confirmation. Evidence of celiac artery compression is an indication for laparoscopic or robotic MAL release, including celiac ganglionectomy. Follow-up included postoperative celiac artery duplex ultrasound and assessment of symptom resolution. If symptoms persist, angiography of the celiac artery with pressure gradient measurement is used to diagnose residual stenosis. If stenosis remains, angioplasty or stenting of the celiac artery is recommended. If symptoms persist, vascular reconstruction should be considered if ischemia is felt to contribute to the patient's pain.³²

CLINICAL CHALLENGES: CASE STUDIES

Often the choice to operate is dependent on satisfying criteria as described above. As with most surgical pathology, the clinical picture may not match the radiographs. Some of the subsequent cases entail radiographic data that may have supported surgery but either surgery failed to improve the patient's symptoms, or surgery was not offered due to a lack of clinical evidence within the patient's history.

Case 1

A 35-year-old female, morbidly obese (BMI 56.8) with poorly controlled DM (A_{1c} 11) presented with multiple admissions for nausea and vomiting. She was poorly compliant with insulin use and she was noncompliant with insulin pump teaching. She had undergone an upper endoscopy on five separate admissions over 2 years due to recurrent hematemesis. Her surgical history was remarkable for a laparoscopic cholecystectomy and parathyroidectomy. She reported chronic nausea, vomiting, epigastric pain, and weight loss of 40 lbs over the preceding 8 months. A nuclear medicine gastric emptying study was normal on two separate occasions at two and four hours. She often presented with pancreatitis and blood glucose levels of 300–500 mg/dL with two admissions for ketoacidosis. Abdominal and pelvic CT with intravenous (IV) contrast (Fig. 136.11) showed findings concerning for MALS on her fourth CT in 2 years. General surgery was consulted and 3 days later she had a triphasic CTA (Fig. 136.12) with pancreatic protocol for chronic pancreatitis. No evidence of MALS was present on repeat imaging using the triphasic protocol. She was too large to obtain an MRI at the admitting facility. Dynamic ultrasound was not available at this institution. General surgical consultation determined that she was not a candidate for MAL release. A third gastric emptying study showed delayed emptying at 2 hours and she received a gastric electrical stimulator. Repeated CT evaluations for ongoing chronic abdominal pain have not documented MALS. She remains poorly compliant with her diabetes management and she has not improved following the gastric electrical stimulator.



Figure 136.11 Patient TB preoperative CT abd/pel illustrating initial reason for consult to evaluate for MALS due to findings of celiac artery compression.



Figure 136.13 Patient KS preoperative CT scan showing celiac compression, “J inflection,” supporting clinical picture of MALS.

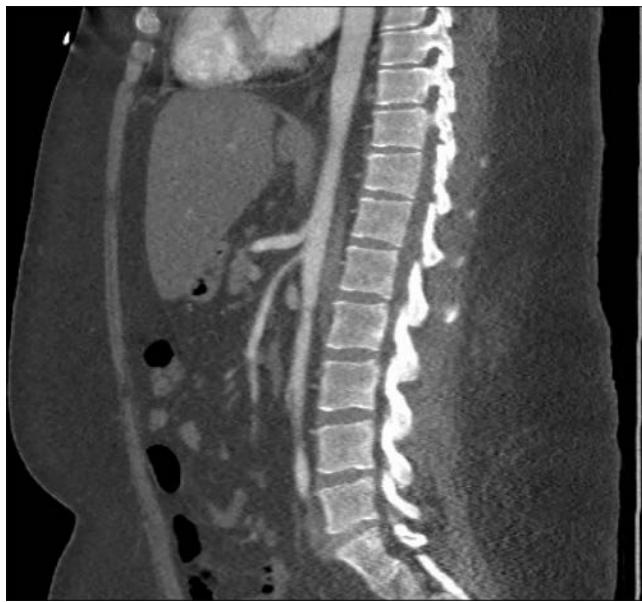


Figure 136.12 Patient TB follow-up 3 days after [Figure 136.11](#) CTA abd/pel illustrating lack of celiac artery compression and supporting lack of clinical evidence of MALS in this patient.

Case 2

KS is a 49-year-old male, BMI 41, with CKD with multiple ER visits for chest pain and abdominal pain. Surgical history includes laparoscopic cholecystectomy and nine upper endoscopies over four years. Multiple CT scans were obtained to assess an associated renal artery stenosis and he was diagnosed with concurrent MALS. Recurrent admissions for nausea, vomiting, weight loss and chest pain occurred over a 7-month period. Repeat imaging with IV contrast over a 2-year period

documented persistent findings of celiac artery compression and poststenotic bulbar dilation ([Fig. 136.13](#)). The patient could not tolerate an MRI due to claustrophobia and failed two separate attempts despite anxiolytics. General surgery was consulted for a minimally invasive MAL release. Ultimately, the patient underwent a MAL release and the patient was discharged on postoperative day one. Repeat imaging 2 months postoperatively ([Fig. 136.14](#)) for similar yet less frequent complaints showed resolution of celiac compression as well as decreased poststenotic dilation. His nausea had resolved with only mild improvement in chest pain. Recurrent admissions continued for chest pain, periodic nausea and vomiting. The patient stated that his abdominal complaints occurred less often and were less severe. He had gained 9 lbs in 3 months and felt like the pain in his chest was different than he experienced preoperatively. Subsequent upper endoscopies for epigastric pain did not show any associated pathology.

Case 3

TH is a 51-year-old female with a BMI of 25 with no other comorbidities. She presented with a 10-month history of epigastric and LUQ pain, exercise-induced pain, nausea and bloating. Her surgical history included laparoscopic appendectomy and cholecystectomy, an upper endoscopy, open left hemicolectomy for “knotted colon” and diverticulosis. A CT scan documented celiac artery compression and suspected MALS ([Fig. 136.15](#)). An MRA was not approved by her insurance. She underwent an uneventful laparoscopic MAL release and was discharged on postoperative day one. She had immediate improvement and resolution of bloating and pain. She was increasing her diet without nausea. At 6 weeks she was jogging but her symptoms abruptly returned with pain during exercise

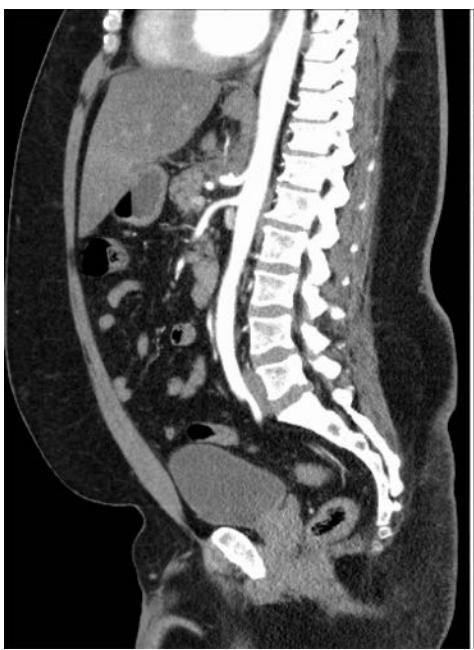


Figure 136.14 Patient KS postoperative CT abd/pel showing 3-month follow-up with resolution of celiac compression and consistent with mild clinical improvement.



Figure 136.15 Patient TH preoperative CT abd/pel with findings of celiac artery compression and support of clinical presentation of MALS.

in her chest but not in her abdomen. Three months later, she had persistent complaints that were decreased in severity and frequency. A follow-up CTA showed resolution of the celiac trunk compression (Fig. 136.16).

Case 4

GF is a 61-year-old male with a BMI of 48 and 4 years of epigastric pain. He had a history of chronic obstructive pulmonary disease and hyperlipidemia with mild claudication but



Figure 136.16 Patient TH postoperative CT abd/pel (2 months postop).

no significant aortic or iliofemoral calcifications. A CTA and follow-up MRA showed celiac compression, however he denied postprandial pain, nausea, vomiting, weight loss or exercise. He was referred to general surgery for a MAL release. He underwent a MAL release and developed acute kidney insufficiency on postoperative day one with pulmonary insufficiency and abdominal distention. He was transferred to the intensive care unit where he spent 2 weeks requiring dialysis. He developed delirium and respiratory insufficiency without ventilatory support. Doppler US of the renal arteries showed patent vessels and a subsequent CTA once his renal function permitted did not show evidence of thrombosis or embolic events. He recovered from his surgery and his epigastric pain had resolved but he had persistent bloating and nausea for nearly 2 years. These symptoms eventually resolved and his renal function improved but did not recover fully to baseline.

Lessons Learned

These cases serve to impress the importance of patient selection. Patients with imaging consistent with MALS without associated clinical symptoms will likely obtain poor outcomes. If there is significant deviation of symptoms to include obesity, lack of exercise-induced pain, refractory epigastric pain not related to food or exercise, and other associated peripheral vascular disease then the surgical outcome is likely to be of little to no benefit with significant risk for bleeding, thrombosis or embolism. These cases and the respective imaging further support that, without use of a predictive formula²³ regardless of the severity of stenosis on conventional imaging, there is no relation to impact on treatment efficacy, and vascular compromise and subsequent release may not be the primary basis of MALS pain. No specific imaging finding of stenosis is predictive of a favorable response.³³

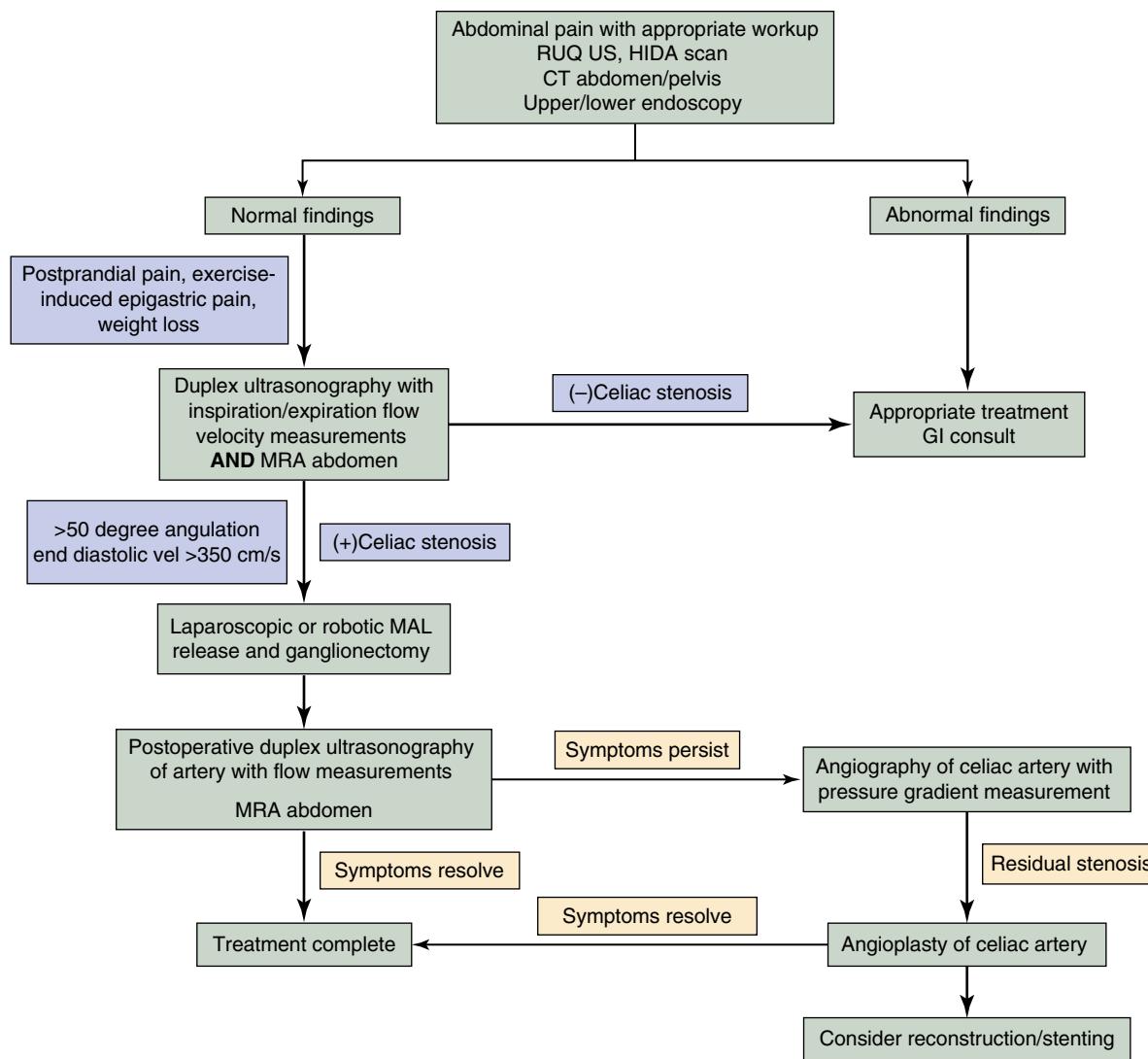
CONCLUSION

MALS can be a difficult disease to diagnose, but recent publications document an increasing incidence of surgical treatment for this apparently rare disease. Compression of the proximal celiac artery by the MAL results in image-apparent stenosis, with detectable changes in dynamic ultrasound velocities. However, celiac compression and change in arterial velocity are only markers for neural compression. The true pathophysiologic dysfunction lies within the neural network of the celiac ganglion, which is subjected to the same compression as the celiac artery by the MAL. The celiac plexus is composed of pain fibers and inhibitory motor fibers to the stomach. The rationale

for MAL release rests on the theory that MALS results from compression of the celiac plexus. The compression creates a variety of symptoms, including nausea, vomiting, and gastric dysmotility. Furthermore, the neural compression may contribute to other neurogenic diseases, such as POTS.¹²

As more patients are accurately diagnosed, treated, and followed, the true parameters that mark a successful treatment continue to evolve. To date, case series remain small, with both open and laparoscopic approaches, and follow-up remains limited to less than three years. The complex nature of the disease process requires subjective and objective data to create an algorithm to identify patients who may benefit from surgical intervention.

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

Brody F, Richards NG. Median arcuate ligament release. *J Am Coll Surg*. 2014;219:e45–e50.

A step-by-step laparoscopic median arcuate ligament release is detailed, with accompanying intraoperative pictures.

Harjola PT. A rare obstruction of the coeliac artery. *Ann Chir Gynaecol Fenn*. 1963;52:547–550.

Dr. Harjola describes the first division of the median arcuate ligament.

Lipshutz B. A composite study of the coeliac axis artery. *Ann Surg*. 1917;65: 159–169.

This classic manuscript provides the first detailed description of the celiac artery and some anomalous variations.

Mensink PB, van Petersen AS, Kolkman JJ, et al. Gastric excise tonometry: the key investigation in patients with suspected celiac artery compression syndrome. *J Vasc Surg*. 2006;44:277–281.

The authors provide a unique preoperative methodology to diagnose median arcuate ligament compression and then provide a relatively large cohort with significant follow-up.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Stanley JC, Fry WH. Median arcuate ligament syndrome. *Arch Surg.* 1971;103:252–258.
2. Lipshutz B. A composite study of the coeliac axis artery. *Ann Surg.* 1917;65:159–169.
3. Harjola PT. A rare obstruction of the coeliac artery. *Ann Chir Gynaecol Fenn.* 1963;52:547–550.
4. Dunbar JD, et al. Compression of the celiac trunk and abdominal angina. *Am J Roentgen Radium Ther Nucl Med.* 1965;95:731–744.
5. Horton KM, Talamini MA, Fishman EK. Median arcuate ligament syndrome: evaluation with CT angiography. *Radiographics.* 2005;25:1177–1182.
6. Weber JM, et al. Median arcuate ligament syndrome is not a vascular disease. *Ann Vasc Surg.* 2016;30:22–27.
7. Mensink PB, van Paterson AS, Kolkman JJ, et al. Gastric excise tonometry: the key investigation in patients with suspected celiac artery compression syndrome. *J Vasc Surg.* 2006;44:277–281.
8. Gloviczki P, Duncan AA. Treatment of celiac artery compression syndrome: Does it really exist? *Perspect Vasc Endovasc Ther.* 2007;19:259–263.
9. Duffy AJ, et al. Management of median arcuate ligament syndrome: a new paradigm. *Ann Vasc Surg.* 2009;23:778–784.
10. Balaban DH, Chen J, Lin Z, et al. Median arcuate ligament syndrome: a possible cause of idiopathic gastroparesis. *J Gastroenterol.* 1997;92:519–523.
11. Linder HH, Kemprud E. A clinicoanatomical study of the arcuate ligament of the diaphragm. *Arch Surg.* 1971;103:600–605.
12. Ashangari C, Suleiman A, Le TH. Median arcuate ligament syndrome in postural orthostatic tachycardia syndrome (POTS). *Auton Neurosci.* 2015;192:124–125.
13. Brody F, Richards NG. Median arcuate ligament release. *J Am Coll Surg.* 2014;219:e45–e50.
14. Duncan AA. Median arcuate ligament syndrome. *Current Treat Options Cardiovasc Med.* 2008;10:112–116.
15. Reuter SR, Bernstein EF. The anatomic basis for respiratory variation in the median arcuate ligament compression of the celiac artery. *Surgery.* 1973;73:381–385.
16. Moneta GL, Lee RW, Yeager RA, et al. Mesenteric duplex scanning: a blinded prospective study. *J Vasc Surg.* 1993;17:79–84.
17. Bech FR. Celiac artery compression syndromes. *Surg Clin North Am.* 1997;77:409–424.
18. Gruber H, Loizides A, Peer S, Gruber I. Ultrasound of the median arcuate ligament syndrome: a new approach to diagnosis. *Med Ultrason.* 2012;14:5–9.
19. Brody, et al. A predictive model for patients with median arcuate ligament syndrome. *Surg Endosc.* 2018;32:4860–4966.
20. Trinidad-Hernandez M, Keith P, Habib I, White JV. Reversible gastroparesis: functional documentation of celiac axis compression syndrome and postoperative improvement. *Am Surg.* 2006;72:339–344.
21. Matsumoto AH, Tegtmeyer CJ, Fitzcharles EK, et al. Percutaneous transluminal angioplasty of visceral arterial stenosis: results and long-term clinical follow-up. *J Vasc Interv Radiol.* 1995;6:165–174.
22. Matsumoto AH, Angle JF, Spinosa DJ, et al. Percutaneous transluminal angioplasty and stenting in the treatment of chronic mesenteric ischemia: results and longterm followup. *J Am Coll Surg.* 2002;194:S22–S31.
23. Do MV, Smith TA, Bazan HA, et al. Laparoscopic versus robot-assisted surgery for median arcuate ligament syndrome. *Surg Endosc.* 2013;27:4060–4066.
24. Cammillieri M. Disorders of gastrointestinal motility in neurologic diseases. *Mayo Clin Proc.* 1990;65:825–846.
25. Reilly LM, et al. Late results following operative repair for celiac artery compression syndrome. *J Vasc Surg.* 1985;2:79–91.
26. Grotemeyer D, Duran M, Iskander F, et al. Median arcuate ligament syndrome: vascular surgical therapy and follow-up of 18 patients. *Langenbecks Arch Surg.* 2009;394:1085–1092.
27. Jimenez JC, Harlander-Locke M, Dutson EP. Open and laparoscopic treatment of median arcuate ligament syndrome. *J Vasc Surg.* 2012;56:869–873.
28. Tulloch AW, Jimenez JC, Lawrence PF, et al. Laparoscopic versus open celiac ganglionectomy in patients with median arcuate ligament syndrome. *J Vasc Surg.* 2010;52:1283–1289.
29. El-Hayek KM, Titus J, Bui A, et al. Laparoscopic median arcuate ligament release: Are we improving symptoms? *J Am Coll Surg.* 2013;216:272–279.
30. Van Peterson JM, et al. Retroperitoneal endoscopic release in the management of celiac artery compression syndrome. *J Vasc Surg.* 2009;50:140–147.
31. Brandt LJ, Boley SJ. Celiac axis compression syndrome: a critical review. *Am J Dig Dis.* 1978;23(7):633–640.
32. Kim EN, et al. Median arcuate ligament syndrome- a review of this rare disease. *JAMA Surg.* 2016;151:e1–e7.
33. Patel, et al. Inability of conventional imaging findings to predict response to laparoscopic release of the median arcuate ligament in patients with celiac artery compression. *J Vasc Surg.* 2019;69:462–469.

Mesenteric Venous Thrombosis

STEFAN ACOSTA and MARTIN BJÖRCK

EPIDEMIOLOGY 1799

PATHOGENESIS 1799

Etiology 1799

Risk Factors 1799

NATURAL HISTORY 1801

PATHOLOGY AND MANIFESTATIONS 1801

DIAGNOSIS 1801

History and Physical Examination 1801

Laboratory Testing 1801

Computed Tomography 1802

TREATMENT AND RESULTS 1803

Medical Treatment 1803

Endovascular and Hybrid Therapy 1804

Surgical Treatment 1806

Prognosis 1807

CHAPTER ALGORITHM 1807

The common definition of mesenteric venous thrombosis (MVT) refers to a single entity involving thrombosis within the superior mesenteric vein with or without extension to the portal or splenic veins. Recovery following resection of infarcted intestine secondary to mesenteric vessel occlusion was first reported by Elliot in 1895.¹ MVT was recognized as an entity distinct from mesenteric arterial occlusion by Warren and Ebhard in 1935.²

EPIDEMIOLOGY

MVT is most commonly encountered in middle-aged and older adult patients.^{3,4} In a population-based study with an average autopsy rate of 87%, MVT was found to be present in 63 of 402 patients (16%) with acute mesenteric ischemia (Fig. 137.1).⁶ Additionally, the overall incidence of MVT with transmural intestinal infarction was estimated to be 1.8 per 100,000 person-years in Malmö, Sweden, between 1970 and 1982, and the cause-specific mortality ratio was 0.9 per 1000 autopsies.⁵ The overall incidence of MVT increased to 2.7 per 100,000 person-years in the same city between 2000 and 2006.⁴ An important factor contributing to an underestimation of the latter incidence estimate was the declining autopsy rate, from 87% to 10%, between the two periods. In contrast, factors increasing the incidence estimate over time were the growing proportion of older adults in the population and the

greater amount of diagnostic activity with higher quality images. Patients with MVT were diagnosed at autopsy, at operation, or with computed tomography (CT) in 12% (6 of 51), 19% (10 of 51), and 69% (35 of 51) of cases, respectively,⁴ during the latter period.

In a recent review including 11 contemporary studies, the pooled estimate of proportion of female gender was 34.5% (95% CI 30.5–38.5), suggesting that MVT is slightly more common in males.⁷

PATHOGENESIS

Etiology

Primary MVT is defined as spontaneous, idiopathic thrombosis of the mesenteric veins not associated with any other disease or etiologic factor. Patients with any condition known to predispose to MVT (Box 137.1) are considered to have secondary MVT.⁸ Approximately 90% of MVTs are secondary.⁹

Risk Factors

Several conditions are associated with MVT (see Box 137.1); these can be divided into three main categories: direct injury, local venous congestion or stasis, and thrombophilia. Splenectomy is a risk factor for the development of thrombus

propagation from the ligated splenic vein to the portomesenteric venous system.¹⁰ In retrospect, after scrutinizing the multidetector computed tomography (CT) images, the prevalence of incidental, probably asymptomatic, nonanticoagulated MVT in patients with inflammatory bowel disease was reported to be as high as 27%¹¹ and was located at the periphery, limited to the adjacent mesentery of inflammatory bowel disease. The detection of MVT was associated with disease severity and factors such as bowel wall thickening, ascites, bowel stenosis, and intestinal surgery.¹¹ Severe acute pancreatitis may lead to MVT but more frequently to splenic vein thrombosis

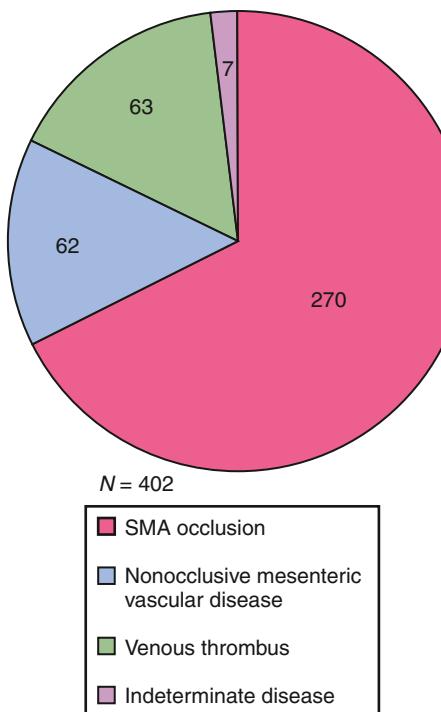


Figure 137.1 Acute mesenteric ischemia: distribution of etiologies in 402 patients in Malmö, Sweden, between 1970 and 1982.^{4,5} Mesenteric venous thrombosis, acute SMA occlusion (embolus/thrombus ratio = 1.4), and nonocclusive mesenteric ischemia were found in 16%, 68%, and 16%, respectively. SMA, superior mesenteric artery.

due to its very close proximity to the inflamed pancreas.^{12,13} In a case-control study, obesity was found to be a risk factor.⁵ Inherited thrombophilia¹⁴ was reported in 42%³ to 55%⁴ of patients with MVT (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).

Factor V Leiden mutation (activated protein C resistance) was present in 45% of the patients with MVT in Malmö, Sweden⁴; considerably higher than the prevalence rate of 7% in the background population.¹⁵ Although factor V Leiden mutation is a genetic defect, peripheral venous thrombotic manifestations are frequently delayed until adulthood, even in homozygotes.^{15,16} Case-control studies suggest that factor V Leiden¹⁷ and prothrombin G20210A gene mutations^{17,18} are overrepresented in patients with MVT. There is a wide range of frequency of inherited thrombophilic factors in different populations.¹⁹ Thus, it is necessary to relate them to background population-based data, in order to estimate their overrepresentation in MVT.

MVT has been reported to be a common first clinical manifestation of patients with newly diagnosed myeloproliferative disorders such as polycythemia vera or essential thrombocytosis and often occurs before a rise in peripheral blood counts. The JAK2 V617F (Janus-activated kinase gain-of-function substitute of valine to phenylalanine at position 617) mutation is diagnostic of myeloproliferative disorders.²⁰ In contrast to patients with other venous thromboembolisms, in a meta-analysis of four case-control studies JAK2 V617F was found to be strongly associated with thrombosis within the mesenteric, portal, and hepatic veins (splanchnic venous thrombosis).²¹

Primary cytomegalovirus infection has also been associated with MVT.²² Synchronous venous thromboembolism in the systemic circulation frequently occurs in patients with MVT, especially pulmonary embolism.⁵ There may be an increased risk of MVT following laparoscopic surgery because of venous stasis from increased intraabdominal pressure, especially in obese patients undergoing Roux-en-Y bypasses, or when there is a more extensive intraoperative mobilization of the mesenteric, portal, or splenic vein. Together with the presence of any

BOX 137.1

Conditions Associated with Mesenteric Venous Thrombosis

Direct Injury

- Abdominal trauma (blunt and penetrating)
- Postsurgical (particularly postsplenectomy)
- Intraabdominal inflammatory states (pancreatitis, inflammatory bowel disease)
- Peritonitis and abdominal abscess

Local Venous Congestion or Stasis

- Portal hypertension; cirrhosis of the liver
- Congestive heart failure
- Hypersplenism
- Obesity
- Increased abdominal pressure; abdominal compartment syndrome

Thrombophilia

- Protein C and protein S deficiency
- Antithrombin III deficiency
- Activated protein C resistance (factor V Leiden gene mutation)
- Presence of 20210 A allele of prothrombin gene
- Methylenetetrahydrofolate reductase mutations
- JAK2 V617F gene mutation
- Neoplasms (particularly pancreatic and colonic)
- Oral contraceptive use
- Polycythemia vera
- Essential thrombocythemia
- Heparin-induced thrombocytopenia
- Lupus anticoagulant–antiphospholipid syndrome
- Cytomegalovirus infection
- Extramesenteric venous thromboembolism

systemic thrombophilic state, development of MVT seems to be more likely.^{23,24}

NATURAL HISTORY

It is difficult to pinpoint the natural history of MVT. Since MVT is uncommon, patients often have diffuse symptoms, and the condition is not always detected, even with contemporary diagnostic modalities. Therefore, we have no absolute knowledge of the total number of patients with symptomatic and asymptomatic disease. However, in a population-based study with a high autopsy rate (87%), it was found that 35 of 31,015 patients (0.1%) examined postmortem had MVT.⁵ The majority of patients with MVT at autopsy (27 of 35, or 77%) had a transmural intestinal infarction, judged to be the cause of death. The patients diagnosed at exploratory laparotomy all had transmural intestinal infarction and required bowel resection for survival. The mortality rate among those undergoing exploratory laparotomy was 30% (12 of 40). Portal venous thrombosis (PVT) was studied in the same cohort, and there were some interesting differences: PVT was 10 times more common than MVT at autopsy, patients with PVT more often had asymptomatic disease, and PVT was seldom considered the cause of death.²⁵ Two studies^{26,27} suggest that superior MVT, in contrast to isolated PVT, is associated with symptoms in the overwhelming majority (92%²⁶) of cases and also often results in bowel gangrene (33%²⁷–45%²⁶), depending on diagnostic and therapeutic management.

PATHOLOGY AND MANIFESTATIONS

The degree of intestinal ischemia that develops depends on the extent of venous thrombosis within the splanchnic venous circulation and whether there is occlusion or adequate collateral flow. Patients with isolated PVT without peripheral propagation to the superior mesenteric vein are asymptomatic in the majority of cases (61%²⁶) and almost never experience intestinal infarction (0%²⁶–10%²⁷). In 270 patients with PVT and MVT found at autopsy, 29 of 31 (94%) patients with MVT had intestinal infarction and 0 of 239 (0%) with isolated PVT had intestinal infarction.²⁷

At operation, MVT is characterized by a limited segment of intestinal ischemia, with edema, swelling, and reddish discoloration of the affected small bowel and its adjacent mesentery and a palpable pulse in the superior mesenteric artery (SMA) and its branches.²⁸ In contrast, intestinal ischemia due to arterial occlusive or nonocclusive disease is often characterized by extensive ischemia that includes the jejunum, ileum, and colon,²⁹ with patchy cyanosis, reddish black discoloration, and no palpable pulsations. MVT can be confirmed during surgery if an infarcted bowel segment is removed. Division of a small part of the adjacent mesentery, without previous vessel ligation, reveals thrombosis within the veins, whereas a pulsatile hemorrhage arises from the arteries. The extent of intestinal infarction is often limited to the jejunum or the ileum (Fig. 137.2).⁵

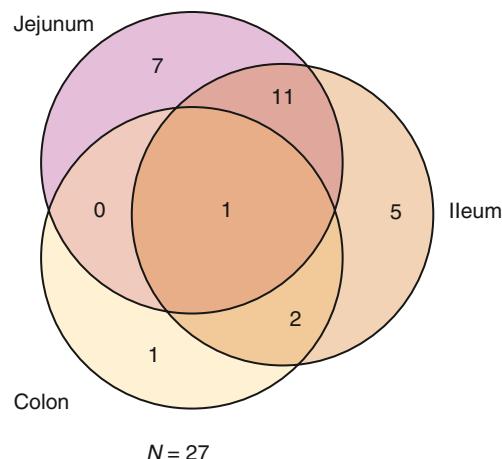


Figure 137.2 Venn diagram showing the extent of intestinal infarction in 27 patients with mesenteric venous thrombosis and transmural intestinal infarction.

DIAGNOSIS

Patients with symptoms of less than 4 weeks' duration are classified as having acute MVT. Those with symptoms lasting longer than 4 weeks but without bowel infarction or those with clinically insignificant MVT diagnosed incidentally on abdominal imaging are classified as having chronic MVT. The majority of patients (71% and 74%) in two large clinical series have acute MVT.^{4,8}

History and Physical Examination

Awareness of the disease, a careful risk factor evaluation, and positive findings at physical examination may lead the clinician to suspect the diagnosis. The onset of acute MVT is often insidious, and diffuse abdominal pain may be present for days or weeks. Abdominal pain is often^{8,9} but not always present at admission. The second most common symptom is nausea/vomiting, whereas diarrhea and lower gastrointestinal bleeding are present in less than 20% of cases.^{30,31} Typically, a middle-aged patient with a personal or a family history of deep venous thrombosis presents with abdominal pain of a few days' duration, vomiting, and abdominal distention as well as an elevated C-reactive protein (CRP) level. The patient may develop localized peritonitis. With progression to transmural intestinal infarction, peristalsis ceases and signs of generalized peritonitis appear. Physicians do, however, find it very difficult to recognize MVT on clinical grounds, since none of the 102 referral letters for initial radiological examination stated a suspicion of MVT, and only three (3%) suspected intestinal ischemia.³²

Laboratory Testing

There are no accurate plasma biomarkers for diagnosing intestinal ischemia. D-dimer has been reported to be a sensitive but not specific marker of acute thromboembolic occlusion of the SMA.³³ From a theoretical point of view, we have reason to believe that a normal D-dimer level may be useful to exclude

MVT as well. This view is supported by experience from a small series of patients.⁴

When MVT is diagnosed, thrombophilia screening is indicated, unless a strong provocative factor such as intraabdominal cancer is present.³⁴ Testing for the inherited disorders factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency is performed. Simultaneously, the patient should be checked for acquired disorders such as *JAK2* V617F mutation,^{20,21} lupus anticoagulant, and cardiolipin antibodies. Whether the presence of these thrombophilic factors influences recurrence rates is not clear.

Since MVT may be diagnosed before a rise in peripheral blood counts in myeloproliferative disorders,²⁰ it may be wise to obtain a full blood count with white blood cell differentiation at follow-up.

Computed Tomography

CT of the abdomen, with intravenous contrast injection and imaging in the portal venous phase, is the most important, available, and accurate diagnostic tool.^{35–37} The protocol for acute CT of the abdomen varies with the clinical history provided by the referring physician who requests the examination. Optimally, the CT protocol would include intravenous contrast and imaging in the arterial and portal phases with 1-mm thin slices and reconstructions in the coronal and sagittal planes.

The vascular and intestinal findings of MVT on CT (Figs. 137.3–137.5) are summarized in Table 137.1.³² CT often demonstrates extensive thrombosis of the portomesenteric system, with extension of thrombosis to at least the extrahepatic portal and splenic veins. Intestinal findings are less common and more subtle. Hence the radiologist should always examine the mesenteric vessels in cases of an acute or unclear abdomen. In a retrospective study³⁸ of 97 events in patients with all four etiologies of acute mesenteric

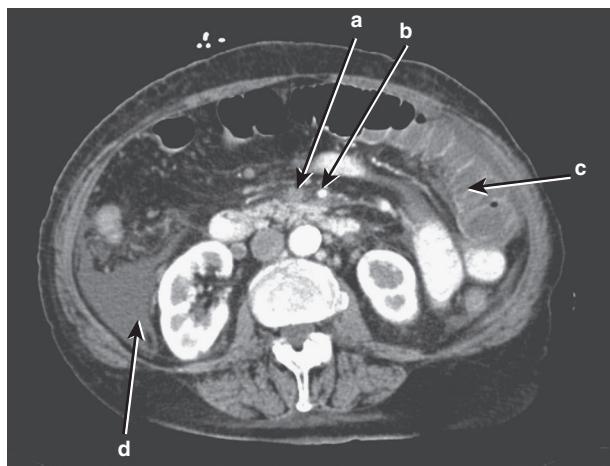


Figure 137.3 Multidetector computed tomography of the abdomen in the portal venous phase, in the axial projection, shows thrombosis of the superior mesenteric vein (*a*), an open superior mesenteric artery (*b*), dilated and edematous small bowel loops (*c*), and ascites (*d*).

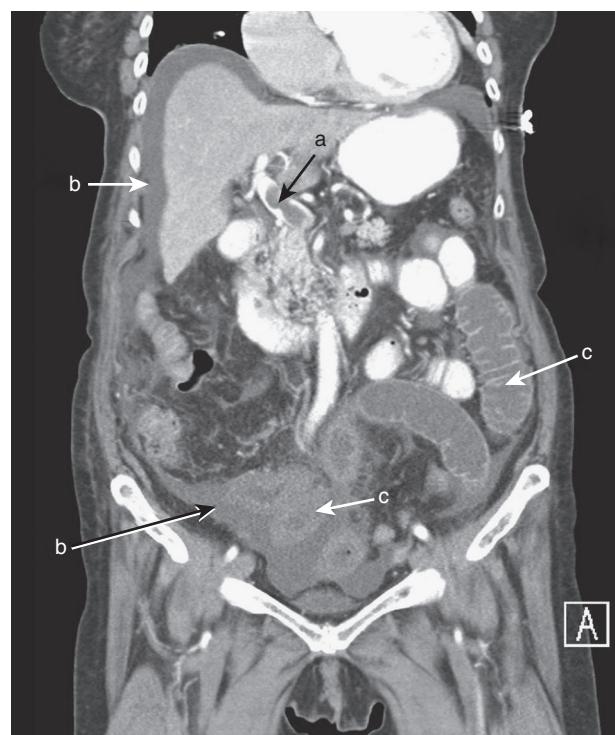


Figure 137.4 Multidetector computed tomography with multiplanar reconstruction in the coronal view shows thrombosis in the extrahepatic portion of the portal vein (*a*), ascites (*b*), and dilated and edematous small bowel loops (*c*).

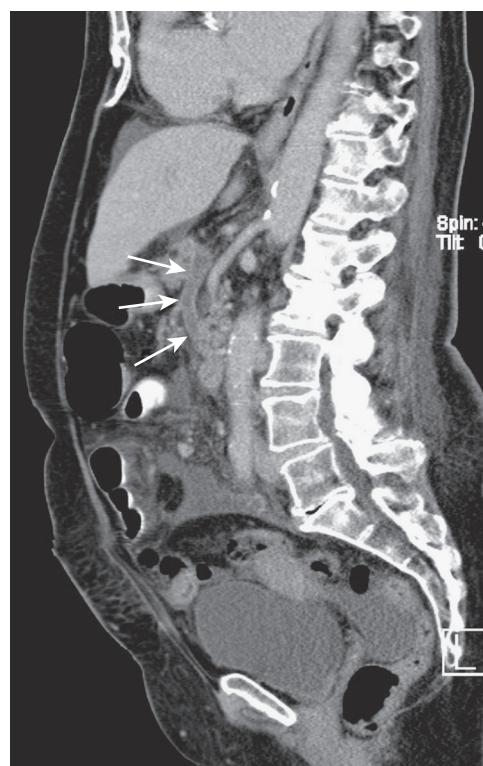


Figure 137.5 Multidetector computed tomography with multiplanar reconstruction in the sagittal view shows thrombosis in the superior mesenteric vein (arrows).

TABLE 137.1

Findings on Computed Tomography of the Abdomen in 102 Patients with Mesenteric Venous Thrombosis³²

Finding	Frequency (%)
Vascular	
Central ^a mesenteric venous thrombosis	98 (96.1)
Peripheral mesenteric venous thrombosis	73 (71.6)
Isolated mesenteric venous thrombosis	14 (13.7)
Portal venous thrombosis	85 (83.3)
Extrahepatic portal venous thrombosis	80 (78.4)
Intrahepatic portal venous thrombosis	60 (58.8)
Splenic venous thrombosis	61 (59.8)
Venous collaterals	52 (51)
Extensive thrombosis ^b	43 (42.2)
Intestinal	
Mesenteric edema	63 (61.8)
Small bowel wall edema	40 (39.2)
Local small bowel dilatation ^c	10 (9.8)
Extensive small bowel dilatation	2 (2.0)
Gas in portomesenteric venous system	0 (0)
Ascites	52 (51.0)

^aThe first 5 cm of the proximal superior mesenteric vein is defined as central.

^bMesenteric central and peripheral, portal, and splenic vein thrombosis.

^cGreater than 4 cm in diameter.

ischemia, sensitivity for the diagnosis of MVT by the first reader was reported to be the highest, 100% (9/9). In another retrospective study based on 109 patients with diagnosis of acute mesenteric ischemia between 2006 and 2014, the inter-reader agreement for 30 patients with MVT and various secondary intestinal abnormalities on CT were 94% and 70%–100%, respectively.³⁹

When the diagnosis of MVT has been established, it is very important that the responsible physicians taking care of the patient scrutinize the CT images, together with the radiologist who has assessed the images. Secondary intestinal abnormalities to MVT such as small bowel wall oedema, small bowel dilatation, mesenteric edema, and ascites, have been found to be prognostic indicators for increased need of bowel resection in a univariable analysis, and small bowel wall edema was found to be associated with bowel resection after multivariable adjustment.³²

TREATMENT AND RESULTS

The first-line treatment option is conservative with anticoagulation,⁴⁰ fasting, nasogastric tube, fluid and electrolyte replacement, analgesics, and administration of total parenteral nutrition. The use of antibiotics directed toward intestinal flora is logical in cases of advanced MVT with risk of sepsis secondary to bacterial translocation or bowel perforation.⁴¹ Patients will undergo laparotomy and bowel resection at three different time points: at admission due to late presentation or diagnosis,

after some weeks due to failure of anticoagulation therapy to reverse the condition, and after some months due to late bowel stricture. Endovascular treatment with mechanical thrombectomy or thrombolysis in combination with heparin infusion, with or without bowel resection, is an additional treatment tool at expert centers in those few patients who do not respond satisfactorily to heparin infusion alone. A multidisciplinary management strategy involves modern surgical and endovascular treatments that focus on early mesenteric venous recanalization and bowel salvage. This is best done in an integrated intestinal stroke center composed primarily of gastroenterologist and gastrointestinal and vascular surgeons.⁴²

Medical Treatment

Immediate full anticoagulation with a continuous infusion of unfractionated heparin is used in surgical as well as nonsurgical cases to obtain an activated partial thromboplastin time of 50 to 70 seconds monitored at 4-hour intervals. In the early phase, unfractionated heparin offers two advantages over LMWH: the anti-inflammatory effect is greater and it can be reversed with protamine if laparotomy becomes necessary. Every patient should initially be closely observed, with repeated abdominal evaluations and body temperature readings as well as daily CRP and leukocyte measurements. In the absence of recovery, with rising CRP values, or in the case of any clinical deterioration, repeat CT examinations with intravenous contrast can show changes such as extension of venous thrombosis and can evaluate the severity of ischemic bowel lesions, providing help in the often difficult decision-making process of when to proceed to laparotomy.⁴³

When gastrointestinal function has normalized, LMWH or oral vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs) are advocated. DOACs have been found to be equally effective and with the same bleeding complications as VKA in a retrospective comparative study⁴⁴ (see Ch. 41, Anticoagulant Therapy), which supports the replacement of VKA in most patients with MVT. The thrombotic status within the mesenteric venous system after anticoagulation therapy, DOACs or VKA, showed a 70% partial or complete recanalization rate after six months of therapy.⁴⁴ Long-term treatment with LMWH is reserved for patients with liver dysfunction, cancer or other conditions in which oral DOACs or VKA treatment is contraindicated, inappropriate, or a less reliable treatment option. Most patients can be treated conservatively if they are diagnosed in a timely manner.⁹ The duration of anticoagulation therapy must be carefully balanced against risk factors for bleeding, such as the presence of varices, low platelet count and previous bleeding, risk for recurrence due to persisting risk factors, previous venous thromboembolism, and consequences of recurrence⁴⁵ or progression due to extensive bowel involvement.⁴⁶ According to the European Society for Vascular Surgery (ESVS) guidelines,⁴⁷ anticoagulation is recommended for 6 months in the presence of an identifiable transient risk factor, and lifelong in patients with underlying thrombophilia or idiopathic MVT, since recurrence of MVT is highly fatal.⁸

Endovascular and Hybrid Therapy

A number of endovascular procedures for the treatment of MVT have been developed in recent years, including percutaneous transjugular intrahepatic portosystemic shunting (TIPS) with mechanical aspiration thrombectomy⁴⁸ and direct thrombolysis (Fig. 137.6A),^{49,50} percutaneous transhepatic mechanical thrombectomy,⁵¹ percutaneous transhepatic thrombolysis (Fig. 137.6B),^{52,53} thrombolysis via the SMA (Fig. 137.6C),⁵⁴ and thrombolysis via an operatively placed mesenteric vein catheter (Fig. 137.6D).⁵⁵ Enhanced thrombus removal or dissolution can be achieved through these techniques, especially after TIPS and stent placement to create a low-pressure runoff.⁵⁶ Mechanical thrombectomy is performed using a variety of thrombectomy devices and is most effective in cases of acute (<1 week) rather than chronic thrombus. Before considering thrombolysis, assessment of relative and absolute contraindications should be performed (see Ch. 43, Thrombolytic Agents). Local direct thrombolysis into the portomesenteric circulation through the transjugular or transhepatic route is useful for clearing residual clots and restoring venous flow. Indirect

thrombolytic therapy via the SMA is less effective and more time-consuming, may require longer infusion times and higher doses of thrombolytic agent, and is thus associated with an increased bleeding risk.⁵⁴

There are no comparative studies between anticoagulation alone and endovascular treatment to help establish the indication for endovascular treatment. Most patients are treated successfully with medical treatment only, but a small proportion (5%) of patients deteriorate during medical treatment.⁴ In those situations, clinical practice in some centers during the last decade has been to initiate endovascular treatment.

In a recent series of nine patients, bowel resection was followed by fluoroscopic-guided balloon thrombectomy followed by completion control venography.⁵⁷ When the balloon catheter could not pass from the superior mesenteric vein into the portal vein, a guide wire was used to gain access for proper thrombectomy of the portomesenteric system. Postoperative systemic anticoagulation was administered, followed by long-term peroral anticoagulation treatment. Albeit a small series, this study presents a feasible option for difficult to manage ongoing thrombosis associated with bowel infarction.

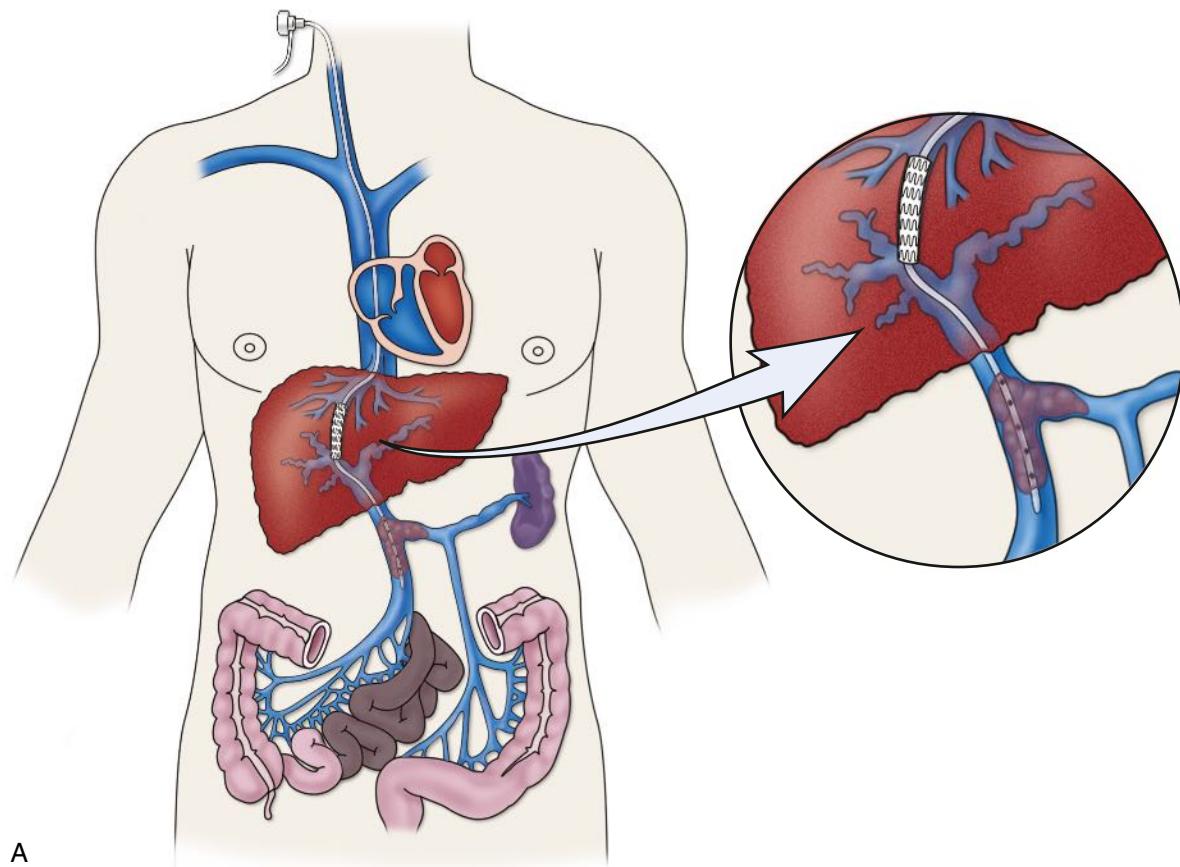
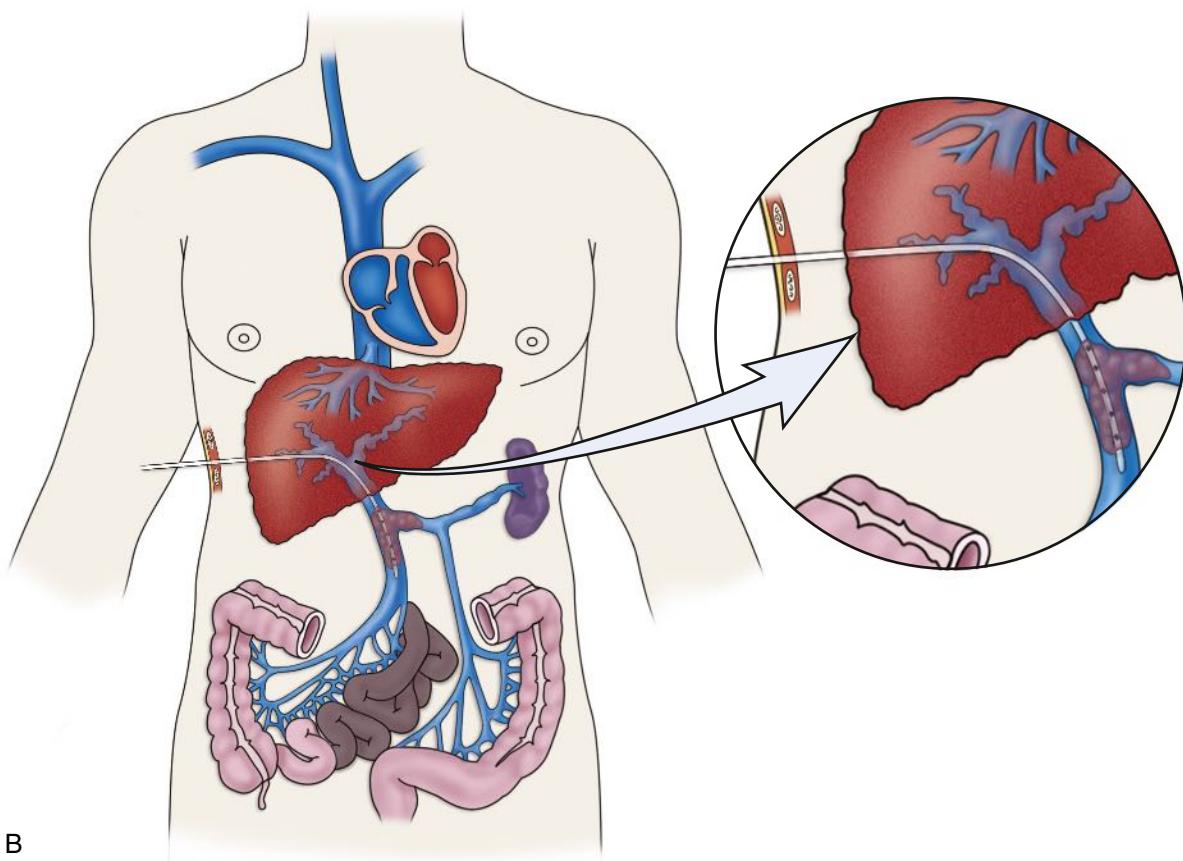
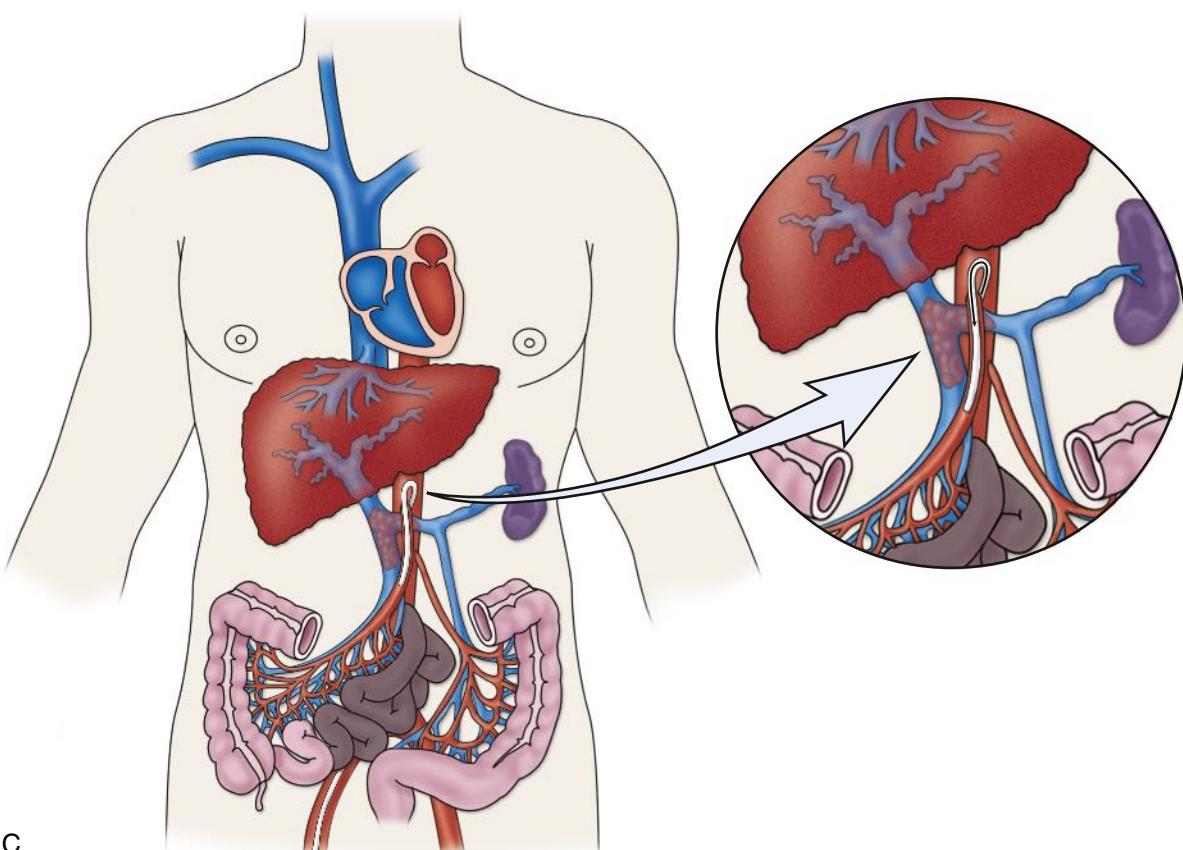


Figure 137.6 Schematic drawings of various ways of local delivery of thrombolysis for MVT. Usually a catheter with multiple side holes will be placed directly in the thrombus (A,B,D). An occluding ball wire at the catheter tip end hole (*not shown*) will allow for even pressure distribution of lytic agent at the side holes. Typically, an intestinal segment of the jejunum and/or ileum will be swollen and ischemic. (A) Percutaneous transjugular intrahepatic portosystemic shunt including stent-graft placement in the shunt.



B



C

Figure 137.6 cont'd (B) Percutaneous transhepatic access. (C) Percutaneous transfemoral access and indirect thrombolysis by an end hole catheter placed in the superior mesenteric artery.

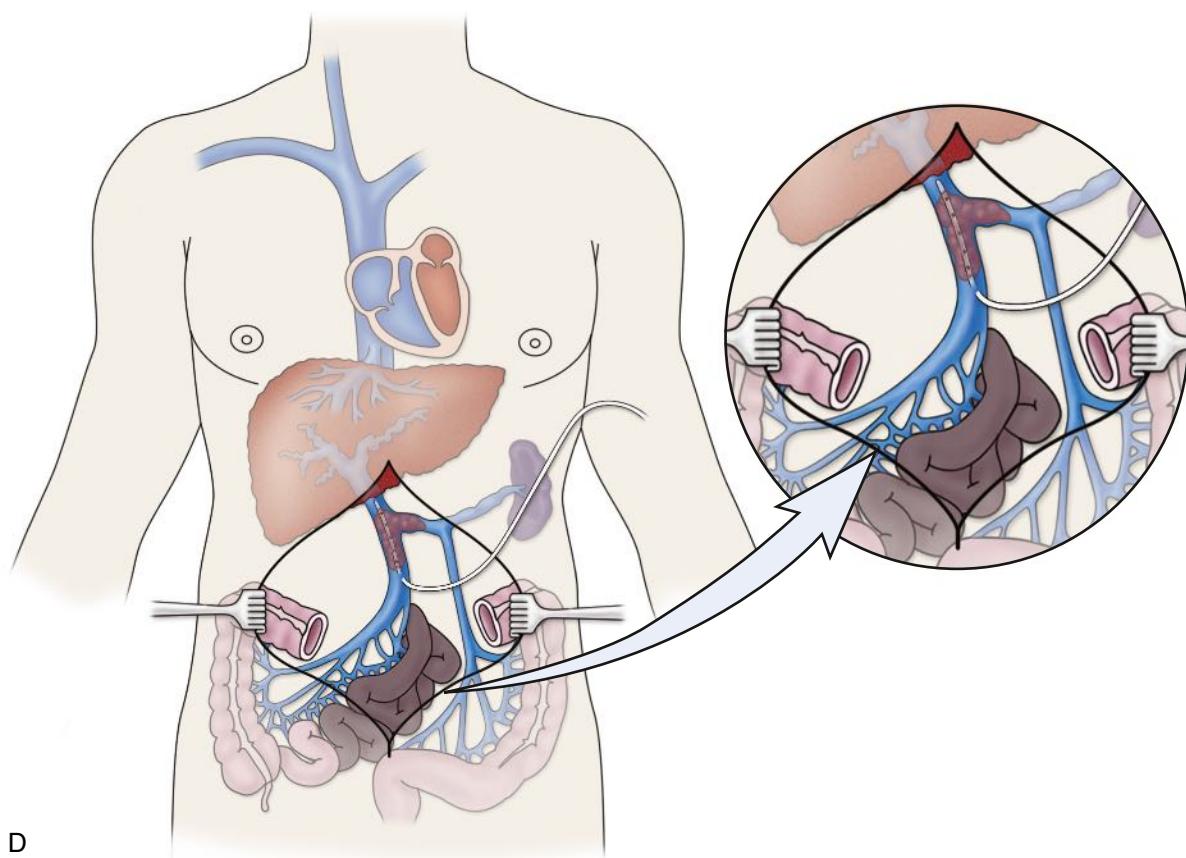


Figure 137.6 cont'd (D) Intraoperatively placed catheter in the superior mesenteric vein at laparotomy. (From Salim S. *On Acute Mesenteric Venous Thrombosis*. Lund: Lund University; 2020. Figures reused by permission from Robin Tran.)

Surgical Treatment

The indications for surgery are peritonitis, severe gastrointestinal bleeding, small bowel perforation, and intestinal stricture (associated with chronic diarrhea). When a clinical deterioration or peritonitis develops in a patient with MVT, laparotomy is indicated. In experienced hands, laparoscopy can be the preferred method to assess intestinal viability.^{58,59} Major obstacles for full visualization and macroscopic evaluation of the small intestines are extensive paralysis with bowel dilatation and prior adhesions. The pooled bowel resection rate in a review of 11 contemporary studies originating from three continents was 43.9%,⁷ indicating that surgery and bowel resection has a central role in the management of this disease. In very select cases, open surgical thrombectomy may be beneficial.⁶⁰ If there are signs of extensive intestinal ischemia, which is rare, surgical thrombectomy combined with bowel resection of the gangrenous bowel, heparinization, and second-look laparotomy may be considered. Bowel resection should be performed in cases of frank transmural intestinal necrosis, uncertain bowel viability, or severe ischemic bowel lesions (Fig. 137.7). However, signs of peritonitis may not

always be associated with transmural intestinal infarction, and rarely patients with rebound tenderness can still be treated conservatively.⁹ Primary bowel anastomosis after resection is recommended. This is a straightforward treatment in the typical patient in whom a short segment of the small bowel is affected. In the less common situation, in which a longer segment of the intestines is threatened, an alternative is to staple off the infarcted intestine, perform skin-only closure rather than fascial closure, and delay reconstruction until a second-look laparotomy, when the viability of the remaining small intestine can be evaluated. At the second look 24–36 hours later, areas of intestinal ischemia with doubtful viability may have recovered, and there is usually a clearer demarcation of the infarcted segments. The purpose of the second-look laparotomy is to reduce unnecessary bowel resections at the primary exploration, thus permitting salvage of segments of bowel with doubtful viability. Intraabdominal pressure may be a helpful adjunct to optimize the care of critically ill patients.⁶¹

Immediately after surgery, a heparin infusion is administered. The patient should be on bowel rest, receive total parenteral nutrition and broad-spectrum antibiotics for a few days



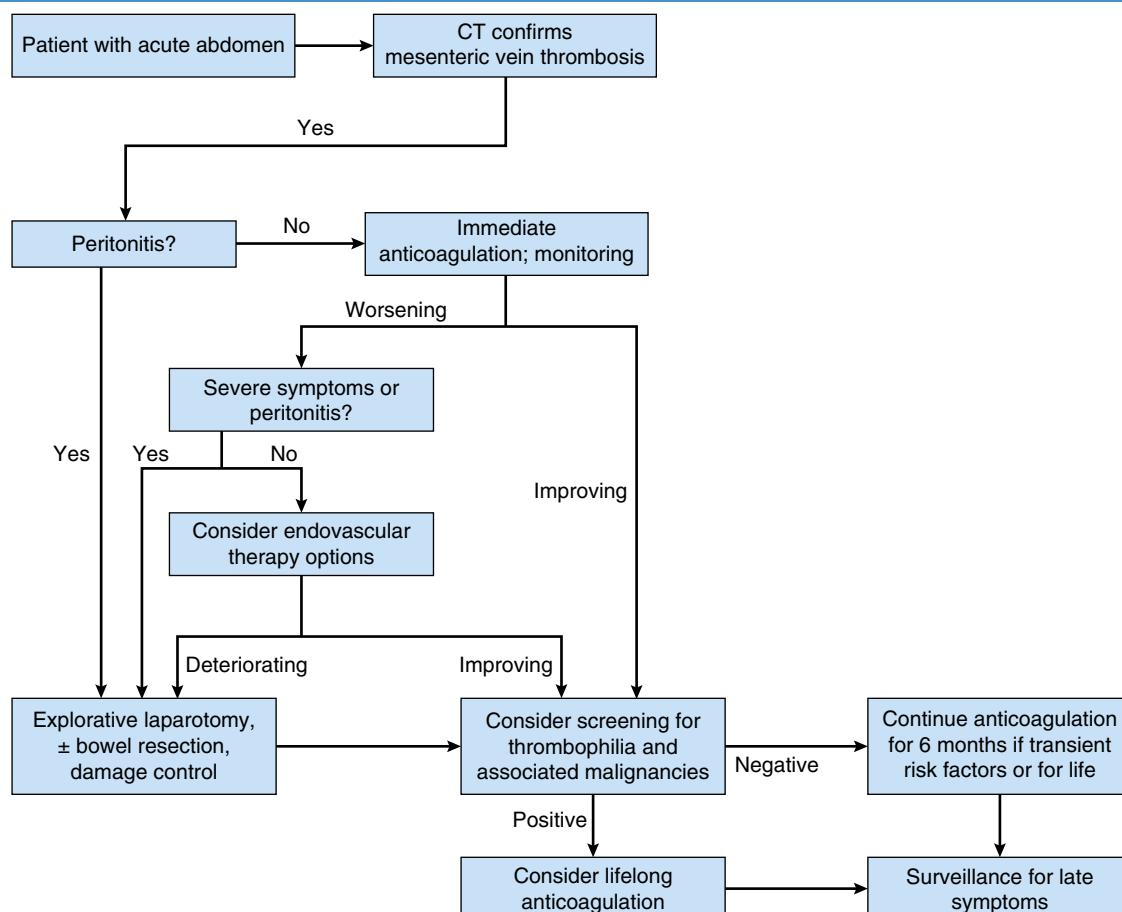
Figure 137.7 Ischemic bowel due to mesenteric venous thrombosis. A 47-year-old man with a history of deep venous thrombosis and pulmonary embolism presented with a 3-day history of lower abdominal pain and obstipation. He had discontinued VKA treatment 4 days previously. At admission, plasma D-dimer was 9.6 mg/L (reference value, <0.2 mg/L), and plasma lactate was normal. He developed signs of generalized peritonitis with rebound tenderness in the abdomen 12 hours after admission. Laparoscopy showed signs of ischemia in the proximal ileum (Video 137.1). At laparotomy, it was decided to remove the two most reddish, discolored, severely ischemic segments (*arrows*) by resecting a total length of 0.4 m, followed by one small bowel anastomosis. Note the edema of the affected small bowel loops and their adjacent mesentery. Treatment with a full dose of low-molecular-weight heparin was started at the end of surgery. Second-look laparotomy and recovery were uneventful, and lifelong treatment with VKA was prescribed. Histopathology of the resected bowel did not show transmural infarction but did show infarcted mucosa and venous thrombosis.

until return of gastrointestinal function. All patients should then receive anticoagulation with either LMWH or oral anti-coagulation. Because of significant postoperative changes, the value of a postoperative CT scan to evaluate the extension of thrombosis and the frequency of thrombus recanalization is unclear.

Prognosis

The 30-day mortality among identified and actively treated patients has decreased to 9.8%,⁷ probably because of earlier detection with CT and identification of a higher proportion of patients without peritonitis not requiring laparotomy.^{3,9} Anticoagulation with or without bowel resection in patients with acute MVT has also improved survival in comparison with observation alone.⁸ The estimated 5-year survival for 51 patients was 70%.⁴ Prognosis of patients with MVT after hospital discharge is associated with the underlying disease, and cancer patients have the poorest survival.⁴ Gastrointestinal bleeding,⁸ late small bowel perforation, intestinal stricture⁹ and short bowel syndrome⁶ have been described as specific gastrointestinal complications. In addition, it is likely that less extensive thrombosis is associated with more complete radiologic recovery, and less risk to develop portal venous hypertension.^{6,2} The most common nongastrointestinal complications following surgery are pneumonia, wound infection, renal failure, and sepsis.^{8,9}

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

Acosta S, Alhadad A, Svensson P, et al. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. *Br J Surg.* 2008;95:1245–1251.

Good epidemiologic work, highlighting the screening for inherited thrombo-phobic disorders.

Björck M, et al. Management of the diseases of the mesenteric arteries and veins. Clinical practice guidelines of the European Society of Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2017;53:460–510.

The recently published clinical practice guidelines from the ESVS includes recommendations on risk factor evaluation, diagnosis, and treatment of mesenteric venous thrombosis.

Salim S, Zarrouk M, Elf J, et al. Improved prognosis and low failure rate with anticoagulation as first-line therapy in mesenteric venous thrombosis. *World J Surg.* 2018;42:3803–3811.

A large review supporting the role of primary conservative management.

Salim S, Ekberg O, Elf J, et al. Clinical implications of CT findings in mesenteric venous thrombosis at admission. *Emerg Radiol.* 2018;25:407–413.

Current review of the impact of CT.

Maldonado TS, Blumberg SN, Sheth SU, et al. Mesenteric vein thrombosis can be safely treated with anticoagulation but is associated with significant sequelae of portal hypertension. *J Vasc Surg Venous Lymphat Disord.* 2016;4:400–406.

Extensive mesenteric venous thrombosis is associated with less complete radiologic recovery and increased risk of long-term sequelae of portal venous hypertension.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Elliott JW. The operative relief of gangrene of the intestine due to occlusion of the mesenteric vessels. *Ann Surg.* 1895;21:9.
2. Warren S, et al. Mesenteric venous thrombosis. *Surg Gynecol Obstet.* 1935;61:102–121.
3. Morasch M, et al. Mesenteric venous thrombosis: a changing clinical entity. *J Vasc Surg.* 2001;34:680–684.
4. Acosta S, et al. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. *Br J Surg.* 2008;95:1245–1251.
5. Acosta S, et al. Mesenteric venous thrombosis with transmural intestinal infarction: a population-based study. *J Vasc Surg.* 2005;41:59–63.
6. Acosta S, et al. Incidence of acute thrombo-embolic occlusion of the superior mesenteric artery—a population-based study. *Eur J Vasc Endovasc Surg.* 2004;27:145–150.
7. Acosta S, et al. Management of acute mesenteric venous thrombosis – a systematic review. *Scand J Surg.* 2021;110(2):123–129.
8. Rhee Ry, et al. Mesenteric venous thrombosis: still a lethal disease in the 1990s. *J Vasc Surg.* 1994;20:688–697.
9. Brunaud L, et al. Acute mesenteric venous thrombosis: case for nonoperative management. *J Vasc Surg.* 2001;34:673–679.
10. Ikeda M, et al. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy. A prospective study with contrast-enhanced CT scan. *Ann Surg.* 2005;241:208–216.
11. Violi NV, et al. Prevalence and clinical importance of mesenteric venous thrombosis in the Swiss Inflammatory Bowel Disease cohort. *AJR Am J Roentgenol.* 2014;203:62–69.
12. Gonzelez H, et al. Splanchnic vein thrombosis in severe acute pancreatitis: a 2-year, single-institution experience. *HPB.* 2011;13:860–864.
13. Rebours V, et al. Extrahepatic portal venous system thrombosis in recurrent acute and chronic alcoholic pancreatitis is caused by local inflammation and not thrombophilia. *Am J Gastroenterol.* 2012;107:1579–1585.
14. Famularo G, et al. Mesenteric and portal vein thrombosis associated with hyperhomocysteinemia and heterozygosity for factor V Leiden mutation. *World J Gastroenterol.* 2005;11:7700–7701.
15. Svensson PJ, et al. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med.* 1994;330:517–522.
16. Samama MM, et al. Diagnosis and clinical characteristics of inherited activated protein C resistance. *Haemostasis.* 1996;26(suppl 4):315–330.
17. Amitrano L, et al. High prevalence of thrombophilic genotypes in patients with acute mesenteric vein thrombosis. *Am J Gastroenterol.* 2001;96:146–149.
18. Colaizzo D, et al. The JAK2 V 617F mutation frequently occurs in patients with portal and mesenteric venous thrombosis. *J Thromb Haemost.* 2007;5:55–61.
19. Zarrouk M, et al. Testing for thrombophilia in mesenteric venous thrombosis. Retrospective original study and systematic review. *Best Pract Res Clin Gastroenterol.* 2017;31:39–48.
20. Owens C. JAK2 V617F mutation, mesenteric vein thrombosis, and myeloproliferative disease. *J Vasc Surg.* 2010;52:205–207.
21. Dentali F, et al. JAK2V617F mutation for the early diagnosis of Ph+ myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis. *Blood.* 2009;113:5617–5623.
22. Van Moerkercke W, et al. Cytomegalovirus-associated superior mesenteric vein thrombosis treated with systemic and in-situ thrombolysis. *Eur J Gastroenterol Hepatol.* 2009;21:587–592.
23. James A, et al. Portomesenteric venous thrombosis after laparoscopic surgery. *Arch Surg.* 2009;144:520–526.
24. Gul W, et al. Thrombosis of portal venous system after laparoscopic cholecystectomy in a patient with prothrombin gene mutation. *J Soc Laparoendosc Surg.* 2012;16:166–168.
25. Ögren M, et al. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23796 consecutive autopsies. *World J Gastroenterol.* 2006;12:2115–2119.
26. Amitrano L, et al. Prognostic factors in noncirrhotic patients with splanchnic vein thromboses. *Am J Gastroenterol.* 2007;102:2464–2470.
27. Acosta S, et al. The clinical importance in differentiating portal from mesenteric venous thrombosis. *Int Angiol.* 2011;30:71–78.
28. Rhee RY, et al. Mesenteric venous thrombosis. *Surg Clin North Am.* 1997;77:327–338.
29. Acosta S, et al. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery. Autopsy findings in 213 patients. *Ann Surg.* 2005;241:516–522.
30. Abraham M, et al. Portomesenteric venous thrombosis: a community hospital experience with 103 patients. *Am J Surg.* 2011;202:759–764.
31. Thatipelli M, et al. Survival and recurrence in patients with splanchnic vein thromboses. *Clin Gastroenterol Hepatol.* 2010;8:200–205.
32. Salim S, et al. Clinical implications of CT findings in mesenteric venous thrombosis at admission. *Emerg Radiol.* 2018;25:407–413.
33. Acosta S, et al. D-Dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. *Br J Surg.* 2004;91:991–994.
34. Salim S, et al. Clinical implications of different risk factor profiles in patients with mesenteric venous thrombosis and systemic venous thromboembolism: a population-based study. *J Thromb Thrombolysis.* 2019;47:572–577.
35. Horton K, et al. CT angiography of the mesenteric circulation. *Radiol Clin North Am.* 2010;48:331–345.
36. Barmase M, et al. Role of multidetector CT angiography in the evaluation of suspected mesenteric ischemia. *Eur J Radiology.* 2011;80:582–587.
37. Duran R, et al. Multidetector CT features of mesenteric vein thrombosis. *Radiographics.* 2012;32:1503–1522.
38. Lehtimäki TT, et al. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: Review of 95 consecutive patients. *Eur J Radiol.* 2015;84:2444–2453.
39. Copin P, et al. Inter-reader agreement of CT features of acute mesenteric ischemia. *Eur J Radiol.* 2018;105:87–95.
40. Salim S, et al. Improved prognosis and low failure rate with anticoagulation as first-line therapy in mesenteric venous thrombosis. *World J Surg.* 2018;42:3803–3811.
41. Grisham A, et al. Deciphering mesenteric venous thrombosis: imaging and treatment. *Vasc Endovasc Surg.* 2005;39:473–479.
42. Yang S, et al. Multidisciplinary stepwise management strategy for acute superior mesenteric venous thrombosis. An initial stroke center experience. *Thromb Res.* 2015;135:36–45.
43. Kernagis LY, et al. *Pneumatosis intestinalis* in patients with ischemia: correlation of CT findings with viability of the bowel. *AJR Am J Roentgenol.* 2003;180:733–736.
44. Salim S, et al. Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis. *Phlebology.* 2019;34:171–178.
45. Dentali F, et al. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists. *Thromb Haemost.* 2009;102:501–504.
46. Bauer KA. Duration of anticoagulation: applying the guidelines and beyond. *Hematology Am Soc Hematol Educ Program.* 2010;2010:210–215.
47. Björck M, et al. Management of the diseases of the mesenteric arteries and veins. Clinical practice guidelines of the European Society of Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2017;53:460–510.
48. Nakayama S, et al. Superior mesenteric venous thrombosis treated by direct aspiration thrombectomy. *Hepatogastroenterology.* 2008;55:367–370.
49. Ferro C, et al. Transjugular intrahepatic portosystemic shunt, mechanical aspiration thrombectomy, and direct thrombolysis in the treatment of acute portal and superior mesenteric vein thrombosis. *Cardiovasc Interv Radiol.* 2007;30:1070–1074.
50. Wang MQ, et al. Acute extensive portal and mesenteric venous thrombosis after splenectomy: treated by interventional thrombolysis with transjugular approach. *World J Gastroenterol.* 2009;15:3038–3045.
51. Takahashi N, et al. Percutaneous transhepatic mechanical thrombectomy for acute mesenteric venous thrombosis. *J Endovasc Ther.* 2005;12:508–511.

52. Zhou W, et al. Percutaneous transhepatic thrombectomy and pharmacologic thrombolysis of mesenteric venous thrombosis. *Vascular.* 2007;15:41–45.
53. Di Minno M, et al. Endovascular thrombolysis in acute mesenteric vein thrombosis: a 3-year follow-up with the rate of short- and long-term sequelae in 32 patients. *Thromb Res.* 2010;126:295–298.
54. Hollingshead M, et al. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. *J Vasc Interv Radiol.* 2005;16:651–661.
55. Ozdogan M, et al. Thrombolysis via an operatively placed mesenteric catheter for portal and superior mesenteric vein thrombosis: report of a case. *Surg Today.* 2006;36:846–848.
56. Marini M, et al. Endovascular treatment of splenomesenteric-portal vein thromboses during orthotopic liver transplantation. *J Vasc Interv Radiol.* 2005;16:1135–1142.
57. Xu R, et al. Hybrid therapy consisting of bowel resection and fluoroscopic-assisted balloon thrombectomy for small bowel infarction caused by acute mesenteric venous thrombosis. *Ann Vasc Surg.* 2019;59:202–207.
58. Cho YP, et al. Role of diagnostic laparoscopy in managing acute mesenteric venous thrombosis. *Surg Laparosc Endosc Percutan Tech.* 2003;13:215–217.
59. Chong AK, et al. Use of laparoscopy in the management of mesenteric venous thrombosis. *Surg Endosc.* 2001;15:1042.
60. Klempnauer J, et al. Results of portal thrombectomy and splanchnic thrombolysis for the management of acute mesentericoportal thrombosis. *Br J Surg.* 1997;84:129–132.
61. Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: update consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39:1190–1206.
62. Maldonado TS, et al. Mesenteric vein thrombosis can be safely treated with anticoagulation but is associated with significant sequelae of portal hypertension. *J Vasc Surg Venous Lymphat Disord.* 2016;4:400–406.

Vasculitis and Other Uncommon Arteriopathies

VICTORIA K. SHANMUGAM

VASCULITIS PRESENTATION 1811

- Histologic Characteristics of Vasculitis 1811
- Angiography 1811
- Noninvasive Vascular Imaging 1811
- LARGE-VESSEL VASCULITIS 1811
 - Takayasu Arteritis 1811
 - Giant Cell Arteritis (Temporal Arteritis) 1811
 - Epidemiology 1811
 - Pathogenesis 1811
 - Clinical Characteristics 1811
 - Diagnostic Criteria 1812
 - Medical Treatment of Giant Cell Arteritis 1813
 - Role for Vascular Surgical Intervention in Giant Cell Arteritis 1813
 - Idiopathic Aortitis 1813
 - Idiopathic Retroperitoneal Fibrosis (Ormond Disease)* 1814
 - IgG4-Related Systemic Disease* 1814
 - Erdheim–Chester Disease 1814
- MEDIUM-SIZED VESSEL VASCULITIS 1814
 - Polyarteritis Nodosa 1814
 - Pathogenesis 1814
 - Histology 1814
 - Laboratory Testing 1815
 - Clinical Features 1815
 - Treatment 1815
 - Prognosis 1816
 - Other Diseases Showing Aneurysms on Abdominal Visceral Angiography 1816
 - Thromboangiitis Obliterans (Buerger Disease) 1816
 - Epidemiology 1816
 - Clinical Presentation 1816
 - Diagnostic Testing 1816

Pathologic Findings 1816

- Treatment* 1816

Kawasaki Disease 1817

SMALL-VESSEL VASCULITIS 1817

- Antineutrophil Cytoplasmic Antibody-Associated Vasculitis 1817

Granulomatosis with Polyangiitis (Previously Known as Wegener Granulomatosis) 1817

Epidemiology 1817

Clinical Presentation 1817

Laboratory Testing 1817

Treatment 1817

Microscopic Polyangiitis 1818

Epidemiology 1818

Clinical Presentation 1818

Laboratory Testing 1818

Renal Histopathology 1818

Treatment 1818

Eosinophilic Granulomatosis with Polyangiitis (Previously Known as Churg–Strauss Syndrome) 1818

Epidemiology 1818

Pathophysiology 1818

Clinical Presentation 1818

Laboratory Findings 1819

Treatment 1819

VASCULITIS SECONDARY TO CONNECTIVE TISSUE DISEASES 1819

Vascular Manifestations of Behçet Disease 1819

Epidemiology 1819

Treatment 1819

Systemic Lupus Erythematosus 1819

Rheumatoid Vasculitis 1820

Relapsing Polychondritis 1820

Cogan Syndrome	1820
Pseudoxanthoma Elasticum	1820
Exercise-Related External Iliac Arteriopathy	1820
VASCULITIS MIMICS	1820
Fibromuscular Dysplasia	1820
Radiation Arteritis	1821
Epidemiology	1821

Pathogenesis	1821
Clinical Presentation	1821
Diagnostic Evaluation	1821
Treatment	1821
Neurofibromatosis Type 1	1821
Drug-Induced Vasculitis	1822

Vasculitis refers to a group of inflammatory disorders that result in inflammation and necrosis of blood vessels with subsequent impairment of flow resulting in ischemia and infarction of distal tissues.^{1,2} Often, vascular surgeons are the first physicians consulted in cases of vasculitis, and vasculitis should be

considered in patients with ischemic occlusive disease or aneurysmal disease in the absence of traditional risk factors and in association with features of a systemic inflammatory process. Prompt involvement of a rheumatologist can expedite diagnostic testing and treatment. Vessels of any location may be

TABLE 138.1 International Chapel Hill Consensus Conference Nomenclature³

NOMENCLATURE		Vasculitis
Large-vessel vasculitis		Giant cell arteritis (also known as temporal arteritis) Takayasu arteritis
Medium-vessel vasculitis		Polyarteritis nodosa Kawasaki disease
Small-vessel vasculitis	Immune complex-mediated	Antiglomerular basement membrane (anti-GBM) disease Cryoglobulinemic vasculitis IgA vasculitis (Henoch–Schönlein purpura) Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis) Granulomatosis with polyangiitis (previously known as Wegener granulomatosis) Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome)
Variable-vessel vasculitis		Behçet disease Cogan syndrome Thromboangiitis obliterans (Buerger disease)
Single-organ vasculitis		Cutaneous leukocytoclastic vasculitis Cutaneous arteritis Primary central nervous system (CNS) vasculitis (isolated angiitis of the CNS) Isolated aortitis Others
Vasculitis associated with systemic disease		Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Others
Vasculitis secondary to other etiology		Hepatitis C-associated cryoglobulinemic vasculitis Hepatitis B-associated vasculitis Syphilis-associated vasculitis Drug-associated immune complex vasculitis (hypersensitivity vasculitis) Cancer-associated vasculitis Others

Thromboangiitis obliterans (Buerger disease) was not classified at the Chapel Hill conference but fits best into the variable-vessel vasculitis group.

affected by vasculitis, and the classification nomenclature has been defined by the International Chapel Hill Consensus Conference,³ as outlined in Table 138.1.

VASCULITIS PRESENTATION

There is no single presentation of vasculitis, but clinical manifestations often suggest the size of vessel affected and thus can help guide the likely diagnosis and necessary work-up. For example, patients with large-vessel vasculitis often present with limb claudication, vascular bruits, asymmetric blood pressures, or absence of pulses. Medium-vessel vasculitis often presents with cutaneous nodules and ulcers, livedo reticularis, digital gangrene, mononeuritis multiplex, and renovascular hypertension. In contrast, patients with small-vessel vasculitis tend to present with palpable purpura, pulmonary–renal syndromes (glomerulonephritis and alveolar hemorrhage), urticarial skin rashes, and scleritis.

Histologic Characteristics of Vasculitis

The vasculitides typically cause characteristic histologic features, including infiltration of the vessel wall by neutrophils, mononuclear cells, and/or giant cells. Fibrinoid necrosis is seen with pan-mural destruction of the vessel wall and evidence of leukocytoclasis (disruption of leukocytes resulting in the histologic finding of “nuclear dust”). It should be noted that perivascular infiltration alone is a nonspecific histologic finding, which is not diagnostic of vasculitis.

Histologic findings in the specific diseases are dependent on the vessel size affected and the underlying disease physiology. Giant cell arteritis (GCA), Takayasu arteritis, and primary central nervous system (CNS) vasculitis are cell mediated, whereas polyarteritis nodosa (PAN), Henoch–Schönlein purpura, cryoglobulinemic vasculitis, and cutaneous leukocytoclastic angiitis are immune complex mediated. ANCA-associated vasculitis (AAV) involves both cellular and humoral immune responses and often involves granulomatous tissue injury without immune complex formation.

Angiography

When tissue biopsy is not feasible, angiography imaging can be helpful for assessing specific types of arteritis. For example, angiography of the celiac trunk, superior mesenteric, and renal arteries can be diagnostic of PAN; imaging of the aortic arch is essential for the diagnosis of Takayasu arteritis and GCA with large-vessel involvement; angiography of the extremities can be helpful in the diagnosis of thromboangiitis obliterans (TO); and angiography of the cerebral circulation is essential for the diagnosis of primary CNS vasculitis. Angiographic findings that are characteristic of vasculitis include irregular asymmetric tapering and narrowing as well as “beading” with segmental stenosis and aneurysm formation.

Noninvasive Vascular Imaging

Noninvasive vascular imaging is used to evaluate some vascular beds, although it is somewhat controversial. In GCA, Doppler

ultrasound of the temporal arteries has been shown to demonstrate inflammatory changes and can be used to assist with biopsy site selection; however, utility as a diagnostic tool is highly dependent on the experience of the sonographer; thus it should not replace temporal artery biopsy as a diagnostic tool.⁴ Magnetic resonance angiography of the aorta has utility in larger vascular beds and can be used to image the aorta in Takayasu arteritis and GCA. Aortic wall enhancement with gadolinium indicates active inflammation.⁵ Positron emission tomography (PET) has also been used to demonstrate enhancement in the aortic and subclavian vascular beds in Takayasu and GCA⁶ but has not gained widespread use as a diagnostic tool.

LARGE-VESSEL VASCULITIS

Takayasu Arteritis

Takayasu arteritis is a cause of large-vessel vasculitis affecting the aorta and its branches that presents in younger individuals. It is discussed in Chapter 140 (Takayasu Arteritis).

Giant Cell Arteritis (Temporal Arteritis)

Epidemiology

GCA primarily affects patients over 50 years of age and is more common in Caucasian patients of Northern European descent. While relatively rare in African Americans, GCA has been reported in all racial groups; thus, patients of other races presenting with a consistent history should be fully evaluated.⁷ The incidence of GCA increases dramatically with age and is approximately 10 times more common in patients in their 80s than in patients aged 50 to 60.⁸ GCA is more common in women than men with a lifetime risk of 1% in women and 0.5% in men.⁹

Pathogenesis

The exact cause of GCA is unknown. Genetic polymorphisms of the human leukocyte antigen class II region, specifically HLA-DRB1*04 and DRB1*01, are associated with susceptibility to GCA.¹⁰ Notably, the T-cell cytokine IFN-gamma is abundantly expressed in GCA but absent from arteries of polymyalgia rheumatica (PMR) patients without GCA.¹¹ It is thought that in response to immunologic injury, the artery releases growth and angiogenic factors that induce proliferation of myofibroblasts, new vessel formation, and marked thickening of the arterial intima. This leads to vessel narrowing and occlusion resulting in symptoms of ischemia including jaw claudication, visual loss, and stroke.

Clinical Characteristics

GCA should be suspected in individuals over the age of 50 presenting with new-onset headache and evidence of systemic inflammation. Approximately 20% of GCA patients present with cranial symptoms, including headache, scalp tenderness, jaw and tongue claudication, diplopia, and blindness. New onset of diplopia in an elderly patient is highly suggestive of GCA.¹² Jaw claudication is also a very specific symptom.¹³ PMR is also a common presentation, with 40% of cases



Figure 138.1 Computed tomography angiography with 3D reconstruction images reveals bilateral subclavian, axillary, and proximal brachial artery stenoses in a patient with giant cell arteritis. Moderate narrowing of both proximal common carotid arteries is also noted.

presenting with complaints of symmetric pain and stiffness of the shoulder and thigh girdle muscles. It should be noted that some patients develop PMR without GCA and only 10% to 20% of patients presenting with PMR go on to develop GCA. In 20% of GCA cases, symptoms of both cranial GCA and PMR are present at presentation. GCA may also have a more indolent presentation with 15% of cases exhibiting fever and systemic symptoms with no other localizing symptoms. GCA is the cause in 15% of elderly patients with an FUO. Finally, around 5% of GCA cases present with claudication symptoms, cough, tenosynovitis, and the syndrome of relapsing seronegative symmetric synovitis with pitting edema can also occur.

Physical findings in GCA include scalp tenderness and reduced pulse and tenderness of the temporal artery. Of GCA patients presenting with cranial and/or PMR symptoms, approximately 20% have clinical evidence of large-vessel vasculitis impacting subclavian arteries and other vascular territories (Fig. 138.1); thus, it is important to check for discrepancies in blood pressure between the extremities, and the carotid and subclavian arteries should be auscultated for bruits. GCA patients have a 17-fold increased risk of development of thoracic aortic aneurysms and a 2.4-fold increased risk of developing abdominal aortic aneurysm compared to controls. Long-term monitoring with periodic imaging of the aorta is recommended.¹⁴

Abrupt onset of painless blindness may occur as a result of ischemic optic neuritis in 15% of patients and this is usually related to arteritis of the posterior ciliary branches of the ophthalmic arteries. Amaurosis fugax is the strongest predictor for future blindness with a relative risk of 6.3.¹⁵ Thrombocytosis is also associated with visual loss. Patients may additionally complain of blurring of vision, iritis, conjunctivitis, scintillating scotoma, photophobia, glaucoma, and ophthalmoplegia from ischemia of extraocular muscles. Retinal and ophthalmic artery thromboses and occipital strokes are less common. It should be noted that risk of visual loss also drops significantly once steroids have been commenced, with less than 10% of patients developing blindness after steroids have been initiated.¹⁶

TABLE 138.2 American College of Rheumatology Criteria for Diagnosis of Giant Cell Arteritis (1990)

Criterion	Definition
Age at disease onset >50 years	Development of symptoms or findings beginning at age 50 or older
New headache	New onset headache
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation without evidence of arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate (ESR)	ESR >50 mm/h by Westergren method
Abnormal artery biopsy	Biopsy specimen showing vasculitis characterized by predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

To meet criteria for a diagnosis of giant cell arteritis, at least three out of the five criteria should be present.¹⁷

Involvement of the intracranial vasculature in GCA is relatively rare, because these vessels lack an internal elastic lamina; however, involvement of internal carotids and vertebral arteries can occur and lead to strokes, seizures, acute hearing loss, vertigo, cerebral dysfunction, and depression.

Diagnostic Criteria

The 1990 American College of Rheumatology criteria for the diagnosis of GCA¹⁷ are listed in Table 138.2. For diagnosis of GCA, at least three out of five criteria must be present. The presence of three or more criteria yields a sensitivity of 93.5% and specificity of 91.2% for distinguishing GCA from other forms of vasculitis. While the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often markedly elevated in GCA, only a minority of patients have a normal ESR. Often, patients will have other evidence of systemic immune response, including normocytic anemia and elevated platelet count (see Table 138.2).

The gold standard diagnostic test for GCA is temporal artery biopsy. An adequate length of temporal artery (2–3 cm) should be obtained at biopsy, and bilateral biopsies (particularly if the first is negative) are recommended by some groups.¹⁸ Up to 50% of biopsies show diffuse lymphocytic infiltrate without evidence of granulomatous inflammation or giant cells. Fragmentation and fraying of the internal elastic lamina can be seen in normal aging, so in the absence of inflammation, this finding is not diagnostic of GCA. Ideally, biopsy specimens should be obtained prior to or within 7 days of starting corticosteroids. However, corticosteroid therapy does not normalize the affected artery; it simply reduces the inflammatory infiltrate, so “healed temporal arteritis” can still be diagnosed by the presence of intimal fibrosis, medial scarring, and asymmetric destruction of the internal elastic lamina.¹⁹

Large-vessel involvement may be assessed using conventional angiography, magnetic resonance angiography, or computed

tomography (CT) angiography.^{5,6,12} Newer imaging modalities including ultrasound and PET are being evaluated as diagnostic tools in GCA.⁶

Medical Treatment of Giant Cell Arteritis

Corticosteroid therapy is standard of care in the management of GCA, and the initial dosing should be 40 to 60 mg daily. In patients with incipient visual loss, intravenous methylprednisolone (1000 mg per day for 3 days) may be considered. The initial prednisone dose should be maintained until inflammatory markers normalize (usually at least 1 month). Various tapering methods are used, but a rule of thumb is to reduce the prednisone by 5 mg every 1 to 2 weeks until 30 mg per day is reached and then to reduce the amount by 2.5 mg every 1 to 2 weeks until 15 mg per day. The subsequent taper should be 2.5 mg every 4 weeks until 10 mg and then 1 mg every 4 weeks until the patient is off prednisone. Alternate-day steroid dosing regimens are not effective. Clinical symptoms, ESR, and CRP should be monitored for every change in dose, and it should be noted that spontaneous recurrence may occur in as many as 50% of cases. Up to 40% of cases (especially women) need long-term corticosteroid therapy for several years. All patients are recommended to also receive low-dose aspirin 81 mg per day to reduce the risk of cardiovascular events and blindness. The anti-IL6 antibody tocilizumab has recently been shown to be effective as a steroid-sparing agent in GCA.²⁰ Other trials

of biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) are ongoing. Figure 138.2 shows marked improvement in diffuse arterial wall thickening caused by GCA in response to steroids.

Role for Vascular Surgical Intervention in Giant Cell Arteritis

Revascularization procedures are rarely required in GCA due to development of collaterals. Balloon angioplasty in combination with immunosuppressive treatment has been tried in small case series, but unless the inflammatory process is well controlled, the risk of restenosis is high. For patients with aortic aneurysms, surgery is indicated with surgical results similar to those seen in patients with aneurysms from other etiologies.²¹

Idiopathic Aortitis

Inflammation of the aorta discovered incidentally on histology is seen in 3% to 10% of surgical aortic aneurysm repairs. A recorded 45 cases of incidental aortitis in a retrospective review of 514 ascending aortic specimens (frequency 8.8%). In the thoracic aorta, some of these lesions are histologically indistinguishable from GCA, but others demonstrate lymphoplasmacytic infiltrate, and 75% of these are due to IgG4-related disease. In the abdominal aorta, lesions can

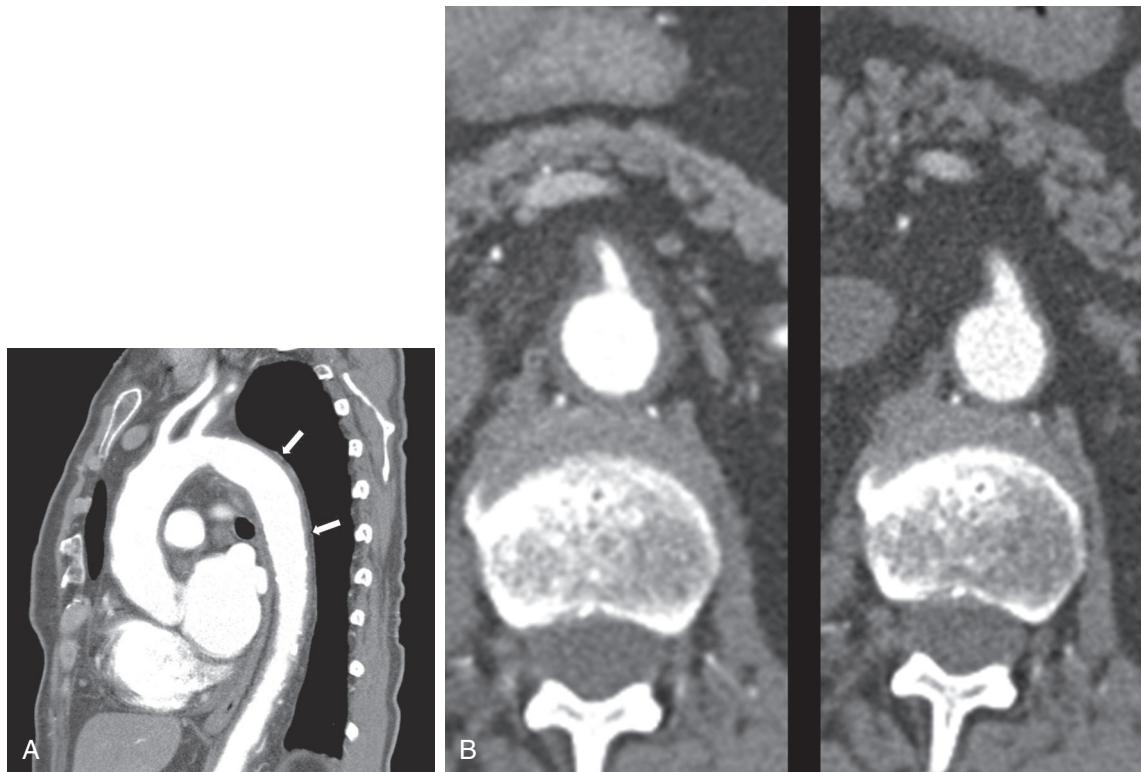


Figure 138.2 Computed Tomography Angiogram of a Patient with Giant Cell Arteritis and Involvement of the Aorta. (A) This sagittal image demonstrates thickened arterial walls, most prominent in the great vessels, and throughout the entire descending thoracic aorta. (B) Arterial wall thickening extended into the upper abdominal aorta and superior mesenteric artery (SMA), which was stenosed (*left panel*). Reimaging after 6 months of treatment with corticosteroids revealed marked improvement in the diffuse arterial wall thickening and SMA stenosis (*right panel*).

be grouped into idiopathic retroperitoneal fibrosis (Ormond disease) and inflammatory aortic aneurysms that are often associated with smoking and a family history of aortic aneurysm, of which some of these lesions are due to IgG4-related systemic disease. The syndrome of idiopathic abdominal periaortitis has also been described without associated aneurysm or retroperitoneal fibrosis. In these patients, rarer etiologies including Erdheim–Chester disease should be considered.

Idiopathic Retroperitoneal Fibrosis (Ormond Disease)

Idiopathic retroperitoneal fibrosis is rare, affects men more than women (3:1), and presents in patients in middle age (40–60 years old). Typically, patients present with pain in the lower back, abdomen, flank, and scrotum. Some patients also demonstrate systemic symptoms including fever, anorexia, and malaise. Patients have hypertension in 75% of cases and lower extremity edema and phlebitis can be seen. Serologic work-up is usually negative, but inflammatory markers are elevated in 75% of cases. Classic CT findings include presence of a homogeneous mass around the aorta following the iliac bifurcation with associated medial deviation of the mid-part of the ureter and secondary hydronephrosis. Usually, lymphadenopathy is absent. Biopsy may be performed laparoscopically or through open procedure, and histology shows sclerosis with infiltration of mononuclear cells. The pathophysiology of this process is unknown, but an exaggerated local inflammatory response to oxidized low-density lipoprotein in aortic plaque has been postulated. Treatment with high-dose prednisone is recommended (60 mg daily for 1 month followed by tapering off to 10 mg/day by 3–6 months). Maintenance therapy with prednisone is recommended for 1 to 3 years. The disease recurs in 10% to 30%, and use of mycophenolate mofetil, tamoxifen, or methotrexate should be considered for these patients. Monitoring with inflammatory markers and CT scan should be continued every 3 months while on treatment and every 6 months when off treatment.

IgG4-Related Systemic Disease

IgG4-related systemic disease affects older males, with 60% to 80% of cases affecting patients older than 50 years. Often, there is a past medical history of allergic diseases and atopy (eczema and asthma). Patients develop tumor-like lesions in one or more organs and on biopsy dense lymphoplasmacytic infiltrates with storiform fibrosis and obliterative phlebitis are seen.²² Lesions should be stained to demonstrate IgG4 positive cells (with >30 per high-powered field and IgG4/IgG positive ratio >50% confirming the diagnosis). Elevated serum IgG4 is seen in 60% to 80% of cases but is not always detected. Serologic work-up is usually negative. Several organs may be affected simultaneously, with the most common presentations being type I autoimmune pancreatitis, sclerosing cholangitis, salivary gland involvement (Mikulicz disease), and sclerosing sialadenitis (Kuttner tumor). The disease may be associated with chronic lymphoplasmacytic aortitis and aneurysm formation. This more commonly affects the thoracic than abdominal

aorta and can be mistaken for idiopathic retroperitoneal fibrosis. Treatment for IgG4-related disease includes high-dose steroids along with DMARDs; in recent years, rituximab (a monoclonal antibody targeting B cells) has been shown to be effective.²³

Erdheim–Chester Disease

Erdheim–Chester disease is a rare histiocytic disease that is associated with periaortic fibrosis (referred to as “coated aorta”), periarterial infiltration of coronary arteries, and pericardial thickening and effusion. Retroperitoneal involvement may also manifest with mass-like infiltrative lesion or with perinephric changes known as “hairy kidney.”²⁴ It may be confused with idiopathic retroperitoneal fibrosis and IgG4-related disease,²⁵ but the distinguishing feature is that most patients also have bone lesions, often in the lower extremities that present with juxta-articular pain. Biopsy of involved tissue reveals tissue infiltration by sheets of foamy histiocytes interspersed with inflammatory and multinucleated giant cells. In recent years, it has become clear that the disease is associated with gain-of-function mutations in the proto-oncogene BRAF (the BRAFV600E mutation), and treatment with BRAF inhibitors has been found to be effective with less toxicity than prior treatment options such as interferon.²⁶

MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis Nodosa

PAN is a necrotizing vasculitis of small and medium arteries and is characterized by the absence of glomerulonephritis and absence of antineutrophil cytoplasmic (ANCA) antibodies.²⁷

Diagnosis is based on presence of 3 out of the 10 American College of Rheumatology criteria (Table 138.3).²⁷

Pathogenesis

PAN may be idiopathic or secondary to hepatitis B infection. In hepatitis B-associated PAN, the mean time between hepatitis diagnosis and PAN is 7 months. PAN may also be associated with other viral infections including HIV and has been seen as a paraneoplastic manifestation of hematologic malignancy (particularly hairy-cell leukemia).

Histology

The histologic lesion in PAN is a focal, segmental necrotizing vasculitis affecting medium-sized arteries. It commonly affects arterioles with sparing of large vessels and veins. The arterial wall inflammation is characterized by fibrinoid necrosis of the media along with neutrophilic and lymphocytic infiltrate. Active necrotizing lesions are often seen alongside healed and fibrotic lesions. Localized thromboses may occur at the site of inflammatory injury, and arterial aneurysms may form as a result of weakening of the vessel wall by the inflammatory process, ultimately leading to end-organ injury from ischemia, infarct, and hemorrhage.

TABLE 138.3

American College of Rheumatology Diagnostic Criteria for Polyarteritis Nodosa

Criterion	Definition
Weight loss >4 kg	Loss of at least 4 kg since illness began without dieting or other confounding factors
Livedo reticularis	Mottled reticular pattern over the skin of extremities or torso
Testicular pain or tenderness	Pain or tenderness of the testicles not due to infection, trauma, or other causes.
Myalgias, weakness or leg tenderness	Diffuse myalgias or weakness of muscles, tenderness of leg muscles.
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
Diastolic BP >90	Development of hypertension with diastolic BP >90 mm Hg
Elevated BUN or creatinine	Elevation of BUN >40 mg/dL or creatinine >1.5 mg/dL
Hepatitis B infection	Presence of hepatitis B surface antigen or antibody in serum
Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of visceral arteries not due to arteriosclerosis, fibromuscular dysplasia, or noninflammatory causes.
Biopsy of small or medium-sized artery demonstrating polymorphonuclear neutrophils	Histologic changes showing presence of granulocytes, and/or mononuclear leukocytes in vessel wall.

BP, blood pressure; BUN, blood urea nitrogen.

Polyarteritis nodosa (PAN) is rare, with annual incidence 2 to 9 cases per million and is declining likely related to reduction in prevalence of hepatitis B infection as vaccination has been more consistent. It may present at any age and in any racial group but is more common in men aged 40 to 60 years. To meet criteria for a diagnosis of PAN, 3 out of the 10 criteria need to be present.²⁷

Laboratory Testing

There are no diagnostic serologic tests for PAN. Elevated systemic inflammatory markers are common, and patients may also exhibit normocytic anemia and thrombocytosis. Usually, complement levels are normal. Hepatitis B serology should be tested, and patients with hepatitis B-associated PAN demonstrate hepatitis B surface antigen positivity, HBeAg, and positive PCR for hepatitis B virus DNA. ANCA testing, rheumatoid factor (RF), cryoglobulins, and antinuclear antibodies (ANA) are typically negative.

Clinical Features

Patients with PAN present with constitutional symptoms (fever and weight loss) in the setting of organ dysfunction. Commonly seen manifestations include skin lesions – including palpable purpura, livedo, necrotic lesions, and digital infarcts; peripheral neuropathy and mononeuritis multiplex; abdominal pain due to mesenteric vasculitis; and

hypertension with microscopic hematuria or proteinuria. Biopsy of affected tissue is crucial for establishing the diagnosis. If the presenting symptoms are related to mesenteric ischemia or renal involvement, then visceral angiogram can be helpful confirming the diagnosis. Angiographic findings include presence of saccular aneurysms, microaneurysms, occlusions and cutoffs with luminal irregularity, and stenosis of small and medium vessels of abdominal viscera. Severe gastrointestinal (GI) involvement is a major cause of morbidity in PAN. Renal biopsy is usually unhelpful, since the renal injury is not glomerular in nature. Microaneurysms of renal artery branches can occasionally rupture and cause renal hematomas. Myalgias due to skeletal muscle involvement and large joint arthralgias are common. Importantly, PAN does not affect the lungs or upper respiratory tract, which is an important feature in distinguishing this disease from ANCA-associated vasculitis.

Treatment

In patients with hepatitis B-associated PAN, antiviral therapy should be initiated prior to immunosuppression. Some patients with severe manifestations of hepatitis virus-associated PAN benefit from short-term treatment with glucocorticoids and plasma exchange until the antiviral therapy becomes effective.²⁸ Plasma exchange has not been shown to be effective in PAN that is not associated with hepatitis B. Prolonged immunosuppression should be avoided to facilitate immunologic clearance of hepatitis B-infected hepatocytes.

In patients with PAN not associated with viral disease, excellent 5-year survival rates of over 80% can be achieved with appropriate immunosuppressive therapy and use of steroids improves survival.²⁹ For mild and isolated cutaneous disease, initial monotherapy with daily oral prednisone (1 mg/kg ideal body weight up to a maximum of 60 mg per day) is recommended. The initial dose should be continued for 4 weeks, and the taper should be guided by clinical improvement, tapering below 20 mg per day should be done slowly, not faster than by 2.5 mg every 14 days. Most patients remain on prednisone for approximately 6 to 8 months. Many patients with mild disease respond to glucocorticoid monotherapy, but for those patients who do not achieve remission with glucocorticoids alone, addition of a DMARD agent, such as azathioprine (2 mg/kg per day) or methotrexate (20–25 mg weekly) is recommended, with monitoring through rheumatology to allow prednisone to be weaned. Methotrexate should not be used in patients with renal disease or hepatitis.

For patients with moderate to severe disease, data from long-term follow-up studies in several cohorts of patients with PAN shows improved outcomes from induction therapy with steroids and cyclophosphamide^{28,30,31} followed by either azathioprine or methotrexate for remission maintenance. There has been no comparison of oral versus IV cyclophosphamide use in PAN; however, one small randomized controlled trial of 18 patients with PAN and 47 with microscopic polyangiitis (MPA) demonstrated that use of steroids with 12 monthly pulses of IV cyclophosphamide had a lower risk of relapse and higher event-free survival than patients receiving only 6 monthly pulses of

IV cyclophosphamide. Mortality did not differ, and this study did not investigate remission maintenance regimens. Some investigators also extrapolate use of the “CYCLOPS” cyclophosphamide dosing regimen that was shown to be comparable to oral cyclophosphamide for induction and remission of ANCA-associated vasculitis, but this has not been studied in PAN. It should be noted that in the management of other forms of vasculitis, the IV dosing of cyclophosphamide often allows effective disease control with lower cumulative dose and potentially reduced bone marrow, bladder, ovarian, and testicular toxicity; but many of the original studies of cyclophosphamide use for vasculitis used the daily oral dosing regimen that is preferred by some due to a higher effective dose and better long-term response rates. In addition, cyclophosphamide should not be dosed without involvement of rheumatology, because this drug carries several adverse effects including cytopenias, gonadal failure, risk for hemorrhagic cystitis, and increased risk of malignancy. Dose reduction is necessary for renal insufficiency and advanced age, and the dose should be adjusted based on the nadir white blood count to minimize bone marrow toxicity. In addition, prophylaxis for *Pneumocystis jirovecii* (PJP) infection should be employed in patients receiving high-dose steroids in combination with DMARDs.

Prognosis

Untreated PAN is associated with poor prognosis (13% 5-year survival) but with treatment the 5-year survival improves (to ~80%).^{32,33} Age greater than 65, cardiac symptoms, GI involvement, and renal insufficiency (creatinine >1.7 mg/dL) are associated with higher mortality. Renal transplant has been performed in patients with PAN and end-stage renal disease. Of the 112 cases reported in the European Renal Association–European Dialysis and Transplant Association registry, transplantation was associated with significantly lower patient and allograft survival compared to those with renal disease from other causes.³⁴ Approximately 13% of graft failures were due to disease recurrence.

Other Diseases Showing Aneurysms on Abdominal Visceral Angiography

Several other diseases may demonstrate aneurysms on abdominal angiography. Segmental arterial mediolysis (SAM) is a rare, nonatherosclerotic, noninflammatory disease that affects muscular arteries and can mimic PAN. Classically, this involves the splanchnic arteries in middle-aged and elderly patients, the basilar cerebral arteries in adults, and coronary arteries in children and young adults, but the aorta is spared. Patients present with life-threatening hemorrhage due to aneurysm rupture, and histologically, there is lysis and loss of the muscular layer of the media, resulting in arterial dilatation and aneurysm formation. It is thought that this is a variant of fibromuscular dysplasia. Other diseases that can mimic PAN include pseudoxanthoma elasticum, neurofibromatosis, and vascular type Ehlers–Danlos syndrome in which a defect in type III collagen results in vascular wall weakening and aneurysm formation. Finally, a newly described syndrome associated with genetic deficiencies in adenosine deaminase-2 can present with a phenotype similar to

PAN, with fever, systemic symptoms, livedoid rash, and early-onset stroke.³⁵

Thromboangiitis Obliterans (Buerger Disease)

TO is an inflammatory obliterative nonatheromatous vascular disease that affects the small and medium-sized arteries, veins, and nerves.³⁶ While it is only associated with mild inflammatory changes, the presence of inflammation means that this disease is considered to be a vasculitis.

Epidemiology

TO is predominantly a disease of young men, most commonly affecting individuals between the ages of 18 and 50 years; and men are more commonly affected than women. The disease is also more common in the Middle and Far East than in North America and Western Europe.³⁶

There is a strong association with tobacco exposure, although TO has been reported even in individuals who only smoke small amounts, and it has also been seen in pipe smokers, marijuana users, and tobacco chewers.³⁷

Clinical Presentation

The initial manifestation of TO is lower extremity claudication, and this sometimes progresses to digital ischemia. Pedal, instep claudication is also a very specific symptom and patients often present initially to podiatrists. Gangrene, ulceration, or rest pain is the presenting complaint in one-third of patients; often, this can be triggered by minimal trauma such as nail trimming or pressure from tight shoes. Superficial thrombophlebitis and Raynaud syndrome are also described.³⁸

Diagnostic Testing

TO is a diagnosis of exclusion. Prothrombotic states, diabetes, and other autoimmune diseases, especially scleroderma, should be excluded before attributing digital gangrene to TO. Patients should also undergo echocardiogram to rule out infectious endocarditis and arteriogram to rule out atherosclerosis. Arteriographic features of TO include bilateral focal segmental stenosis and occlusion with relatively normal intervening vessels. Collateral development around areas of occlusion lead to the appearance of “tree-root,” “spiders web,” or “corkscrew” collaterals. The most important finding is that proximal arteries are normal, without evidence of atherosclerosis or emboli.³⁶

Pathologic Findings

Most pathologic specimens come from amputated limbs and show panvasculitis with highly cellular thrombosis and microabscesses in the thrombus and vessel wall. In the subacute phase, the thrombus is less cellular and may recanalize. Unlike most other forms of vasculitis, the internal elastic lamina is preserved, and venulitis is often seen.

Treatment

Treatment of TO involves total cessation of tobacco, and nicotine replacement products. Calcium channel blockers and pentoxifylline are sometimes helpful. Intravenous iloprost can

assist with the period of critical ischemia.³⁹ Sympathectomy can also be tried.³⁶ Approximately 50% of patients who continue to smoke will require amputation.⁴⁰ Surgical recanalization and bypass grafting is challenging, but several groups are now reporting promising results in patients who remain abstinent from nicotine.^{40–42}

Kawasaki Disease

Kawasaki disease is an acute vasculitis typically seen in children, in which there is involvement of small and medium-sized arteries, especially the coronary arteries.⁴³ Most patients are under the age of 5 years, boys are more commonly affected than girls (1.5:1), and high-grade fever is one of the cardinal presenting signs in Kawasaki disease. Coronary artery dilatation and aneurysm formation can occur in up to 20% to 29% of patients,⁴⁴ and the main cause of death is myocardial infarction. Treatment with high-dose aspirin and IV immunoglobulin is effective and reduces the incidence of coronary artery aneurysms.⁴⁵ A variant of Kawasaki disease known as multisystem inflammatory syndrome in children (MIS-C) has been reported in children following infection with the SARS-CoV2 virus.⁴⁶

SMALL-VESSEL VASCULITIS

Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

AAV primarily affects small arteries, and are associated with the presence of ANCA. ANCAs are antibodies directed against specific proteins in granules in the cytoplasm of neutrophils and lysosomal proteins in monocytes. Classification of the diseases associated with ANCA was recently revised to granulomatosis with polyangiitis (GPA, previously known as Wegener syndrome), MPA, and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg–Strauss syndrome).

Granulomatosis with Polyangiitis (Previously Known as Wegener Granulomatosis)

GPA is a granulomatous vasculitis of the upper and lower respiratory tract that also causes pauci-immune focal, segmental, crescentic glomerulonephritis. There is a strong association with cANCA antibodies with proteinase-3 specificity (PR-3). Patients may be classified by organ involvement into generalized GPA, where there is involvement of upper and lower respiratory tract and kidney, and limited GPA, where there is only respiratory tract involvement with sparing of the kidney.

Epidemiology

GPA is rare, affecting 8 to 10 patients per million per year. The mean age at diagnosis is 41 years, although it has been reported in children as young as 5 years old and in elderly patients. Only 16% of cases present in childhood. The disease is more common in Caucasians than in African Americans (7:1).

Clinical Presentation

Patients present with chronic sinusitis, epistaxis, and chronic purulent nasal drainage along with chronic inflammation of the auditory canal causing acute suppurative otitis media and chronic serous otitis media. New onset of otitis media in an adult should prompt rheumatologic evaluation for GPA. Chronic inflammation of the laryngeal and tracheal mucosa can lead to hoarseness and subglottic stenosis. The peripheral nervous system may also be involved with development of mononeuritis multiplex. CNS involvement includes chronic pachymeningitis, cranial neuropathies, pituitary involvement, brainstem, and spinal cord lesions.

Pulmonary involvement is seen at presentation in 50% of cases and ultimately affects almost 90% of patients. Some patients may be only mildly symptomatic, but pulmonary imaging should be completed. Nodules and fixed infiltrates are often seen. During the acute phase, pulmonary capillaritis develops with infiltration of neutrophils, and other inflammatory cells in the alveolar septa. As lesions become chronic, granulomas develop in the alveolar septa and within vessels and airway walls. These nodules may cavitate and sometimes become secondarily infected.

Renal involvement is present at presentation in 15% to 30% of cases and ultimately affects 50% to 80%. Renal pathology shows pauci-immune, focal, segmental, crescentic, necrotizing glomerulonephritis. Immunofluorescence demonstrates absence of immunoglobulin, immune complex, and complement deposition.

Laboratory Testing

ANCA positivity is seen in 90% of patients with generalized GPA and approximately 60% of limited cases. Of the patients with positive ANCA 80% to 90% have cANCA positivity with PR-3 specificity. The overall specificity of PR3-ANCA for generalized GPA is thus 98%. All patients with possible GPA should have screening urinalysis to check for evidence of active urinary sediment (hematuria, pyuria, proteinuria, or casts).

Often, ANCA titers correlate with GPA disease activity, and rising ANCA titer may herald a flare, a feature that is helpful and may distinguish flare from infection in patients with chronic disease.⁴⁷ Patients on maintenance therapy with PR-3 positivity have an increased risk of flare if therapy is stopped; thus, current recommendations are for this group of patients to remain on maintenance immunosuppression.⁴⁸

Treatment

Patients with severe GPA should receive induction therapy with IV steroids (methylprednisolone 1000 mg daily for 3–5 days) followed by daily oral prednisone at tapering doses. If alveolar hemorrhage is present, plasmapheresis is also used acutely. Therapy with rituximab or monthly IV cyclophosphamide should be used for induction of remission. Rituximab is as effective as cyclophosphamide and is particularly useful for patients who have relapsed and those who do not respond to cyclophosphamide.^{49–51} It should be noted that rituximab is removed by plasmapheresis but not hemodialysis, and thus dosing should be timed accordingly. In limited GPA, prednisone plus methotrexate has been used if the renal function is normal.

During the remission maintenance phase, clinical trials show that azathioprine is equally effective as cyclophosphamide at maintaining remission⁵² but carries fewer side effects. The MAINRITSAN study recently showed that rituximab every 6 months was further superior to azathioprine in maintaining remission and preventing relapse.⁵³

The relapse rate of GPA is high. Patients who have been in complete remission for 12 to 18 months have a 50% risk of relapse when therapy is weaned. Maintenance therapy for more than 36 months is associated with lower relapse rate; however, many rheumatologists continue patients on long-term maintenance therapy due to the known high relapse rate in this disease.

All patients receiving immunosuppression with steroids and biologic or nonbiologic DMARDs should also receive prophylactic therapy for PJP⁵⁴ and therapy to reduce osteoporosis.⁵⁵ Patients receiving cyclophosphamide are at risk for gonadal failure and should be monitored for hemorrhagic cystitis and secondary malignancy.

Microscopic Polyangiitis

MPA is a systemic necrotizing vasculitis of small vessels (capillaries, venules, and arterioles) that is associated with ANCA formation but classically on histology has few or no immune deposits (pauci-immune) and in which there is no granuloma formation.⁵⁶

Epidemiology

MPA can affect men and women and may occur at any age, although it is most common between the ages of 30 to 50 years.

Clinical Presentation

Patients present with pulmonary–renal syndrome with almost all patients developing a rapidly progressive pauci-immune glomerulonephritis and approximately 30% of patients developing pulmonary capillaritis with diffuse alveolar hemorrhage.

Laboratory Testing

pANCA with myeloperoxidase specificity (MPO) is seen in 60% of patients, although some patients have evidence of cANCA with specificity against PR-3. In the presence of PR-3, patients with MPA can be distinguished from GPA by the absence of upper respiratory tract involvement.

Renal Histopathology

Renal histopathology shows focal, segmental necrotizing glomerulonephritis with crescent formation, but on immunofluorescence and electron microscopy, no immune deposits are seen (pauci-immune). Lung biopsy shows pulmonary capillaritis with negative immunofluorescence, and biopsy of involved skin usually reveals leukocytoclastic vasculitis.^{56,57}

Treatment

Treatment for MPA is similar to that for GPA and EGPA with induction therapy with IV steroids followed by oral daily

prednisone and either cyclophosphamide or rituximab. During the acute phase of pulmonary hemorrhage, plasmapheresis with IVIG has been used. Maintenance therapy is similar to that for GPA.^{58,59} The prognosis for MPA is guarded,⁶⁰ with 33% of patients relapsing and 20% of patients requiring dialysis. The overall 5-year survival rate is 70% to 75%.

Eosinophilic Granulomatosis with Polyangiitis (Previously Known as Churg–Strauss Syndrome)

Epidemiology

EGPA is a rare (1–4 patients per million) granulomatous vasculitis of the small and medium-sized vessels associated with eosinophilia. Patients with EGPA often have a prior history of allergic disease with 70% having a history of rhinitis often with nasal polyps, and greater than 95% having a history of adult-onset asthma.^{61,62} The ACR criteria for EGPA include asthma, eosinophilia greater than 10%, mono- or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy showing eosinophilic infiltrate. The presence of more than four of these six criteria carries sensitivity of 85% and specificity 99.7% for the diagnosis.⁶²

Pathophysiology

Characteristic histopathologic changes in EGPA include extra-vascular small necrotizing granulomas near small arteries and veins. In contrast to other granulomatous lesions that have a basophilic core, the granulomas in EGPA have a central eosinophilic core surrounded radially by macrophages and giant cells.⁶¹ It is thought that the disease is driven by cytokine pathways that stimulate eosinophils including IL-5. There have been suggestions that leukotriene inhibitors such as montelukast (Singulair) may contribute to the pathogenesis of this disease, since it often becomes clinically apparent when a patient with chronic asthma is started on a leukotriene inhibitor and systemic corticosteroids are weaned. This co-temporal relationship is well recognized, but it remains unclear whether it is causative.⁶¹

Clinical Presentation

The clinical presentation of EGPA is often a triphasic process, although it should be noted that these phases are not always sequential and may present simultaneously. The prodromal phase lasts on average 28 months but may persist for 2 to 7 years. Patients present with symptoms of allergic rhinitis, asthma, and nasal polypsis. In 50% of cases, there are symptoms of recurrent fevers. In addition, during the second phase, peripheral blood and tissue eosinophilia develop with shifting pulmonary infiltrates, chronic eosinophilic pneumonia, and eosinophilic gastroenteritis. Flares during this phase are associated with fever, and myocarditis may also develop during this phase. Life-threatening systemic vasculitis develops on average 3 years after the onset of the prodromal phase, and at this time, the asthma dramatically resolves.⁶³ Patients develop myocarditis, valvular insufficiency, vasculitic peripheral neuropathy, eosinophilic gastroenteritis, purpura, and testicular pain.

Laboratory Findings

The cardinal laboratory finding in EGPA is eosinophilia (>1500 cells/ μ L).⁶² Serologic testing reveals pANCA pattern with anti-MPO specificity, and patients also sometimes have a positive RF. Patients who are ANCA positive have a higher risk of renal disease, alveolar hemorrhage, mononeuritis multiplex, and purpura.

Treatment

Treatment of EGPA involves induction therapy with IV glucocorticoids followed by daily oral prednisone and monthly IV cyclophosphamide. The anti-IL5 monoclonal antibody mepolizumab has recently been shown to be effective as a steroid-sparing agent in EGPA.⁶⁴

VASCULITIS SECONDARY TO CONNECTIVE TISSUE DISEASES

Vascular Manifestations of Behçet Disease

Behçet disease (BD) is a systemic vasculitis of unknown etiology that classically presents with oral and genital ulcers (Fig. 138.3), uveitis, skin lesions, and vascular manifestations. Vascular issues were seen in up to 50% of patients in a large study in Turkey,⁶⁵ and vascular complications are more common in men who develop the disease at a young age. Vascular manifestations include arterial and venous thrombosis and unusual aneurysms, particularly affecting the pulmonary arteries.⁶⁶ Patients are at high risk for thrombotic complications and may develop superficial and deep vein thrombosis, as well as thrombosis of the large central veins, especially the superior and inferior vena cava. Other recognized manifestations include development of hepatic vein thrombosis causing Budd–Chiari syndrome, mesenteric vein thrombosis, renal vein thrombosis, and intracranial thrombosis involving the dural sinus. In BD, thrombus is adherent to the vessel wall and thrombosis may progress despite anticoagulation. Arterial complications are less common than venous problems, occurring in 1% to 7% of patients. Occlusive arterial disease can involve both upper

and lower extremities resulting in ischemic symptoms. The aorta is the most common site of aneurysm formation, with pulmonary, femoral, popliteal, brachial, and iliac arteries also reported in descending order of frequency. Patients often have multiple arterial aneurysms with a saccular configuration, and there is a high risk of rupture, thrombosis, and aneurysm recurrence. Pulmonary artery aneurysms, in particular, can lead to massive and fatal hemoptysis.⁶⁷ Intracranial aneurysms can occur in BD, and successful endovascular treatment has been reported. Care should be taken with line insertion in these patients, since arterial puncture for angiography can result in aneurysm rupture.

Epidemiology

BD is seen worldwide but it is more common in Turkey, the Mediterranean basin, and the Middle and Far East along the historic Silk Road trade route. Typically, the disease presents in young adults aged 20 to 40 years. The pathogenesis of BD is unknown but genetic, infectious, and immunologic factors have been implicated. There is a high prevalence of disease in patients with HLA-B51 genotype, and it is thought that polymorphisms in genes for several proinflammatory cytokines might play a role in disease susceptibility.⁶⁸

Treatment

Treatment of BD involves systemic immunosuppression with glucocorticoids and steroid-sparing DMARD agents, and mucocutaneous lesions often respond to colchicine.⁶⁹ Thalidomide has been used for refractory oral and genital ulcers, and high-dose steroids and cytotoxic agents are used in patients with vasculitis. Relapses are frequent and patients should be closely monitored.⁶⁹

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by autoantibodies to various nuclear antigens. Vasculitis may occur in up to one-third of SLE patients⁷⁰ and most commonly affects the small vessels of the skin (leukocytoclastic vasculitis). Patients often present with tender punctate lesions on the fingertips and palms, but ischemic lesions, nodules and ulcers may also occur. Vasculitis of medium-sized vessels can result in mononeuritis multiplex and lesions in the abdominal viscera, and large-vessel vasculitis with a similar distribution to Takayasu arteritis has also been described. Pulmonary capillaritis in SLE may present with alveolar hemorrhage and carries a high risk of mortality. Inflammatory vasculitis in SLE merits escalation of therapy with steroids and DMARD agents.

Ischemic events related to the antiphospholipid syndrome may mimic vasculitis in SLE and should be considered in the differential diagnosis in lupus patients presenting with digital and skin ulcerations.^{71,72} If antiphospholipid antibodies are present, then anticoagulant therapy and therapy with the antimalarial agent hydroxychloroquine can be of benefit.



Figure 138.3 Large, Painful, Oral Ulcers in a Patient with Behçet Disease.

Rheumatoid Vasculitis

Rheumatoid arthritis vasculitis is a known complication of longstanding rheumatoid arthritis (RA), an inflammatory symmetric polyarthritides. Vasculitis occurs in 10% to 15% of cases, which is usually those with more aggressive disease and high-titer RF. Patients may develop cutaneous ulcers,⁷³ peripheral neuropathy, and scleritis, and mesenteric vasculitis and aortitis may also occur but are rare. Rheumatoid vasculitis is associated with significant morbidity and mortality and should be treated aggressively with high-dose steroids and biologic DMARDs.^{74–77}

Relapsing Polychondritis

Relapsing polychondritis is a rare autoimmune disease manifested with recurrent inflammation of cartilaginous tissues. This disease can also be complicated by large-vessel involvement with aortitis leading to thoracic and abdominal aortic aneurysms.⁷⁸

Cogan Syndrome

Cogan syndrome may present with large and medium-sized vasculitis in a Takayasu-like distribution.⁷⁹ Cogan syndrome is an immune-mediated disorder characterized by interstitial keratitis, vestibular dysfunction, and sensorineural hearing loss. Keratitis symptoms include bilateral redness, pain, and photophobia with increased lacrimation. Other forms of ocular inflammation, including uveitis, scleritis, choroiditis, and retinal artery occlusion, may also occur with or without concomitant keratitis. Vestibular dysfunction presents with tinnitus, vertigo, and sensorineural hearing loss, which may be fluctuating but leads to deafness in more than 50% of cases. Eye and ear involvement usually develop within 1 to 6 months of each other. The mean age of onset is around 30 years, although it has been reported in children and in the elderly. The syndrome is equally distributed in men and women, and there is no racial predilection. Typically at presentation, patients are systemically unwell with constitutional symptoms, fever, arthralgias, serositis, mononeuritis, hepatomegaly, and splenomegaly. Laboratory work-up reveals elevated inflammatory markers but negative autoantibodies, and keratitis usually responds to topical steroids. Vestibular dysfunction merits oral prednisone, and if systemic manifestations are also present, then a steroid-sparing agent such as azathioprine, methotrexate, mycophenolate, or cyclosporine should be added.^{80,81}

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is an inherited systemic disease that can cause early and diffuse arteriopathy in the absence of traditional risk factors.⁸² Small and medium-sized arteries are affected more commonly than the aorta, and patients often present with symptoms of claudication in the lower extremities. Both traditional surgical bypass and percutaneous angioplasty have been used successfully in the management of claudication due to pseudoxanthoma elasticum. In patients with

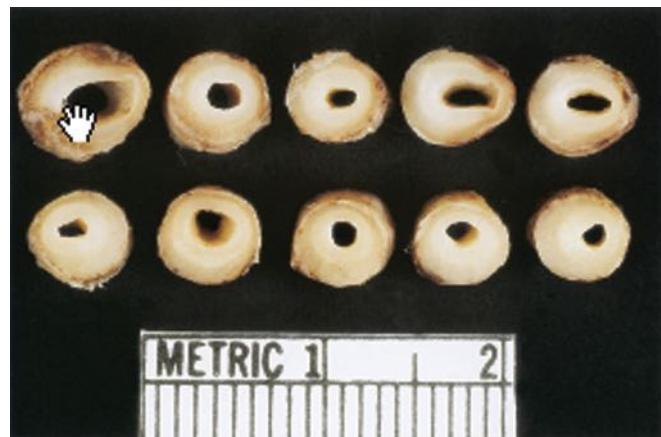


Figure 138.4 Exercise-Related External Iliac Arteriopathy. Photograph of resected external iliac artery, cut in cross-sections, showing luminal stenosis.

pseudoxanthoma presenting with peripheral vascular symptoms, screening for coronary disease is advised since equally severe coronary disease can be identified and can manifest with heart failure due to widespread coronary ischemia or restrictive cardiomyopathy. Because pseudoxanthoma can affect the internal mammary arteries, vein conduits are recommended for coronary bypass. In addition, arterial rupture can occur in the GI and genitourinary tracts, resulting in a higher risk of bleeding with antiplatelet and anticoagulant therapy.

Exercise-Related External Iliac Arteriopathy

Exercise-related external iliac arteriopathy is a syndrome seen in competitive bicyclists and those cycling on average 8000 to 33,000 km/year. The condition occurs in both men and women, and both external iliac arteries may be affected. Repetitive bending and compression of the external iliac artery between the psoas branch, circumflex iliac, and internal epigastric arteries lead to fibrosis and thickening of the arterial wall. Smooth muscle proliferation and intimal thickening is seen (Fig. 138.4), and some cases report complete occlusion as well as spontaneous dissection of the external iliac artery. Typically affected patients report claudication with exercise and diagnosis can be confirmed with resting and exertional ABI following an exercise that is known to induce symptoms. Treatment includes bypass with prosthetic grafts, endarterectomy with patch angioplasty, and bare metal stenting. Patch angioplasty results in better reoperation rates and higher patient satisfaction than balloon angioplasty.

VASCULITIS MIMICS

Several disorders can mimic vasculitis and should be considered in the differential diagnosis when evaluating a patient. Typically, these syndromes do not require long-term immunosuppressant therapy.

Fibromuscular Dysplasia

Fibromuscular dysplasia is a noninflammatory vascular disease that most commonly affects the renal and carotid arteries but

may also affect any vascular bed.⁸³ It should be considered in the differential diagnosis of a patient presenting with noninflammatory vascular lesions and is well reviewed in Chapter 143 (Fibromuscular Dysplasia).

Radiation Arteritis

Epidemiology

External beam radiation for malignancies may cause inflammation and fibrosis in adjacent large arteries and lead to clinically significant stenosis and aneurysm formation. The prevalence of stenosis following radiotherapy can be as high as 30% in the carotid arteries.⁸⁴ In the early phase after irradiation, pathologic changes include endothelial damage, intimal thickening, and smooth muscle loss with fibrosis; over time, calcification and more typical atherosclerosis develop, in some cases, leading to bulky stenosis. Radiation-related vasculopathy has been described in many vascular beds, including cervicocranial stenosis following radiotherapy for esophageal squamous cell carcinoma, the visceral vessels following treatment for lymphoma, and in the iliac arteries after treatment for cervical cancer. There may be a delay of decades between the initial radiation exposure and the presentation with vascular insufficiency.⁸⁵

Pathogenesis

Radiation arteritis results in damage to all layers of the arterial wall, and endothelial cell injury with resultant inflammation predisposes to thrombus formation. Medial necrosis has been described with late fibrosis, and the vasa vasorum may be obliterated as a result of adventitial scarring. Structural injury further predisposes to atherogenesis with lipid deposition and atheroma formation in the region of the prior scar. The result is stenotic lesions similar to those seen in atherosclerosis but in the region of prior radiation exposure rather than a typical location (Fig. 138.5).

Clinical Presentation

Presentation of radiation-induced arteritis is similar to vascular insufficiency from atherosclerotic disease. Carotid lesions may present with transient ischemic attacks, amaurosis fugax, or stroke. Visceral involvement presents with mesenteric angina, and irradiation of iliac and pelvic vasculature can result in

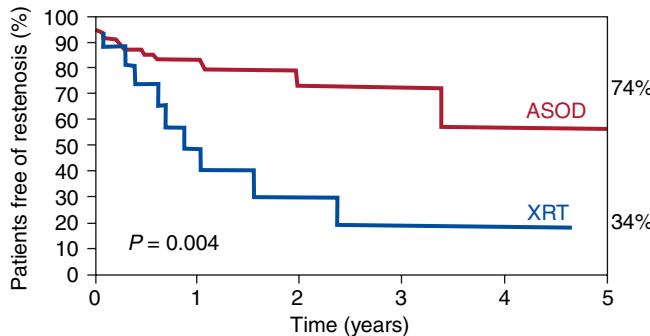


Figure 138.5 Rates of Restenosis Following Carotid Artery Stenting for Radiation-Induced Carotid Artery Stenosis. *ASOD*, atherosclerotic occlusive disease; *XRT*, radiation-induced occlusive disease. (From Protack CD, Bakken AM, Saad WE, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg*. 2007;45:110–117.)

lower extremity intermittent claudication. Embolization with acute vascular ischemia has also been described. Aneurysm formation and rupture are rare but may occur spontaneously or following surgical repair or stenting.

Diagnostic Evaluation

Angiography is the mainstay of work-up with lesions appearing similar to the tapered narrowing of extracranial GCA. The development of accelerated atherosclerosis in regions of previous radiation-induced vascular damage may also lead to the angiographic appearance of friable, typical atheromatous lesions.

Treatment

Because of the risks of postoperative wound infection and poor wound healing associated with open surgical procedures, the use of endovascular techniques to manage radiation-induced arterial stenosis is growing. The most prominent example is carotid stenting (CAS) for symptomatic, and sometimes asymptomatic, radiation-induced carotid stenoses.⁸⁶ In a recent series of 23 patients treated with primary CAS, the 30-day survival and 3-year neurologic event-free survival rates were similar, but the risk of restenosis was greater compared with 127 patients treated with CAS for atherosclerotic carotid disease (Fig. 138.6).⁸⁷ In this series, late restenosis occurred up to about 2.5 years following the procedure. Case series also describe good results from endovascular treatment of renal artery stenosis related to radiation for Hodgkin lymphoma and iliofemoral stenosis related to radiation for genitourinary malignancies.⁸⁸

Neurofibromatosis Type 1

Neurofibromatosis type 1 is an autosomal dominant disorder that results in a loss-of-function mutation of the tumor

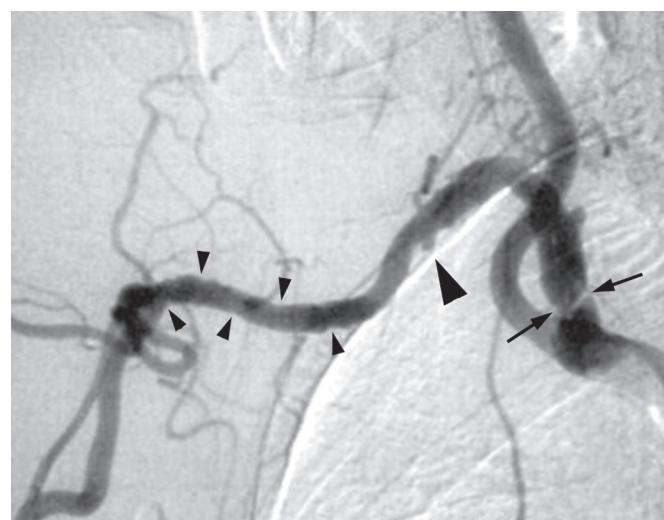


Figure 138.6 Angiogram of a 66-year-old patient presenting with acrocytosis of the fingers and livedo of the skin occurring 21 years after local adjuvant radiation therapy for breast adenocarcinoma. This view of the aortic arch and right upper extremity demonstrates radiation-induced atherosclerosis with an ulcerated plaque at the origin of the subclavian artery (arrows) with diffuse atheromatous changes in the area of prior radiation (arrowheads). (From Rubin DI, Schomberg PJ, Shepherd RF, Panneton JM. Arteritis and brachial plexus neuropathy as delayed complications of radiation therapy. *Mayo Clin Proc*. 2001;76:849–852.)

suppressor gene NF-1. The disease affects 1:3000 individuals. Patients develop neurofibromas along with other tumors including schwannomas and pheochromocytomas. Vascular manifestations are a known complication of NF-1 but are rare,⁸⁹ affecting only 0.4% to 6.4% of NF-1 patients. In young patients, the vascular lesions resemble fibromuscular dysplasia with development of saccular and fusiform aneurysms, stenotic lesions, arteriovenous malformations, and extrinsic compression from neurofibromas. The average age for vasculopathy diagnosis is 38 years. Spontaneous aneurysm rupture can result in life-threatening hemorrhage, and rupture of vertebral artery aneurysms may lead to cervical vertebral arteriovenous malformations. Surgical intervention for vascular lesions in NF-1 is safe and has been determined to be effective and durable.⁸⁹

Drug-Induced Vasculitis

Several drugs are known to result in hypersensitivity vasculitis⁹⁰ including chemotherapeutic agents, growth factors, interferons, antithyroid drugs,^{91,92} hydrochlorothiazide,^{93,94} hydralazine,⁹⁵ minocycline, penicillamine, and vaccines.

Beta-blockers can cause a milder form of vasospasm and exacerbate Raynaud phenomenon. Ergot preparations used to treat migraine headaches can cause a diverse spectrum of vascular syndromes including acute arterial thromboembolism, dissection, and severe vasospasm that angiographically resemble Takayasu arteritis.

Cocaine has been associated with venous and arterial thrombosis, aortic dissection, and hemispheric and lacunar

stroke. Cocaine adulterated with levamisole causes a dramatic small-vessel cutaneous vasculitis that results in skin necrosis and causes tissue loss in the nose, ears, breasts, and digits.⁹⁶ Lesions classically begin as palpable purpura, but as they enlarge, they develop a “cookie cutter” edge. Typically, these lesions are multicentric, do not conform to typical vascular territories, and they are extremely painful. The pain is worse with elevation and improves with dependency. Unless concomitant atherosclerosis is present, patients should have normal pulses. Lesions typically respond to withdrawal of the offending agent, and aggressive wound care and immunosuppressive therapy, occasionally, is warranted.

SELECTED KEY REFERENCES

- Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65(1):1–11.
Revised consensus criteria for classification of vasculitis.
- Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med.* 2013;369(5):417–427.
- Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med.* 2010;363(3):221–232.
Efficacy of rituximab as induction therapy in ANCA-associated vasculitis.
- Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med.* 2003;349(2):160–169.
Review of large- and medium-vessel vasculitis.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Weyand C, Goronzy J. Multisystem interactions in the pathogenesis of vasculitis. *Curr Opin Rheumatol.* 1997;9(1):3–11.
2. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med.* 2003;349(2):160–169.
3. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65(1):1–11.
4. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JP. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med.* 2005;142(5):359–369.
5. Bley TA, Wieben O, Uhl M, et al. High-resolution MRI in giant cell arteritis: imaging of the wall of the superficial temporal artery. *AJR Am J Roentgenol.* 2005;184(1):283–287.
6. Scheel AK, Meller J, Vosshenrich R, et al. Diagnosis and follow up of aortitis in the elderly. *Ann Rheum Dis.* 2004;63(11):1507–1510.
7. Smith CA, Fidler WJ, Pinals RS. The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. *Arthritis Rheum.* 1983;26(10):1214–1219.
8. Kermani TA, Schafer VS, Crowson CS, et al. Increase in age at onset of giant cell arteritis: a population-based study. *Ann Rheum Dis.* 2010;69(4):780–781.
9. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum.* 2011;63(3):633–639.
10. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. The HLA-DRB1 locus as a genetic component in giant cell arteritis. Mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. *J Clin Invest.* 1992;90(6):2355–2361.
11. Weyand CM, Younge BR, Goronzy JJ. IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis. *Curr Opin Rheumatol.* 2011;23(1):43–49.
12. Buttgeriet F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. *J Am Med Assoc.* 2016;315(22):2442–2458.
13. Kuo CH, McCluskey P, Fraser CL. Chewing gum test for jaw claudication in giant-cell arteritis. *N Engl J Med.* 2016;374(18):1794–1795.
14. Bongartz T, Matteson EL. Large-vessel involvement in giant cell arteritis. *Curr Opin Rheumatol.* 2006;18(1):10–17.
15. Liozon E, Herrmann F, Ly K, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. *Am J Med.* 2001;111(3):211–217.
16. Aiello PD, Trautmann JC, McPhee TJ, et al. Visual prognosis in giant cell arteritis. *Ophthalmology.* 1993;100(4):550–555.
17. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* 1990;33(8):1122–1128.
18. Hall S, Persellin S, Lie JT, et al. The therapeutic impact of temporal artery biopsy. *Lancet.* 1983;2(8361):1217–1220.
19. Achkar AA, Lie JT, Hunder GG, et al. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? *Ann Intern Med.* 1994;120(12):987–992.
20. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med.* 2017;377(4):317–328.
21. Zehr KJ, Mathur A, Orszulak TA, et al. Surgical treatment of ascending aortic aneurysms in patients with giant cell aortitis. *Ann Thorac Surg.* 2005;79(5):1512–1517.
22. Stone JH, Brito-Zeron P, Bosch X, Ramos-Casals M. Diagnostic Approach to the Complexity of IgG4-Related Disease. *Mayo Clin Proc.* 2015;90(7):927–939.
23. Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol.* 2015;67(7):1688–1699.
24. Campochiaro C, Tomelleri A, Cavalli G, et al. Erdheim-Chester disease. *Eur J Intern Med.* 2015;26(4):223–229.
25. Gianfreda D, Musetti C, Nicastro M, et al. Erdheim-Chester disease as a mimic of IgG4-related disease: a case report and a review of a single-center cohort. *Medicine (Baltimore).* 2016;95(21):e3625.
26. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood.* 2013;121(9):1495–1500.
27. Lightfoot Jr RW, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum.* 1990;33(8):1088–1093.
28. Guillevin L, Mahr A, Callard P, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore).* 2005;84(5):313–322.
29. Leib ES, Restivo C, Paulus HE. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med.* 1979;67(6):941–947.
30. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med.* 1979;301(5):235–238.
31. Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010;62(2):616–626.
32. Balow JE. Renal vasculitis. *Kidney Int.* 1985;27(6):954–964.
33. Frohnert PP, Sheps SG. Long-term follow-up study of periarteritis nodosa. *Am J Med.* 1967;43(1):8–14.
34. Briggs JD, Jones E. Renal transplantation for uncommon diseases. Scientific Advisory Board of the ERA-EDTA Registry. European Renal Association-European Dialysis and Transplant Association. *Nephrol Dial Transplant.* 1999;14(3):570–575.
35. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med.* 2014;370(10):911–920.
36. Olin JW. Thromboangiitis Obliterans (Buerger's Disease). *N Engl J Med.* 2000;343(12):864–869.
37. Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol.* 2006;18(1):18–24.
38. Puechal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. *Rheumatology (Oxford).* 2007;46(2):192–199.
39. Fiessinger JN, Schafer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. The TAO Study. *Lancet.* 1990;335(8689):555–557.
40. Sasajima T, Kubo Y, Inaba M, et al. Role of infrainguinal bypass in Buerger's disease: an eighteen-year experience. *Eur J Vasc Endovasc Surg.* 1997;13(2):186–192.
41. Dilege S, Aksoy M, Kayabali M, et al. Vascular reconstruction in Buerger's disease: is it feasible? *Surg Today.* 2002;32(12):1042–1047.
42. Nishikimi N. Fate of limbs with failed vascular reconstruction in Buerger's disease patients. *Int J Cardiol.* 2000;75(suppl 1):S183–S185; discussion S183–S185.
43. Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol.* 2016;67(14):1738–1749.
44. Printz BF, Sleeper LA, Newburger JW, et al. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease. *J Am Coll Cardiol.* 2011;57(1):86–92.
45. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2004;110(17):2747–2771.
46. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med.* 2020;383(4):334–346.
47. Jayne DR, Gaskin G, Pusey CD, Lockwood CM. ANCA and predicting relapse in systemic vasculitis. *QJM.* 1995;88(2):127–133.

48. Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum.* 2008;58(9):2908–2918.
49. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med.* 2010;363(3):211–220.
50. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med.* 2010;363(3):221–232.
51. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med.* 2013;369(5):417–427.
52. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003;349(1):36–44.
53. Guillemin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med.* 2014;371(19):1771–1780.
54. Ognibene FP, Shelhamer JH, Hoffman GS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. *Am J Respir Crit Care Med.* 1995;151(3 Pt 1):795–799.
55. Hant FN, Bolster MB. Drugs that may harm bone: Mitigating the risk. *Cleve Clin J Med.* 2016;83(4):281–288.
56. Kallenberg CG. The diagnosis and classification of microscopic polyangiitis. *J Autoimmun.* 2014;48–49:90–93.
57. Kallenberg CGM, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. *Nat Clin Pract Rheumatol.* 2006;2(12):661–670.
58. Lopalco G, Rigante D, Venerito V, et al. Management of small vessel vasculitides. *Curr Rheumatol Rep.* 2016;18(6):36.
59. Khasnis A, Langford CA. Update on vasculitis. *J Allergy Clin Immunol.* 2009;123(6):1226–1236.
60. Yegin EG, Can M, Yilmaz N, et al. Activity and damage in granulomatosis with polyangiitis. *Int J Rheum Dis.* 2013;16(1):61–71.
61. North I, Strek ME, Leff AR. Churg-Strauss syndrome. *Lancet.* 2003;361(9357):587–594.
62. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990;33(8):1094–1100.
63. Lanham JG, Elkorn KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore).* 1984;63(2):65–81.
64. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med.* 2017;376(20):1921–1932.
65. Sarica-Kucukoglu R, Akdag-Kose A, Kayabal IM, et al. Vascular involvement in Behcet's disease: a retrospective analysis of 2319 cases. *Int J Dermatol.* 2006;45(8):919–921.
66. Hamuryudan V, Er T, Seyahi E, et al. Pulmonary artery aneurysms in Behcet syndrome. *Am J Med.* 2004;117(11):867–870.
67. Seyahi E, Yazici H. Behcet's syndrome: pulmonary vascular disease. *Curr Opin Rheumatol.* 2015;27(1):18–23.
68. Yazici H, Fresko I, Yurdakul S. Behcet's syndrome: disease manifestations, management, and advances in treatment. *Nat Clin Pract Rheumatol.* 2007;3(3):148–155.
69. Hatemi G, Silman A, Bang D, et al. EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis.* 2008;67(12):1656–1662.
70. Cozzani E, Gasparini G, Papini M, et al. Vasculitis associated with connective tissue diseases. *G Ital Dermatol Venereol.* 2015;150(2):221–232.
71. Shanmugam V, Schilling A, Attinger C. Connective tissue disease associated vasculopathic wounds. *Clin Transl Sci.* 2011;4(2):100.
72. Shanmugam V, Steen V, Cupps T. Lower extremity ulcers in connective tissue disease. *Isr Med Assoc J.* 2008;10(7):534–536.
73. Shanmugam V, DeMaria D, Attinger C. Lower extremity ulcers in rheumatoid arthritis: features and response to immunosuppression. *Clin Rheumatol.* 2011;30(6):849–853.
74. Assmann G, Pfreundschuh J, Voswinkel J. Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers. *Clin Exp Rheumatol.* 2010;28(1 suppl 57):81–83.
75. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. *Br J Dermatol.* 2002;147(5):905–913.
76. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. *Ann Rheum Dis.* 2003;62(6):587–588.
77. Watts RA, Mooney J, Lane SE, Scott DGI. Rheumatoid vasculitis: becoming extinct? *Rheumatology.* 2004;43(7):920–923.
78. Chopra R, Chaudhary N, Kay J. Relapsing polychondritis. *Rheum Dis Clin North Am.* 2013;39(2):263–276.
79. Espinoza GM, Prost A. Cogan's syndrome and other ocular vasculitides. *Curr Rheumatol Rep.* 2015;17(4):24.
80. Greco A, Gallo A, Fusconi M, et al. Cogan's syndrome: an autoimmune inner ear disease. *Autoimmun Rev.* 2013;12(3):396–400.
81. Kessel A, Vadasz Z, Toubi E. Cogan syndrome-pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* 2014;13(4–5):351–354.
82. Chassaing N, Martin L, Calvas P, et al. Pseudoxanthoma elasticum: a clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations. *J Med Genet.* 2005;42(12):881–892.
83. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004;350(18):1862–1871.
84. Moritz MW, Higgins RF, Jacobs JR. Duplex imaging and incidence of carotid radiation injury after high-dose radiotherapy for tumors of the head and neck. *Arch Surg.* 1990;125(9):1181–1183.
85. Aoki S, Hayashi N, Abe O, et al. Radiation-induced arteritis: thickened wall with prominent enhancement on cranial MR images report of five cases and comparison with 18 cases of Moyamoya disease. *Radiology.* 2002;223(3):683–688.
86. Leseche G, Castier Y, Chataigner O, et al. Carotid artery revascularization through a radiated field. *J Vasc Surg.* 2003;38(2):244–250.
87. Protack CD, Bakken AM, Saad WE, et al. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg.* 2007;45(1):110–117.
88. Jurado JA, Bashir R, Burkett MW. Radiation-induced peripheral artery disease. *Catheter Cardiovasc Interv.* 2008;72(4):563–568.
89. Oderich GS, Sullivan TM, Bower TC, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. *J Vasc Surg.* 2007;46(3):475–484.
90. Grau RG. Drug-induced vasculitis: new insights and a changing lineup of suspects. *Curr Rheumatol Rep.* 2015;17(12):71.
91. Miller RM, Savige J, Nassif L, Cominos BI. Antineutrophil cytoplasmic antibody (ANCA)-positive cutaneous leucocytoclastic vasculitis associated with antithyroid therapy in Graves' disease. *Australas J Dermatol.* 1998;39(2):96–99.
92. Gunton JE, Stiel J, Clifton-Bligh P, et al. Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. *Eur J Endocrinol.* 2000;142(6):587.
93. Shah P, Chillag S. Leukocytoclastic vasculitis due to hydrochlorothiazide. *JSC Med Assoc.* 2007;103(7):194–196.
94. Bjornberg A, Gisslen H. Thiazides: a cause of necrotising vasculitis? *Lancet.* 1965;2(7420):982–983.
95. Agarwal G, Sultan G, Werner SL, Hura C. Hydralazine induces myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibody vasculitis and leads to pulmonary renal syndrome. *Case Rep Nephrol.* 2014;2014:868590.
96. Belfonte CD, Shanmugam VK, Kieffer N, et al. Levamisole-induced occlusive necrotising vasculitis in cocaine abusers: an unusual cause of skin necrosis and neutropenia. *Int Wound J.* 2013;10(5):590–596.

Thromboangiitis Obliterans

AHMET RÜÇHAN AKAR, MUSTAFA BAHADIR İNAN, and MEHMET CAHIT SARİCAOĞLU

INTRODUCTION	1823
Definition	1823
Brief Historical Review	1824
EPIDEMIOLOGY	1824
Population Affected	1824
Risk Factors	1824
Etiology	1825
<i>Immune-Mediated Injury</i>	1825
<i>Genetic Predisposition</i>	1826
<i>Hypercoagulability</i>	1826
<i>Oral Infection–Inflammatory Pathway</i>	1826
<i>Rickettsia Infection</i>	1826
<i>Vascular Endothelium and Circulating Progenitor Cells</i>	1826
Pathology	1826
CLINICAL PRESENTATION	1827
DIAGNOSIS	1829
Vascular Evaluation	1830
Noninvasive Testing	1830
Laboratory Testing	1831
Angiography	1832
Biopsy	1832
Differential Diagnosis	1833
Natural History	1834
TREATMENT	1835
Lifestyle Changes	1835
<i>Smoking Cessation</i>	1835
<i>Exercise Training</i>	1835
<i>Trigger Avoidance, Foot, Hand, and Dental Care</i>	1836
Pharmacologic Treatment	1836
<i>Calcium Channel Blockers</i>	1836
<i>Prostacyclin Analogs</i>	1836
<i>INTRAVENOUS ILOPROST</i>	1836
<i>ORAL ILOPROST</i>	1837
<i>Prostaglandin E1 Analogs</i>	1837
<i>Phosphodiesterase (PDE) Inhibitors</i>	1837
<i>PDE3 INHIBITORS (CILOSTAZOL)</i>	1837
<i>PDE5 INHIBITORS (SILDENAFIL, TADALAFIL)</i>	1837
<i>Endothelin Receptor Antagonists</i>	1837
<i>Thrombolytics</i>	1837
<i>Folate Supplementation</i>	1838
<i>Statins</i>	1838
<i>Analgesia</i>	1838
<i>REGIONAL SYMPATHETIC BLOCKADE</i>	1838
<i>SPINAL CORD STIMULATION</i>	1838
Surgery	1838
<i>Lumbar or Thoracic Sympathectomy</i>	1838
<i>Distal Surgical Revascularization</i>	1838
<i>Pedicled Omental Graft</i>	1839
<i>Distal Venous Arterialization</i>	1839
<i>Local Wound Care</i>	1839
<i>Endovascular Treatment</i>	1839
<i>Other Interventional Procedures</i>	1839
<i>Immunoabsorption</i>	1839
<i>Growth Factors</i>	1839
<i>Stem Cell-Based Therapeutic Angiogenesis</i>	1840
CHAPTER ALGORITHM	1841

INTRODUCTION

Definition

Thromboangiitis obliterans (TAO), also known as Buerger disease (BD) or von Winiwarter–Buerger syndrome, is a rare inflammatory, nonatherosclerotic, occlusive, peripheral vascular

disease primarily involving infrapopliteal and infrabrachial medium and small-sized arteries and veins.^{1–14} It is predominantly a disease of young men, with onset typically before the age of 45 to 50 years.^{3–16} The prevalence in women, however, has been increasing related to increased tobacco use.^{1,11–13,17,18} The disease is more common among people of the Middle East, Asia, Mediterranean region, and Eastern Europe but is rare in

Africa, Western Europe, and North America.^{11–13} TAO is typically manifested by distal extremity ischemia involving the feet, legs, or hands leading to critical limb ischemia (CLI), ischemic ulcerations, digital gangrene, and limb infection.^{3,11–13,19}

TAO develops as a response to environmental factors primarily with smoking, resulting in major and minor amputations with a high degree of morbidity and disability resulting in unemployment, psychological, behavioral, social, and financial costs.^{3,11–13} Pathologically, TAO is characterized by a highly inflammatory thrombus and preservation of all layers of the arterial wall, including internal elastic lamina.^{11–13,20} The disease frequently involves adjacent or superficial veins and nerves. TAO has been classified under non-necrotizing, non-granulomatous, medium, and small-vessel vasculitis.¹⁷ However, TAO has not been included in the revised 2012 Chapel Hill consensus conference nomenclature of vasculitis.^{21,22} Absence of markers of inflammation and autoantibodies is unique for TAO compared to other types of vasculitis.^{3,23} Patients experience periods of acute exacerbation leading to CLI associated with smoking. Remissions follow abstinence from tobacco or occur in the fifth to sixth decades of life. Rare reports of cerebral, coronary, visceral, ophthalmic, and multi-organ involvements have also been described. Reduction in the extremity amputation rate can be achieved by smoking cessation. For optimal outcomes, an interdisciplinary care team approach is required for the management of TAO patients.²⁴

Brief Historical Review

Reports resembling TAO have appeared in medical writings since the mid-1800s, but the cases were labeled arteriosclerosis obliterans (ASO) or frostbite because of the lack of pathologic confirmation.²⁵ In 1879, Felix von Winiwarter described a 57-year-old man with a lengthy history of foot pain that eventually progressed to gangrene and limb loss, which is now recognized as the first published case of a patient with CLI.^{3,25,26} In 1898, Haga reported similar clinical features resulting in spontaneous gangrene.²⁷ In 1908, Leo Buerger described a new and unusual form of progressive vaso-occlusion in Polish and Russian immigrants who underwent amputation for “Spontan-gangrān”.¹ Based on his findings, Buerger called the disease “*thromboangiitis obliterans*” to distinguish it from ASO. Subsequently, Buerger emphasized the association of migrating thrombophlebitis with thrombo-angiitis.²⁸ Buerger’s 32-chapter, 628-page monograph entitled “*The Circulatory Disturbances of the Extremities*” was published in 1924.²⁹ Allen and Brown reviewed 200 patients diagnosed with TAO who were evaluated at the Mayo Clinic from 1922 to 1926.³⁰ However, between the 1930s and 1960s, numerous investigators expressed skepticism concerning the identity of TAO.^{31–33} In the early 1960s, several authorities considered TAO a distinct diagnosis that should be separated from ASO.^{34–38} Today, TAO is accepted as a definite medium and small-vessel vasculitis with a typical clinical picture, natural history, and histopathology.^{3,6,7,18,39,40}

EPIDEMIOLOGY

Population Affected

According to the World Health Organization (WHO), there are currently an estimated 1.3 billion smokers globally, and over 80% live in low- and middle-income countries. TAO is found worldwide and affects both sexes and all races; however, the incidence varies by geographic location,^{3,7,17,23,41,42} and uneven gender distribution.^{3,43–46} Buerger’s view of the disease as being restricted mainly to the Jewish race is no longer valid.^{29,47} TAO is more common in the Middle East, Asia, the Mediterranean, and Eastern Europe but is rare in Africa, central Europe, and North America. The prevalence of TAO among all patients with peripheral arterial disease varies throughout the world; 0.75% in North America, 0.5 to 5.6% in Western Europe, 3%–39% in Eastern Europe, 6.6% in Turkey, 80% Israel among Jews of Ashkenazi ancestry, 16% in Japan, 66% in Korea, and 45%–63% in India.^{3,44,48–52}

TAO has a striking predominance in men, especially in series reported before 1960. The reported incidence of TAO in women was less than 1% in most published series in that era.⁵³ Indeed, only two of Buerger’s 500 reported cases were women.²⁹ However, TAO is no longer exclusively seen in the male population.^{17,54–57} Rising use of tobacco products by young women lead to the decrease in gender differences in the current series, in which 9.8% to 30% of patients were women.^{5,18,44,58,59} Currently, TAO affects men at a 4-fold to a 10-fold higher rate than women.^{5,7,44,54,59,60} A limited number of pregnancies among patients with active TAO has also been reported.^{61–64}

There was an 8-fold decrease in the annual incidence of TAO at the Mayo Clinic (from 104 in 1947 to 12.6 in 1986, per 100,000 patient registrations).^{18,65} The number of new patients with TAO in Japan has also been decreasing⁶⁶; the ratio of TAO to ASO patients has declined from 1:3 in the 1990s to 1:10 after 2000 in Japan.⁶⁶ Currently, TAO affects approximately 10 in 100,000 people in the European Union (estimated from the applications to the Committee for Orphan Medicinal Products). The number of patients affected by TAO is estimated at 51,000 in the European Union, and 4000 in Japan.⁶⁷ The pooled characteristics of patients with TAO are listed in Table 139.1.

Risk Factors

The only risk factor consistently reported is smoking. The strong correlation between tobacco use and the pathogenesis, initiation, and progression of the disease is well established.^{5,7,8,39,41,68–70} There is also a higher incidence of TAO among individuals with cigar and pipe smoking; habitual home-made cigarette smoking such as “*bidi*” smoking in India, Bangladesh, and Ceylon⁷¹; “*kawung*” smoking in Indonesia^{72,73}; and chewed “*miang*” (steamed tea leaves) or “*khiyo*” (the home-made raw tobacco in hand-rolled banana leaves) smoking in Thailand, or mixing cannabis with tobacco in hand-rolled cigarettes in France⁷⁴ as

TABLE 139.1

Pooled Characteristics of Patients with Thromboangiitis Obliterans from Different Regions Globally

Prevalence	Uncommon
Prevalence in woman	Increasing
Incidence	Declining
Involved arterial size	Medium and small
Age at onset of symptoms (years)	29–44
Age at diagnosis (years)	29–42
Age at hospital admission (years)	42.5± 8.4
Male, %	77–98
Female, %	2–23
History of tobacco smoking, %	93–98.7
History of cannabis smoking, %	22.8
Familial history, %	1–6.7
Intermittent claudication, %	17–62
Upper limb only, %	1.8
Lower limb only, %	41.5
Both upper and lower limb, %	7.1
Rest pain, %	13–89
Upper limb only, %	26.3
Lower limb only, %	37.5
Both upper and lower limb, %	7.1
Ischemic ulcers and gangrene, %	31.5–85
Upper limb only, %	8.5
Lower limb only, %	19.2
Both upper and lower limb, %	3.1
Limb infection	8.8
Migratory superficial phlebitis, %	16–62
Deep vein thrombosis, %	Unusual
Raynaud phenomenon, %	10–45
Sensory findings, %	69
Abnormal Allen test, %	63
Joint manifestations, %	7.6–12.5

Analysis adapted from refs 3, 7, 23, 52, 149, 266.

well as in users of smokeless tobacco and marijuana.^{7,75–78} Lower socioeconomic status, poor oral hygiene, nutritional deficits, a history of viral or fungal infection, cold injury, abuse of sympathomimetic drugs, and arsenic intoxication are reported as other possible risk factors.^{20,72,79–85} An emerging body of evidence demonstrates that ischemia induced by cocaine, amphetamines, and cannabis addiction can closely mimic TAO symptoms^{86–91} or may accelerate TAO onset and presentation.⁹¹ Furthermore, a close relation between long-term arsenic exposure from artesian well water and endemic Blackfoot disease has been reported in Taiwan.^{92,93} In fact, arsenic adulteration of tobacco as a causative agent for TAO has been suggested in populations smoking bidis or kawung.^{83,94–96}

Etiology

The etiology of TAO is unknown; however, the close association between disease activity and tobacco use in any form is beyond any debate.^{3,9,18,45,70,97,98} Genetic predisposition, immune-mediated mechanisms, hypercoagulable states, endothelial dysfunction, and an oral infection–inflammatory pathway have been implicated as potential etiologic factors.^{59,99–101}

Immune-Mediated Injury

Several observations implicate an immunologic phenomenon and hypersensitivity to tobacco antigens in the etiology of TAO.¹⁰² There is a close relationship between active smoking (high levels of urinary cotinine) and the aggravation of TAO.^{103,104} Increased cellular sensitivity to collagen type I,^{105–107} type III,¹⁰⁶ and type IV¹⁰⁸ has been reported in patients with TAO compared to ASO patients and healthy male controls. Circulating immune complexes have been reported in the peripheral arteries of some patients with TAO.^{109–111} It has been suggested that an unidentified antigen possibly related to a constituent of tobacco smoke triggers immunologic damage to the arterial intima.¹¹² Recent research has shown that T cell-mediated cellular and B cell-mediated humoral immunity associated with the activation of macrophages or dendritic cells in the intima play a key role in TAO.²⁰

Previous studies showed activation of endothelial cells associated with TNF-alpha secretion by tissue-infiltrating mononuclear inflammatory cells and expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin on endothelial cells in TAO patients.¹¹³ Increased levels of TNF-alpha, IL-1beta, IL-4, IL-6, IL-12, IL-17 and IL-23, and reduced expression of IL-10 were reported in patients with TAO compared to the controls suggesting the involvement of autoimmune pathology.^{114,115} An experimental study further reported the critical role of high-mobility group box protein 1 (HMGB1), which may contribute to TAO's pathogenesis by binding its receptor RAGE in sodium laurate-induced TAO rats.¹¹⁶ HMGB1 not only induces the production of inflammatory mediators by mononuclear cells but also activates endothelial cells, leading to the upregulation of the adhesion molecules. rA box, the antagonist of HMGB1, improved the pathologic condition by inhibiting the release and injury of inflammatory mediators and improving the hypercoagulable state of the blood.¹¹⁶ Furthermore, a recent clinical study confirmed significant increases in HMGB-1, MMP-9, and ICAM-1 levels compared with controls in patients with TAO.¹¹⁷ Thus, immunologically mediated inflammation of the vessels is thought to be the cause of arterial or venous thrombosis and vascular occlusions in TAO.

The clinical picture of antiphospholipid syndrome in young smokers may mimic TAO symptoms.¹¹⁸ The prevalence of anticardiolipin antibodies was significantly higher in patients with TAO (36%) than in those with premature atherosclerosis (8%; $P = 0.01$) and in healthy individuals (2%; $P = 0.001$).¹¹⁹ Patients with TAO and high anticardiolipin antibodies tended to be younger and had a significantly higher rate of major

amputations and poor prognosis than those without the antibody.^{120,121} Antineutrophil cytoplasmic antibodies (AN-CAs)¹²² and antiendothelial cell antibodies¹²³ were also reported in small series of TAO; however, in another study from Germany ANCA was not detected in any of the active or inactive TAO patients.¹²⁴

Genetic Predisposition

Some evidence supports the hypothesis that TAO may have a genetic predisposition to tobacco sensitivity.^{106,112,125} One percent of TAO cases in Japan consisted of members of the same family.¹²⁶ Various human leukocyte antigen (HLA) class I (A, B) and class II (DRB1) haplotypes have been demonstrated with a higher frequency in the TAO population from different countries.^{127–132} Current concepts suggest that the arterial vasospasm of TAO may be caused by an interaction between smoking and several gene polymorphisms that reduce endogenous nitric oxide, an endothelium-derived vasodilator. Recently, a higher incidence of mutations associated with arterial vasospasm, for example 5A/6A stromelysin-1, also called matrix metalloproteinase-3, homozygosity, were reported in TAO cases compared to controls.¹³³ A case-control study from China reported that single-nucleotide polymorphisms, namely rs376511 and rs10178082, were associated with TAO in the Uyghur population.^{134,135} Findings regarding the genetic predisposition of TAO should be confirmed in larger studies.

Hypercoagulability

The role of thrombotic risk factors in the etiology of TAO remains controversial.^{136–145} Most authorities have failed to identify a specific hypercoagulable state in patients with TAO^{7,136}; others have shown one or more abnormalities.^{136,137}

Oral Infection–Inflammatory Pathway

Historically, Buerger and then Allen and Brown suspected that infectious foci, including oral and throat infections, might serve as contributory factors in TAO.³⁰ A higher prevalence of the severe periodontal disease in TAO patients is well documented,^{99,146–148} suggesting oral infection–inflammatory pathway as a possible etiologic link in TAO.⁹⁹ Elevated immunoglobulin G titers against *T. denticola*, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* were detected in patients with TAO.¹⁴⁷ Several bacterial DNAs of periodontal pathogens were identified in the biopsies from the arterial samples and samples of migrating phlebitis in patients with TAO.^{99,149,150}

Rickettsia Infection

Initially, Bartolo et al.¹⁵¹ claimed Rickettsia as the main etiological factor in TAO, after showing antibodies against different species of Rickettsia in TAO patients. Recently, Fazeli et al.¹⁵² reported *Rickettsia rickettsii* antibodies in 26 among 28 patients and Rickettsia by a polymerase chain reaction in 3 out of 25 biopsy samples from the amputated limb of a young man diagnosed with TAO. Some investigators believe that *Rickettsia rickettsii* infection could be the missing piece in the Buerger disease etiology.¹⁵³

Vascular Endothelium and Circulating Progenitor Cells

Endothelium-dependent vasorelaxation was impaired even in the non-diseased limbs of patients with TAO.¹⁵⁴ During the exacerbation phase, TAO is associated with a diffuse increase in vasoconstrictor tone in the conduit arteries that aggravates ischemia.¹⁵⁵ In another study, similar to ASO patients, flow-mediated vasodilation was impaired compared to normal control subjects; however, the number and function of circulating progenitor cells (CPCs) were restored despite endothelial dysfunction in patients with TAO.¹⁵⁶ Increased levels of plasma endothelin-1 were also reported during the exacerbation periods of TAO.¹⁵⁷

Pathology

The specific pathologic mechanisms in TAO are still unknown.¹⁰⁰ Buerger disease is characterized by segmental inflammatory cell infiltration of the vessel wall and arterial or venous thrombotic occlusions.^{20,41,158} Hypercellular, inflammatory thrombus formation and preserved architecture of vessel walls are well established in TAO.¹⁵⁹ Earlier studies suggested TAO as a thrombotic disorder complicated by vasculitis, namely transmural neutrophilic infiltration.^{47,160} Today, there are compelling reasons to believe that the first event is the activation of antigen-presenting cells following endothelial cell damage induced by an unidentified antigen, possibly tobacco glycoproteins.^{20,66,112,159} Cellular and humoral inflammation, which leads to thrombotic occlusion of the blood vessels, is restricted to the intima of the artery, which defines TAO as an endarteritis.^{20,66} Intimal inflammation followed by T-cell infiltrations might result in early arterial occlusion, which is the pathognomonic finding in TAO.¹⁶¹ Inflammatory cell infiltration is found in the intimal layer and the thrombus.^{20,162}

The evolution of TAO is often categorized into three stages.⁴⁷ In the acute phase, inflammation affecting the small-caliber and medium-caliber (1- to 5-mm diameter) arteries and veins is observed (Fig. 139.1). The primary features of TAO during the acute phase include occlusive, highly cellular arterial thrombus, polymorphonuclear cell infiltration, giant cells, and micro-abscess formation; marked inflammation of the entire vessel wall and neurovascular bundle.^{35,65,69} However, most of the infiltrating cells are detected in the intima.⁶⁶ The intense inflammatory infiltration and cellular proliferation seen in acute lesions are distinctive, especially when veins are involved. Multinucleated giant cells can be seen, but fibrinoid necrosis and granuloma are not observed.²⁰ During the intermediate or subacute phase, there is a progressive organization of the occlusive thrombus, with partial recanalization and disappearance of the microabscesses.²⁰ An inflammatory response, including CD3+ pan-T cells, CD4+ T helper-inducer cells, and CD20+ pan-B cells, against the internal elastic lamina of the affected vessels, has been shown in detail (Fig. 139.2).^{20,161,162} In addition, CD68+ macrophages or S-100+ dendritic cells are found in the intima during both the acute and subacute stages.⁶⁶ IgG, IgM, and IgA and complement factors 3d and 4c are deposited along the inner aspect of the

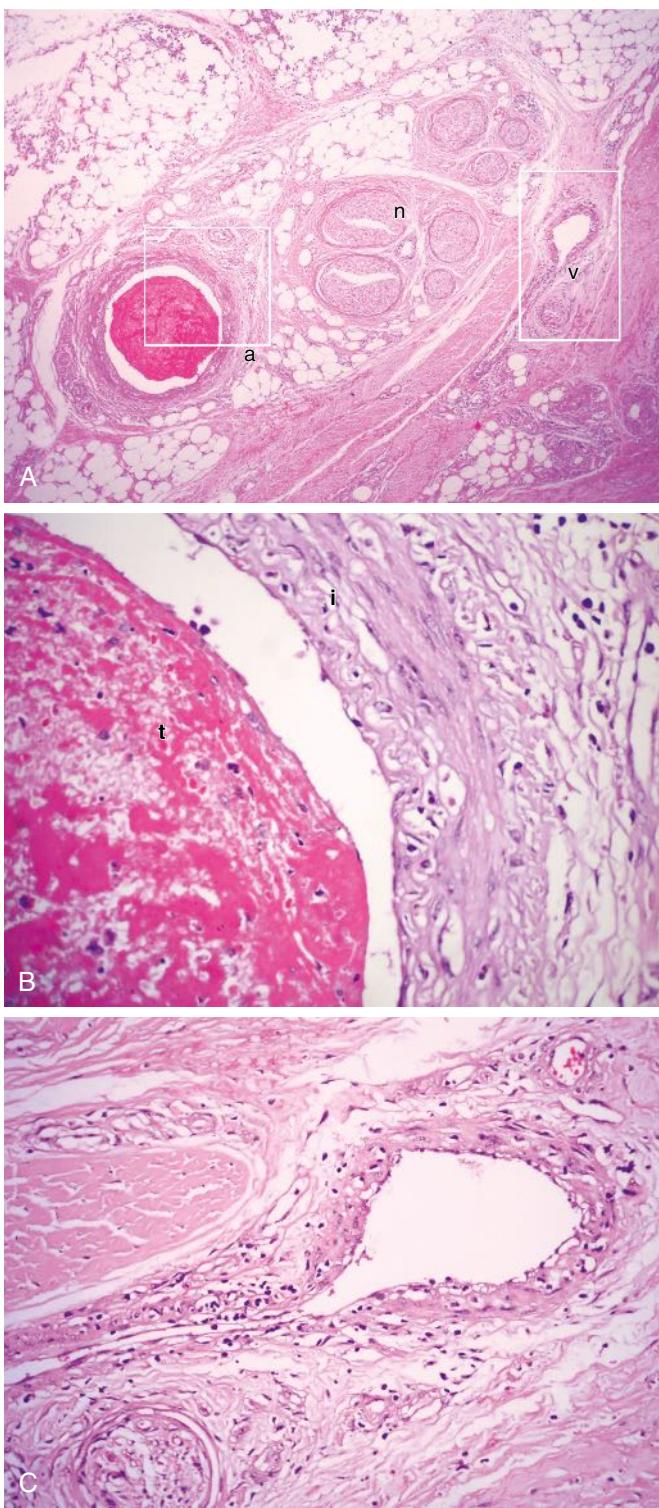


Figure 139.1 (A) Typical subacute thrombotic occlusion of the right digital artery in a 37-year-old male smoker with Buerger disease (H&E, $\times 64$). (B) High-power view of area *a* in A demonstrating the digital artery with cellular arterial thrombus (*t*) and remarkable inflammation in the intima (*i*) (H&E, $\times 400$). (C) High-power view of area *v* in A demonstrating the adjacent digital vein with phlebitis (H&E, $\times 400$). *n*, nerve.

internal elastic lamina.²⁰ The chronic phase or end-stage lesion is characterized by thrombus organization followed by recanalization, prominent vascularization of the media, and perivascular fibrosis.^{47,69,158} Regardless of the pathologic stage, the internal elastic lamina and the architecture of the vascular walls

are well preserved in TAO, in contrast with atherosclerosis and other types of systemic vasculitis (Fig. 139.3).^{3,20,47,69,163}

CLINICAL PRESENTATION

TAO usually presents with distal extremity ischemia in a smoker younger than 50 years old.^{6,164} The median age at diagnosis is 34 years.^{7,165} Characteristically, distal extremity ischemia involves the feet, legs, hands, or arms (Fig. 139.4A and B). As the disease progresses, it may affect more proximal arteries.⁶⁹ Frequently identified signs and symptoms of TAO are listed in Table 139.1. The most common symptoms are forefoot arch or lower calf claudication as a manifestation of infra-popliteal occlusive disease.⁶⁹ Foot claudication is particularly characteristic.¹⁶⁶ Foot or arch claudication may be misattributed to orthopedic problems. Early symptoms may include coldness or burning pain in the feet and hands, associated findings of dependent rubor,¹⁶⁷ cyanosis, migratory superficial thrombophlebitis (Fig. 139.4C),^{149,168} and Raynaud phenomenon.^{5,72,169,170} Patients with TAO commonly report cold sensitivity, and sensory findings may be one of the earliest manifestations. In the Cleveland Clinic series published by Olin and colleagues, 69% of cases revealed sensory findings.⁵ Ischemic neuritis or superficial thrombophlebitis may also produce severe pain.¹⁷¹ Migrating phlebitis (phlebitis saltans) may occur as an early sign and has been reported in 40% to 65% of TAO patients during the course of the disease.^{168,172,173} Ascending venography and histological investigations suggest that 60% of the cases have venous involvement.¹⁷⁴ Occasionally, superficial thrombophlebitis may extend into the deep venous system. However, deep venous thrombosis in Buerger disease is unusual.¹⁷³ In the acute phase of the disease, involved vessels are tender and indurated and reflect the local inflammatory reaction.

Late findings may present as trophic nail changes, ischemic ulcerations, and digital gangrene.^{7,46,52,69,172,175,176} Almost all ulcers occur in patients between the age of 20 and 50 years.¹⁷⁷ Superinfection commonly develops, and the ischemic ulcerations progress toward necrosis and distal gangrene. At this stage, the pain is often excruciating. Ischemic ulcerations often appear dry and irregular, with a pale base and various shapes.^{56,178} Joint manifestations – mainly transient, migratory episodes of large joint arthritis involving wrist and knees – may occur in approximately 12.5% of patients before the onset of digital ischemia.^{23,173,179,180} Subungual splinter hemorrhages may be detected as an early sign.^{173,181,182} Coexisting psychological conditions are also common, primarily anxiety, depression, amputation, and unemployment-related fears.¹⁸³ No difference in clinical presentation in women compared with men has been observed.^{5,184}

TAO does not occur in only one limb.¹⁷³ Multiple limb involvement is a common feature of TAO.^{3,69,76,185,186} In the series reported by Shionoya, two limbs were affected in 16% of patients, three limbs in 41%, and all four limbs in 43% of patients.¹⁸⁵ The Intractable Vasculitis Syndromes Research Group of Japan reported isolated lower extremity involvement in 75%, only upper extremity involvement in 5%, and both upper and lower extremity involvement in 20% of patients with TAO (Table 139.2).¹⁸⁷ Therefore, it is recommended that noninvasive imaging of all extremities be performed in patients

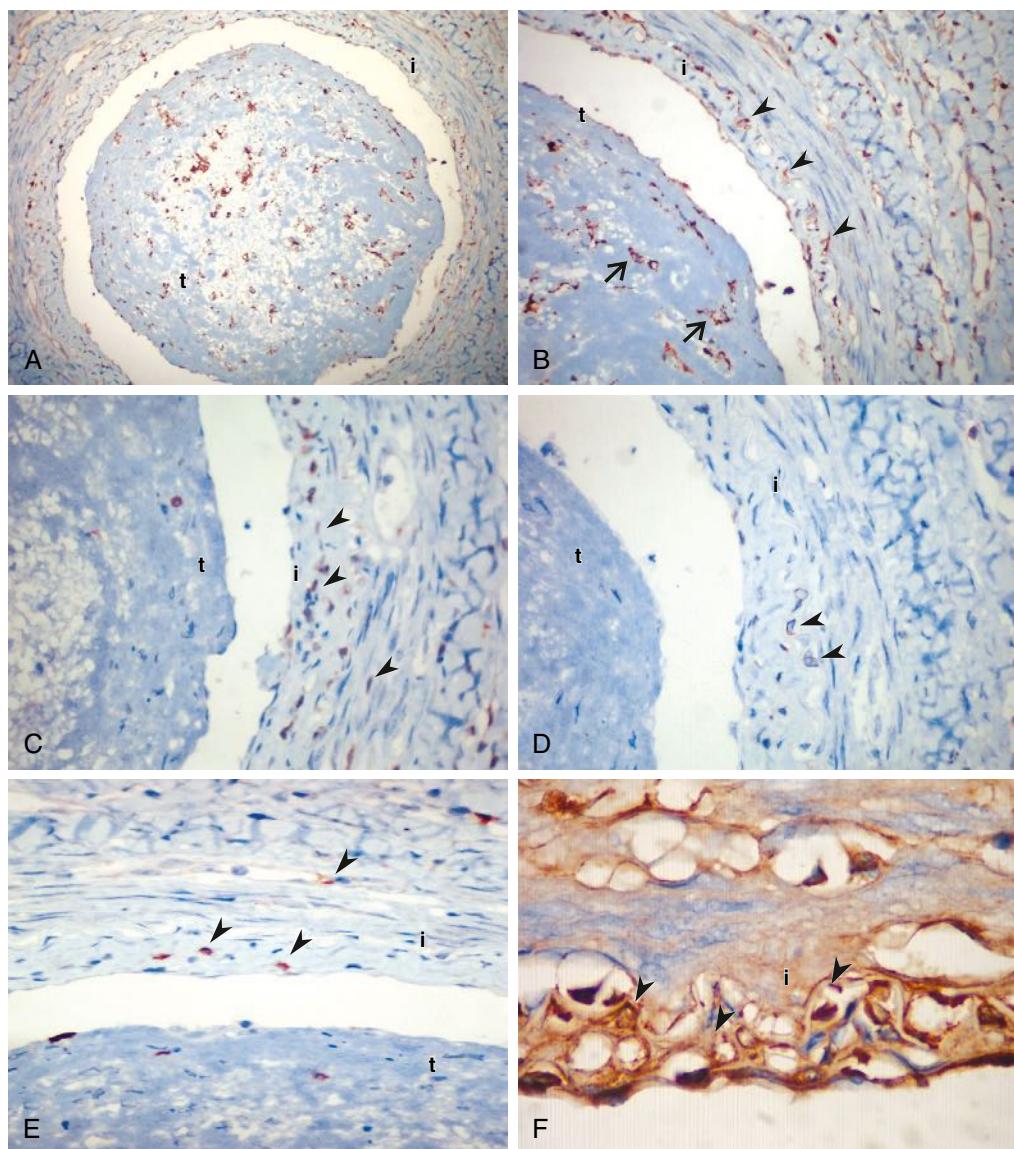


Figure 139.2 (A) Microphotograph of an acute-stage lesion with highly cellular thrombus (*t*) and inflammatory infiltration along the vessel wall with increased anti-CD68⁺ (clone: KP1) histiocytes. (B) High-power view showing highly cellular thrombus (*t*, arrows) and abundant histiocytes in the intimal layer (arrowheads). (C to E) Anti-CD3⁺ (rabbit polyclonal) stained T cells (C), anti-CD4⁺ (clone: IF6) T-helper cells (D), and anti-CD8⁺ (clone: C8/144B) cytotoxic T cells (E) in the intimal layer (arrowheads; brown membrane staining, $\times 400$). (F) Deposition of immunoglobulin G (brown, arrowheads) within the interstitial intimal tissue ($\times 600$). Immunohistochemistry was performed with a Ventana iVIEW DAB detection system. *i*, intima.

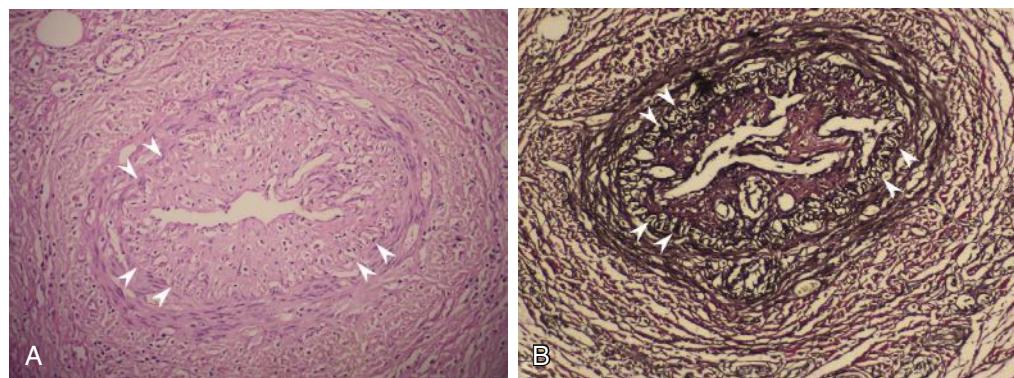


Figure 139.3 (A) Microphotograph of a chronic-stage lesion of Buerger disease, with recanalized arterial thrombus and striking intimal thickening (H&E, $\times 200$). The internal elastic lamina (arrowheads) and the architecture of the vascular wall are well preserved. (B) The same vessel stained with elastic van Gieson ($\times 200$).

with suspected TAO.^{3,188} It is common to see angiographic abnormalities consistent with TAO in limbs that are not yet clinically involved. Rarely, TAO has been associated with visceral,^{189–209} cerebral,^{210–214} coronary,^{215–224} internal thoracic artery,^{217,218} and multi-organ involvement.^{225,226} The cerebral vessels' involvement may result in progressive cognitive decline and migraine,²²⁷ transient ischemic attack, ischemic stroke, or

schizophrenia-like symptoms.^{210–214} Coronary artery involvement may result in myocardial ischemia or infarction.^{215–223} Visceral vessel involvement may manifest as abdominal pain, nausea, vomiting, fever, diarrhea, melena, weight loss, and anorexia and result in ileus, ischemic colitis, mesenteric infarction, intestinal perforation, or liver hypoxia.^{190–195,199,201,206–208} Involved vascular beds exhibit similar pathologic characteristics



Figure 139.4 (A) Ischemic ulceration of the right second toe with a previously amputated great toe in a 42-year-old man who smoked three packs of cigarettes a day for 15 years. (B) Necrosis of the ends of almost all fingers led to autoamputation in the same patient after continued smoking. (C) One of the cardinal signs of thromboangiitis obliterans is superficial thrombophlebitis, seen here on the left leg of a 28-year-old smoker. Note the hairless skin distally. (D) Infected left metatarsal ulceration with osteomyelitis untreated for several weeks in a 32-year-old male patient with previous great and 5th toe amputations.

TABLE 139.2

Distribution of Arterial Involvement in 825 Patients with Thromboangiitis Obliterans (1650 Upper and 1650 Lower Extremities)

Lower extremity involvement only	616 (74.7%)
Upper and lower extremity arteries	167 (20.2%)
Upper extremity involvement only	42 (5.1%)
Lower extremity (n = 783)	
Anterior tibial artery	683 (41.4%)
Posterior tibial artery	667 (40.4%)
Dorsalis pedis artery	349 (21.2%)
Peroneal artery	304 (18.4%)
Popliteal artery	301 (18.2%)
Digital arteries	180 (10.9%)
Plantar arteries	149 (9.0%)
Other	296 (19.8%)
Upper extremity (n = 209)	
Ulnar artery	189 (11.5%)
Digital arteries	133 (8.1%)
Radial artery	115 (7.0%)
Superficial or deep palmar arch	75 (4.5%)
Brachial artery	13 (0.8%)
Other	26 (1.6%)

Adapted from Sasaki S, Sakuma M, Kunihara T, Yasuda K. Distribution of arterial involvement in thromboangiitis obliterans (Buerger's disease): results of a study conducted by the Intractable Vasculitis Syndromes Research Group in Japan. *Surg Today*. 2000;30(7):600–605.

as vessels in the extremities. Even rarer, TAO instances in saphenous vein arterial grafts,²²⁸ the temporal arteries,²²⁹ the ophthalmic circulation,^{230–232} and intrarenal arterial branches²³³ of smokers have been reported. The occurrence of TAO in pudendal,^{234,235} testicular, and spermatic arteries and veins, was too uncommon, as was initially described by Buerger.²⁹ Rare cases of nephropathy as a result of mesangial immunoglobulin A deposition,²³⁶ or renal artery thrombosis; cutaneous manifestations presenting as painful nodular erythema with livedo reticularis,²³⁷ and avascular necrosis of femoral heads²³⁸ have also been reported. TAO in unusual locations should be diagnosed when the histopathologic findings are classic for the acute-phase lesion, and the clinical presentation is consistent with the diagnosis of TAO.¹⁸⁸

DIAGNOSIS

After its first description, the primary clinical challenge in TAO is still the absence of universally accepted diagnostic criteria.^{3,39,239–241} Shionoya has identified five major criteria that are still valid for the diagnosis of TAO.^{8,39} In 1996, Papa and colleagues proposed various clinical, angiographic, histopathologic positive and negative criteria, and in a second report, they introduced a point-based scoring system to improve the diagnostic certainty.^{10,70} Mills and Porter developed more stringent major and minor supportive criteria on a cohort of patients in Oregon.¹⁹ Olin's diagnostic criteria added the classification of ischemic limbs as claudication, pain at rest, ischemic ulcers, or gangrene and the consistency of arteriographic findings.^{3,5} All investigators accepted the exclusion of atherosclerotic risk factors other than smoking. A comparative analysis of current diagnostic clinical criteria for TAO is summarized in Table 139.3.

Vascular Evaluation

A complete vascular examination is critical for the diagnosis. Physical examination reveals the involvement of medium and small-sized arteries with regular brachial and femoral pulses. The radial, ulnar, dorsalis pedis, or posterior tibial pulses may be absent. Digital arteries may be occluded. An abnormal Allen test, which suggests ulnar artery occlusion in a young smoker with lower extremity ulcerations, is highly suggestive of TAO. Abnormal Allen tests occurred in 63% of cases in the Cleveland Clinic series.⁵ Superficial phlebitis may be another clue to the diagnosis. Neurological examination may document peripheral nerve involvement, with sensory findings in up to 70% of patients.³ Calculation of the ankle–brachial index (ABI), toe–brachial index (TBI), and wrist–brachial index at rest and after exercise is recommended as the initial screening test. Seasonal variation, with exacerbation of TAO occurring more frequently in the winter, has been reported^{242,243}; this may be attributed to cold weather and the stimulation of vasospasm and Raynaud phenomenon.²⁴²

Noninvasive Testing

Four-limb segmental arterial pressure measurements and pulse volume recordings are usually normal above the knee and markedly reduced distally.⁹⁷ Abnormal digital plethysmographic patterns in both lower and upper extremities would objectively

document distal occlusive disease in a patient meeting the clinical criteria for TAO.^{7,9,70,82,244} Calcification of the involved arterial wall is almost always absent on plain radiography.⁴¹ Arterial duplex scanning is used not only to exclude proximal atherosclerotic lesions and to demonstrate distal arterial occlusive disease but also to visualize and functionally evaluate the corkscrew-shaped collaterals. Using continuous wave Doppler ultrasound monophasic waveform pattern within the corkscrew-shaped collaterals is also known as Martorell's sign ("snake" or "dot" sign) (Fig. 139.5).^{245–247} These findings indicate selective impairment of vascular endothelium, but not smooth muscle cells in native arteries in patients with TAO.²⁴⁸ Besides, superb microvascular imaging may have a role in the identification and classification of corkscrew collaterals.²⁴⁹ Furthermore, blood flow patterns within the corkscrew collateral arteries using computational fluid dynamics simulation from CT-angiography images may help a better understanding of the disease progression.²⁵⁰ Laser Doppler flowmetry, transcutaneous oxygen, and carbon dioxide pressures can be useful to evaluate the severity of ischemia and the effectiveness of treatment.²⁵¹

Emboli as a cause of distal ischemia should be ruled out, as the signs and symptoms of embolic occlusions can mimic those of TAO. Cardiac investigations, including electrocardiography, rhythm monitoring, and echocardiography, are recommended to rule out cardiac and thoracic aortic sources of emboli to the involved extremity.²⁵² Abdominal

TABLE 139.3 Comparative Analysis of Current Diagnostic Clinical Criteria for Thromboangiitis Obliterans

	Shionoya (Nagoya) ^{3,39}	Papa et al. (Tel Aviv) ⁹	Mills et al. (Oregon) ^{7,58}	Olin (Cleveland) ^{1,5}
Age at onset	<50 years	<40 years	<45 years	<45 years
Smoking habit	Smoking history	Smoking history	Tobacco abuse	Current (or recent) history of tobacco use
Clinical manifestations	<ul style="list-style-type: none"> • Distal extremity ischemia • Infrapopliteal arterial occlusions, • Either upper limb involvement or phlebitis migrans 	<ul style="list-style-type: none"> • Foot intermittent claudication • Upper limb involvement • Superficial vein thrombosis • Raynaud syndrome 	<ul style="list-style-type: none"> • Instep claudication • Upper limb involvement • Phlebitis migrans • Raynaud syndrome 	<ul style="list-style-type: none"> • Distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers, or gangrene)
Diagnostic tests			Objective documentation of distal occlusive disease by <ul style="list-style-type: none"> • segmental arterial Doppler studies and • 4-limb plethysmography; • arteriography; or • histopathology 	<ul style="list-style-type: none"> • Symptoms documented with noninvasive testing • Consistent arteriographic findings in the clinically involved and noninvolved limbs
Location of the disease	Infrapopliteal arterial occlusions	Distal disease	Distal disease Non-diseased arteries proximal to the popliteal or distal brachial level	Distal extremity ischemia (infrapopliteal and/or infrabrachial)
Exclusion criteria	Atherosclerotic risk factors other than smoking	Arteriosclerosis obliterans, hypertension, diabetes mellitus, hyperlipidemia, proximal source of emboli, trauma, collagen disease and hypercoagulable states	Atherosclerosis (diabetes mellitus, hyperlipidemia, hypertension, renal failure), proximal source of emboli, trauma and local lesions, autoimmune disease, hypercoagulable states	Diabetes mellitus, autoimmune disease, connective tissue diseases, proximal source of emboli, hypercoagulable states

ultrasonography may be considered to rule out a proximal source of emboli from an abdominal aortic aneurysm or atherosclerotic aorta.

Gadolinium-enhanced magnetic resonance angiography and multidetector computed tomographic angiography (Fig. 139.6) may be useful diagnostic alternatives in patients with TAO. Furthermore, ischemic ulcerations with signs and symptoms of secondary infection should be evaluated using conventional radiography and magnetic resonance imaging to determine osteomyelitis.²⁵³ Recently, ¹⁸F-fluorodeoxyglucose positron emission tomography has been investigated in TAO case series but found to be an unsuitable investigative procedure for the diagnosis of TAO.²⁵⁴

Laboratory Testing

There are no specific laboratory tests for the diagnosis of TAO; however, serologic testing for autoimmune antibodies, thrombophilia, and vasculitides should be included in the screening process. Acute-phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are typically normal or slightly elevated in the absence of extensive trophic lesions. Absence of immunological markers, including complement levels, rheumatoid factor (RF), antinuclear antibodies (ANA), anti-centromere antibodies, anti-SCL-70 antibodies, ANCA, and cryoglobulins, is characteristic for TAO. However, anti-cardiolipin antibodies may be present in patients with TAO.

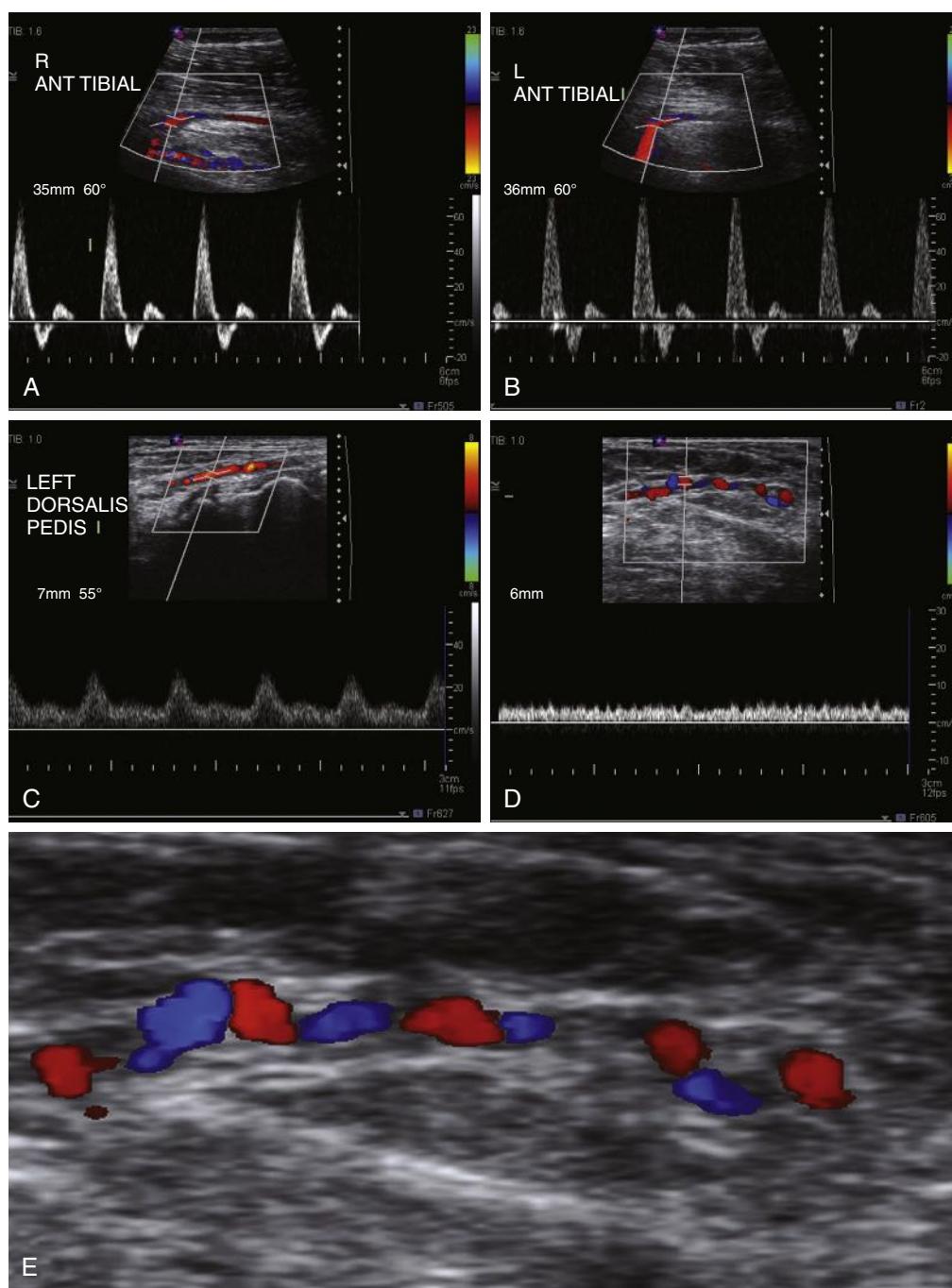


Figure 139.5 Color-flow Doppler studies demonstrating triphasic flow within the right (A) and left (B) anterior tibial arteries, monophasic flow within the left dorsalis pedis artery (C), and the “dot” sign because of continuous flow within corkscrew collaterals at the toe level (D and E).



Figure 139.6 (A and B) Abrupt right tibial vessel occlusion with corkscrew collaterals (arrows) in a 34-year-old man detected with 64-slice multidetector computed tomographic angiography.

Toxicology panel should include cocaine, amphetamines, and cannabis. A suggested diagnostic algorithm for the diagnosis of TAO is summarized in Table 139.4.

Angiography

Thoracoabdominal digital subtraction angiography plays an essential role in supporting the diagnosis of TAO and ruling out other causes of ischemia. Arteriographic findings in TAO may be suggestive but not pathognomonic. Thus, this method is not a “gold standard” for diagnosis. Segmental occlusive lesions (diseased arteries interspersed with normal-appearing arteries), more severe disease distally, the involvement of digital arteries,⁸² normal proximal arteries without evidence of atherosclerosis, and collateralization around areas of occlusion with corkscrew shape (Martonell's sign) also known as “tree root” or “spider's leg” collaterals are the characteristic features of TAO (Fig. 139.7).^{59,255} The infrapopliteal or infrabrachial arteries are the most common sites of occlusion. Small corkscrew patterns (types III and IV) are associated with a higher prevalence of ischemic ulcers compared to large corkscrew collaterals (types I and II).²⁵⁶ Although corkscrew collaterals, which represent widened vasa vasorum, suggest TAO to many clinicians,⁵⁹ this finding is not pathognomonic. In one study, 27% of 144 limbs

affected by TAO had a corkscrew appearance.²⁵⁷ Corkscrew-shaped collaterals can also be seen in connective tissue diseases such as scleroderma, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal disease, sclerodactyly, telangiectasia), systemic lupus erythematosus, rheumatoid vasculitis, and the antiphospholipid–antibody syndrome.³ Furthermore, cocaine, amphetamine, or cannabis addiction can cause Buerger-like clinical and angiographic signs.^{87–90,95,173,258} The angiographic features that support a diagnosis of TAO are listed in Table 139.5. A study from Japan determined the distribution of arterial involvement in TAO on the basis of a nationwide survey in 1993 by the Intractable Vasculitis Syndromes Research Group (see Table 139.3).¹⁸⁷

Biopsy

A biopsy is rarely needed unless the patient presents with atypical features. Biopsy could be considered in patients aged >45 years at disease onset, with proximal vascular disease, superficial thrombophlebitis, subcutaneous nodules, diabetes, central nervous system involvement, positive antinuclear antibodies, elevated anticardiolipin antibodies. Biopsy of acute superficial thrombophlebitis often demonstrates the typical histopathologic lesions of acute TAO.⁶⁵

TABLE 139.4 Suggested Diagnostic Algorithm for the Diagnosis of Thromboangiitis Obliterans

1. Young smoker (confirm tobacco, cannabis, bidi, kawung, or cocaine use)
2. Document distal lower or upper extremity ischemic symptoms and signs (claudication, ischemic rest pain, ulcerations, gangrene, limb infection)
3. Note the maximal pain-free walking distance, and pain scale (0–10 scale)
4. Document distal nature of disease
 - Blood pressure measurements (ABI, TBI)
 - Transcutaneous oxygen tensions
 - Arterial duplex scanning
 - Intra-arterial digital subtraction angiography (IA-DSA)
 - Computed tomographic angiography (CTA)
 - Magnetic resonance angiography (MRA)
5. Laboratory tests to exclude connective tissue diseases and hypercoagulable states
 - Routine complete blood count and biochemistry including fasting blood glucose, renal function, and liver enzymes
 - Thyroid function tests
 - Urinalysis
 - Lipid profile
 - Serum homocysteine, vitamin B₁₂, red blood cell folate
 - Coagulation profile: prothrombin time, activated partial thromboplastin time, protein C, protein S, antithrombin III, factor V Leiden, prothrombin gene mutation 20210, antiphospholipid antibodies, anticardiolipin antibodies
 - Autoimmune screen: ESR, CRP, complement measurements, ANA, ANCA, RF, cryoglobulins, antibodies SCL-70
 - Measurements of serologic markers for the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal disease, sclerodactyly, telangiectasia), anticentromere antibodies
 - Hand radiographs (to exclude calcinosis)
 - Hepatitis B, C serology
 - Venereal Disease Research Laboratory (VDRL) test
6. Exclusion of proximal sources of emboli
 - Electrocardiography, rhythm monitoring
 - Echocardiography (transthoracic, transesophageal if necessary)
 - Abdominal ultrasonography
 - Arteriography (IA-DSA, CTA, MRA)
7. Nielsen digital hypothermic challenge test (Raynaud evaluation)
8. Toxicology screen for cocaine, amphetamine and cannabis
9. Biopsy indicated only for unusual features
 - Age >45 years at onset
 - Documented disease in unusual locations (proximal disease)
 - Superficial thrombophlebitis
 - Subcutaneous nodules
 - Diabetes
 - Central nervous system disease
 - Positive antinuclear antibodies
 - Elevated anticardiolipin antibodies

ABI, ankle–brachial index; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasm antibody; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; RF, rheumatoid factor; SCL-70, scleroderma-specific antibodies; TBI, toe–brachial index.

Adapted from refs 3, 7, 188, 259, 266.

Differential Diagnosis

Differential diagnosis of TAO includes a broad range of disorders (see Chapter Algorithm). Diagnostic evaluations should exclude ASO, thromboembolism, and other vasculitides.^{17,69,241} TAO differs from ASO with infrapopliteal or infrabrachial arterial involvement and associated migratory thrombophlebitis. TAO differs from most other types of vasculitis with non-necrotizing, non-granulomatous inflammation of medium and small size arteries, preserved internal elastic lamina and media; and usually serologic markers (elevated acute phase reactants such as ESR and CRP, presence of circulating immune complexes, and presence

of autoantibodies such as antinuclear antibody, rheumatoid factor, and complement levels) are normal or negative.^{23,69} Causes of distal arterial ischemia, including scleroderma, CREST syndrome, systemic lupus erythematosus, Takayasu arteritis, polyarteritis nodosa, giant cell arteritis, rheumatoid vasculitis, mixed connective tissue disorders, antiphospholipid syndrome, vascular compression syndromes (thoracic outlet syndrome, hypothenar hammer syndrome, repetitive vibratory injury, popliteal artery entrapment, carpal tunnel syndrome), malignancies, hematologic thrombophilia disorders (lupus anticoagulant, anticardiolipin antibody syndrome), drug-induced hypersensitivity, ergot

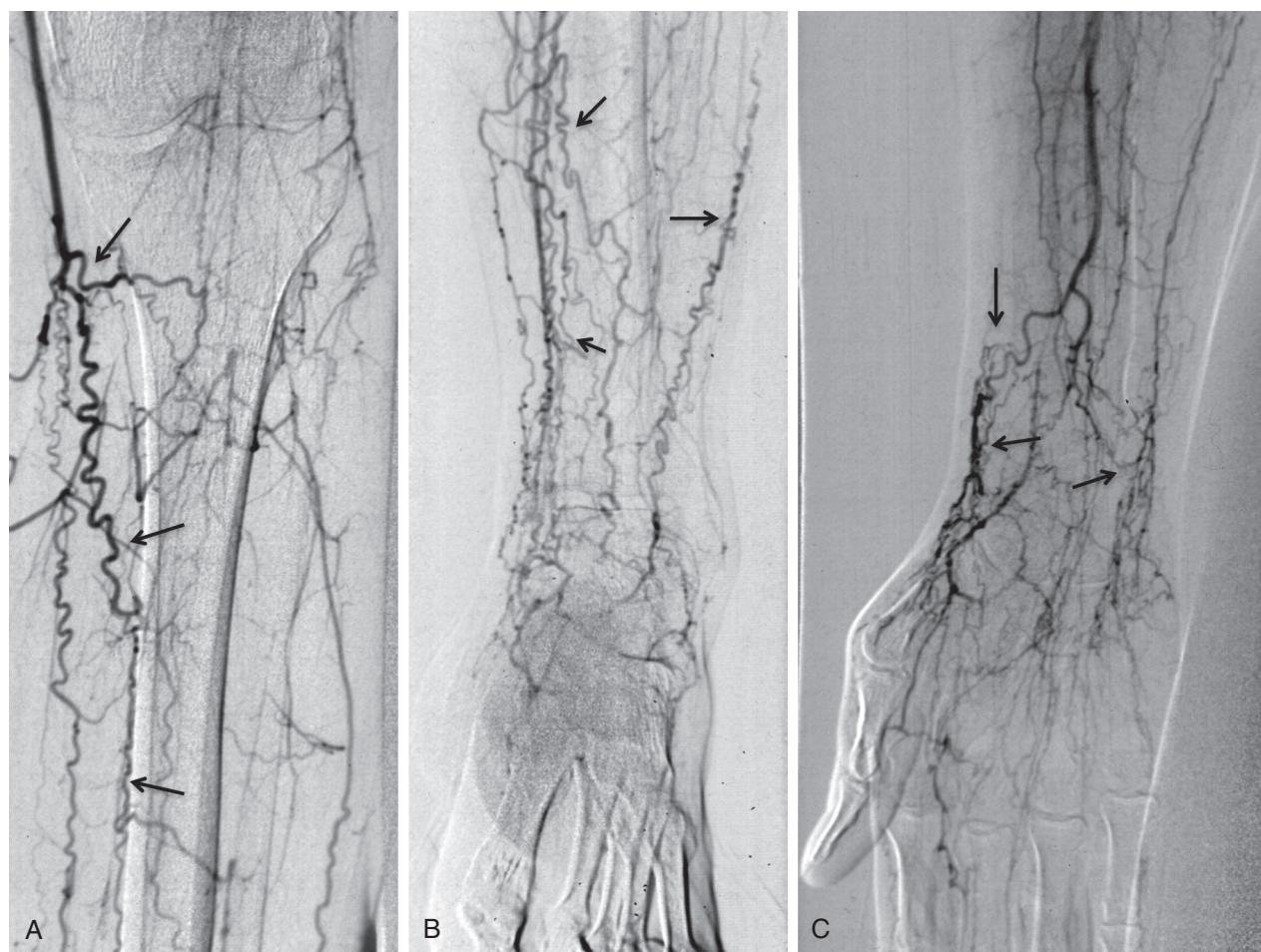


Figure 139.7 Digital subtraction angiography reveals left popliteal and tibial vessel occlusions with corkscrew collaterals (arrows) proximally (A) and distally (B) and right radial and ulnar artery involvement (C) in a 32-year-old man with a nonhealing left toe ulceration.

TABLE 139.5

Angiographic Findings in Thromboangiitis Obliterans

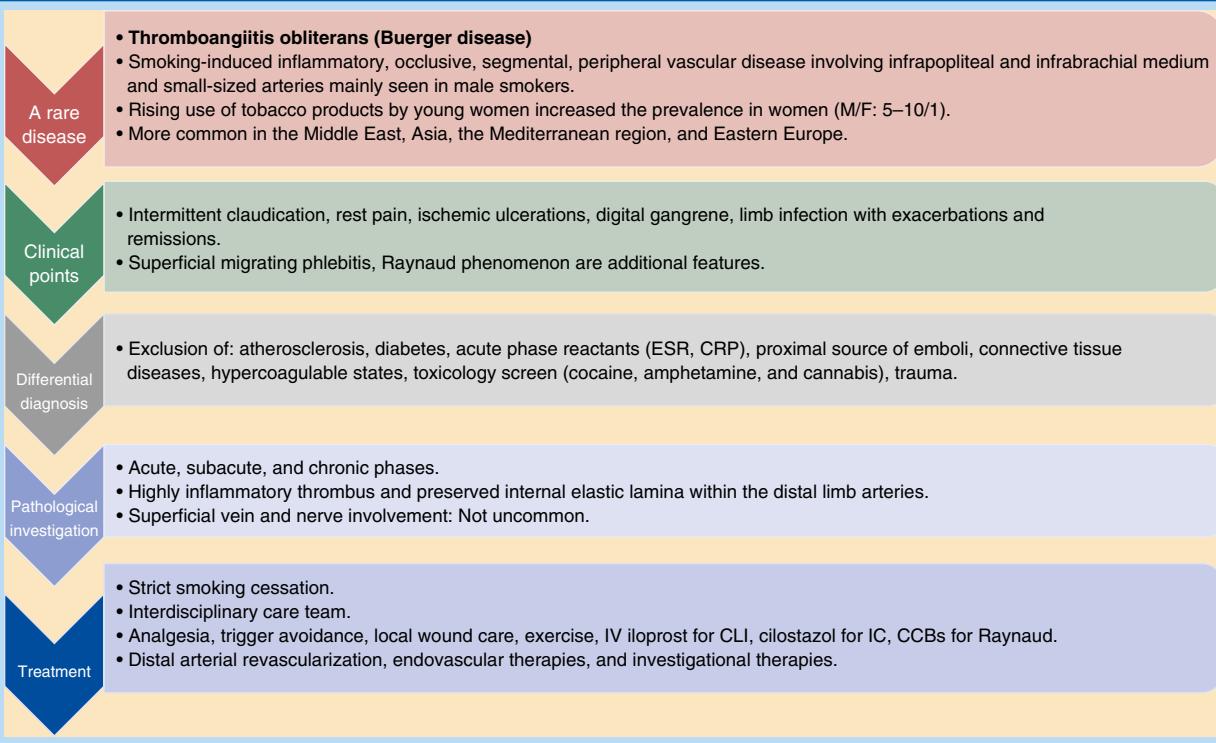
- Involvement of small and medium sized arteries
Digital arteries of fingers and toes
Palmar, plantar, tibial, peroneal, radial and ulnar arteries
- Segmental occlusive lesions: diseased arterial segments interspersed with normal-appearing segments
- More severe disease distally
- Tapering or abrupt arterial occlusions with collateralization around areas of occlusion: described as “corkscrew collaterals,” “spider leg” or “tree root appearance” (not pathognomonic)
- Normal proximal arteries free of atherosclerosis, aneurysms, or other sources of emboli

abuse, cannabis arteritis, and microbial infection, should also be considered in the differential diagnosis. If TAO and ASO or other vasculitides cannot be differentiated, the diagnosis can be confirmed by biopsy of a subcutaneous nodule or affected vein, which may show the characteristic acute-phase lesion.^{69,173} TAO has essential features distinguished from other forms of vasculitis,¹⁸⁸ a highly inflammatory thrombus, with relative sparing of

the blood vessel wall. Preservation of the internal elastic lamina distinguishes TAO from the actual necrotizing forms of vasculitis.^{51,259,260} Kimura disease presenting with Raynaud phenomenon and digital infarcts, and marked eosinophilia may mimic TAO symptoms.²⁶¹

Natural History

Exacerbations and remissions are characteristic features of TAO. In one study, at a mean follow-up of 10.7 (range: 2–30) years, patients experienced an average of 5.4 (range: 1–20) acute episodes with severe symptoms.¹⁶⁵ Patients have a significantly diminished quality of life compared with age- and sex-matched controls.^{262–264} TAO population and a matched coronary artery disease population had similar degrees of tobacco dependence and Fagerström scores.²⁶⁵ In one study, the life expectancy of patients with TAO was comparable to that of the average population.³⁶ In contrast, Cooper and colleagues reported that survival among the TAO cohort was significantly lower than that in the matched U.S. population in the TAO group, and the average age at death was 52.2 ± 8.9 years.²⁶² The risk of any amputation during a mean follow-up of 15.6 years was 25% at 5 years, 38% at 10 years, and 46% at 20 years.²⁶²

BOX 139.1**Thromboangiitis Obliterans (Buerger Disease)**

The risk of major amputation – defined as above-knee, below-knee, or hand amputation – was 11% at 5 years, 21% at 10 years, and 23% at 20 years.²⁶² In this analysis, the amputation rate was significantly reduced in those who stopped tobacco use. In this analysis, the amputation rate was significantly reduced in those who discontinued tobacco use. The authors concluded that the risk of amputation in previous smokers is eliminated 8 years after smoking cessation.²⁶² Cumulative survival rates in the series reported by Ohta and colleagues were 97.0% at 5 years, 94.4% at 10 years, 92.4% at 20 years, and 83.8% at 25 years (mean follow-up, 10.6 years).²⁶³ These investigators also demonstrated that the occurrence or recurrence of necrotic lesions was usually arrested in patients older than 60. There was a strong correlation between continued smoking and limb amputation leading to poor quality of life and job loss.²⁶³ Another study from Turkey reported similar survival rates: 95.0% at 2 years, 92.4% at 5 years, and 88.4% at 10 years (mean follow-up, 11.6 years).⁵² A study from Japan confirmed that failure to cease smoking was the most significant factor affecting the risk of ulcer formation (OR: 1.71) and risk for amputation (OR: 2.73; 95% CI: 1.86–4.01).¹⁷² A recent French nationwide multicenter study among 224 TAO patients fulfilling Papa's criteria was the most extensive series on the long-term outcome from a Western country.^{266,267} The mean follow-up was 5.7 years, and there were three deaths of unknown origin. The vascular event-free survival was 41% at 5 years and 23% at 10 years. Nonwhite ethnic origin and limb infection at diagnosis were independent risk factors of vascular event-free survival.²⁶⁶

TREATMENT

Lifestyle Changes

Smoking Cessation

The first step in the management of TAO is complete and permanent discontinuation of smoking in any form,^{7,42,69,98,188,268} including passive smoking (Box 139.1).¹⁰⁴ The hazards of continued smoking in patients with TAO seems to be independent of factors such as the number of cigarettes smoked per day¹⁸⁸; whether the tobacco product is in the form of cigarettes, bidis, cigars, chewing tobacco, or snuff^{71,76,269}; cigarette characteristics; and smoking behavior, including the degree of inhalation. Counseling, smoking-cessation programs, pharmacotherapy using bupropion or varenicline and exercise training form the cornerstone of treatment.⁶⁰ Nicotine replacement therapy may result in disease progression, and thus should be avoided.^{3,270} However, in terms of limb salvage in a stage of CLI in patients with TAO, smoking cessation may not be sufficient.²⁷¹

Exercise Training

The benefits of exercise training in claudication are well established.^{272,273} Regular exercise training (sessions lasted more than 30 minutes and 3–5 times per week) improves pain-free walking time by an average of 180% and maximal walking time by an average of 120 percent in patients with claudication.²⁷⁴ The Buerger–Allen exercise and the Ratschow's exercise may be performed in patients with CLI.²⁷⁵ RCTs confirmed that ischemic exercise training triggers the release of CPCs from the

bone marrow and promote homing of CPCs into vascular networks.²⁷⁶ ACC/AHA²⁷⁷ and Japanese Circulation Society Joint Working Group²⁷⁸ recommend supervised exercise training for patients with intermittent claudication whenever it is not contraindicated (Level of Evidence: A).

Trigger Avoidance, Foot, Hand, and Dental Care

Daily foot and hand hygiene, as well as avoidance of trauma, thermal injury, vibration, chemicals, and cold, are easily applied measures to prevent ischemic ulcers.²⁷⁹ Any injury to the involved extremity should be treated promptly. Adequate oral hygiene, controlling the bacterial biofilm, and periodontal treatment might be useful measures preventing the recurrence of the disease.^{149,280}

Pharmacologic Treatment

Treatment must be tailored to the individual and is often based on the patient's clinical presentation (Fig. 139.8). TAO has conventionally been treated with antiplatelet agents including oral anticoagulants, clopidogrel, dextran, pentoxifylline, phenylbutazone, pyridinolcarbamate, inositol niacinate, nonsteroidal anti-inflammatory agents, and immunosuppressive drugs including cyclophosphamide²⁸¹ and corticosteroids.²⁸² However, no randomized controlled trials (RCTs) have been reported assessing the efficacy of previously mentioned agents in TAO. Two reported cases of steroid-responsive TAO²⁸² with remarkable eosinophilia is controversial.²⁶¹ Appropriate antibiotics and nonsteroidal anti-inflammatory agents should be used in patients with complicated phlebitis, cellulitis, or osteomyelitis.

Calcium Channel Blockers

CCBs have been used for TAO patients associated with the secondary Raynaud phenomenon. Meta-analysis from 23 trials with 528 participants (five trials with secondary Raynaud phenomenon, $n = 63$), indicated that CCBs were superior to placebo in reducing the frequency of attacks with moderate-quality evidence.²⁸³ The investigators suggested that higher doses may be more effective than lower doses.²⁸³ Nifedipine, nicardipine or amlodipine may similarly be used in patients with significant vasospasm.³

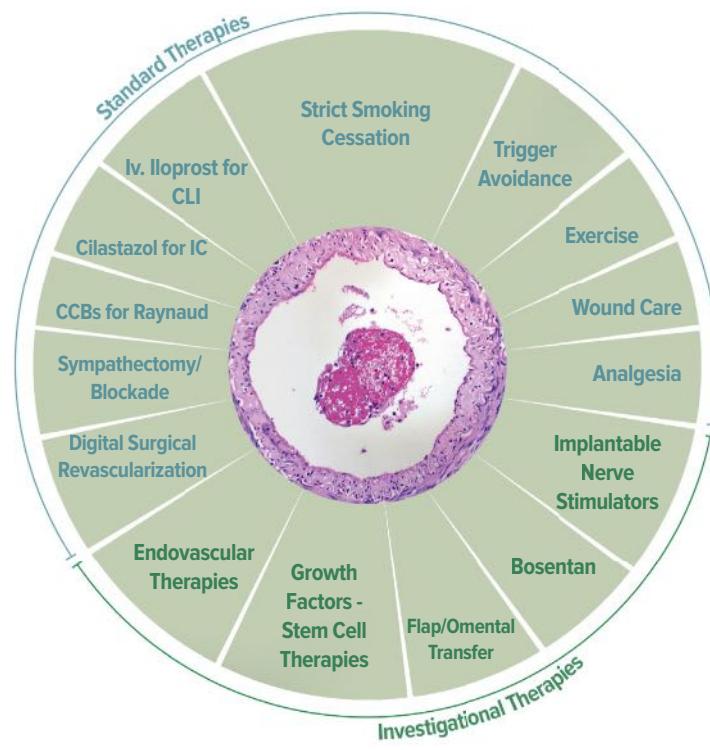
Prostacyclin Analogs

Prostaglandin I2 (prostacyclin), the main product of arachidonic acid metabolism by endothelial cells, is a potent vasodilator through vascular smooth cell relaxation, and it inhibits platelet aggregation, chemotaxis, and cell proliferation.^{284,285} Epoprostenol is a freeze-dried preparation of prostacyclin for intravenous administration.²⁸⁶ Iloprost is a stable and synthetic analog of epoprostenol with a plasma half-life of 20–30 min. It is commonly used to treat peripheral vascular disease because of its vasodilating and platelet inhibitory effects. Iloprost also downregulates the expression of intercellular adhesion molecule-1 and endothelial leukocyte adhesion molecule-1 on interleukin-1 β -stimulated endothelial cells and inhibits lymphocyte adhesion to endothelial cells.²⁸⁷

Intravenous iloprost

Moderate quality of evidence exists with a limited number of RCTs in the pharmacological treatment of TAO with CLI.²⁸⁸ In a European multicentre randomized, double-blinded trial involving patients with TAO and CLI, Fiessinger and Schafer compared 6-hour infusion of intravenous prostacyclin analog

TAO Treatment Strategies



Wound Care

- Local Debridement
- Antibiotics and NSAIDs
- Hyperbaric Oxygen Therapy
- Negative-pressure Wound Therapy
- Regional Sympathetic Blockade
- Amputation

Unproven Therapies

- Antiplatelet Agents
- Anticoagulants
- Thrombolytics
- Pentoxifylline
- Cyclophosphamide
- Statins
- Oral Prostaglandin Analogues
- Folate Supplementation
- Cannabinoid receptor antagonists
- PDE5 inhibitors
- Immunomodulation
- Arterial Flow Pump Therapy
- Intermittent Pneumatic Compression Pump
- Intramedullary K-wire

Figure 139.8 Current treatment strategies for Buerger disease.

iloprost (0.5 to 2.0 ng/kg/min) and oral aspirin (100 mg/day) for a 28-day trial period.²⁸⁹ Among 152 patients, 133 patients fulfilled the entry criteria of rest pain, ischemic ulceration, or gangrene.²⁸⁹ At 28 days of treatment, iloprost was superior to aspirin at achieving ulcer healing or relief of ischemic pain; 85% of patients in the iloprost group improved versus 17% in the aspirin group. Furthermore, at 6 months, the response rate was 45 of 51 (88%) patients treated with iloprost, compared with 12 of 44 (21%) patients treated with aspirin. Only 6% of patients in the iloprost group ultimately required amputation, compared with 18% in the aspirin group.²⁸⁹ In a randomized, multicenter study, the Turkish Buerger's Disease Research Group compared the results of lumbar sympathectomy ($n = 78$) to 28 days of intravenous iloprost ($n = 84$) in 162 patients with CLI and TAO.²⁹⁰ The primary endpoint of the study was complete healing without pain or major amputation at 4 and 24 weeks. Complete healing was achieved in 61.9% of the iloprost group and 41% of the lumbar sympathectomy group at 4 weeks ($P = 0.012$) and 85.3% versus 52.3%, respectively, at 24 weeks ($P < 0.001$).²⁹⁰ The risk of amputation is also reduced with a combination of IV iloprost infusion and supervised smoking cessation in TAO patients with CLI.²⁹¹ Thus, reported evidence suggests that intravenous iloprost is an effective pharmacological treatment option in healing ulcers and relieving rest pain in patients with TAO and CLI.²⁹² A recent Cochrane systematic review and meta-analysis, concentrating on pharmacological therapy for TAO by Cacione et al.²⁸⁸ showed that intravenous iloprost was more effective than aspirin to eradicate rest pain and heal ischemic ulcers by moderate-certainty evidence.

Oral iloprost

The European TAO Study Group conducted a double-blinded, randomized, placebo-controlled trial comparing oral iloprost (100 or 200 µg) with placebo for 8 weeks among 319 patients with ischemic rest pain or ulcerations recruited from 22 centers in six countries in Europe.²⁸⁴ Duration of treatment was 6 weeks. The primary endpoint was total healing of the most critical lesion, and the secondary endpoint was complete relief of pain at rest without the need for analgesics at 6 months. The combined endpoint consisted of the patient's being alive with no major amputation, no lesions, no rest pain, and no analgesic use. After 6 months of therapy, low-dose iloprost was significantly better than a placebo at relieving rest pain without analgesics.²⁸⁴ However, neither dose of oral iloprost showed a significant effect on the total healing of lesions than the placebo. A recent meta-analysis also confirmed that oral iloprost was not more effective than a placebo by moderate-certainty evidence.²⁸⁸

Prostaglandin E1 Analogs

Limaprost alfadex, a prostaglandin E1 analog, was developed in Japan to treat ischemic symptoms of TAO, has also strong vasodilatory and antiplatelet activity similar to prostacyclin. In a randomized, double-blinded trial in 136 Japanese patients primarily with TAO, there was no significant difference in the improvement of ischemic symptoms between patients receiving limaprost 30 µg/day and those receiving oral ticlopidine 500 µg/day.²⁹³

Phosphodiesterase (PDE) Inhibitors

PDE3 inhibitors (Cilostazol)

The PDE3 isoenzyme is found in vascular smooth muscle and platelets. Inhibition of PDE3 isoenzyme relaxes smooth muscle by increasing intracellular cAMP and decreases platelet aggregation.²⁹⁴ In one small study, cilostazol effectively improved ischemic ulcerations in patients with TAO and refractory digital ischemia.²⁶⁰ In an RCT from Turkey, the addition of cilostazol (100 mg twice a day for 6 months) to iloprost infusion ($n = 30$) resulted in better symptomatic relief and improved quality of life in patients with TAO and CLI, compared to iloprost infusion alone ($n = 30$).²⁹⁵ Another recent study showed that cilostazol could significantly reduce inflammatory mediators, including ICAM-1, VCAM-1 expression in TAO patients.²⁹⁶ Indeed, cilostazol received Class IA recommendation as an effective therapy to improve symptoms and increase walking distance in patients with claudication.^{24,297,298}

PDE5 inhibitors (Sildenafil, Tadalafil)

PDE5 isoenzyme is found in the corpus cavernosum of the penis and vascular smooth muscle. Inhibition of PDE5, a cGMP-dependent phosphodiesterase, increases intracellular cGMP, which results in decreased intracellular calcium and increased nitric oxide leading to vascular smooth muscle relaxation and vasodilation. There are few reported cases of TAO with digital symptoms successfully treated with off-label use of PDE5 inhibitors, namely sildenafil (20 mg three times daily) or tadalafil (40 mg every other day).^{299–301}

Endothelin Receptor Antagonists

Bosentan, an oral dual endothelin-1 receptor antagonist targeting the transmembrane receptors ETA and ETB, has been useful in patients with TAO and ischemic lesions.^{301–304} Bosentan has selective vasodilatory, anti-inflammatory, and antifibrotic properties. Previous case series showed clinical and angiographic improvement in 10 out of 12 patients with ulcers and pain at rest.³⁰⁵ De Haro et al. reported that bosentan therapy (125 mg/12 h) maintained for 4 months resulted in clinical improvement and complete healing of the ulcers in a single-center prospective study with 48 months follow-up data in patients with TAO and ischemic ulcers unresponsive to conventional therapies.³⁰⁶ Only 2 out of 22 extremities (9%) underwent major amputation. In another observational study of case series, eight patients with TAO and severe ischemic ulcerations refractory to conventional methods and analysis of 18 previous documented cases showed that therapeutic response was achieved in 80%, with an amputation rate (major and minor) of 8%.³⁰⁷ However, well-conducted RCTs are still needed, especially in patients with pain at rest and ischemic ulcers.

Thrombolytics

Selective intra-arterial infusion of urokinase and streptokinase as a treatment option for TAO has been reported.^{308–312} However, in the series of Hussein et al., limb salvage rate was 33%, and bleeding complications occurred in 17% of the patients treated with intra-arterial streptokinase.³⁰⁹ Matsushita and associates administered a continuous intra-arterial infusion of urokinase

(20,000 U/h) and heparin (800 U/h) in a 19-year-old woman with CLI and TAO.⁵⁵ Although her symptoms improved temporarily, thrombolytic therapy did not enable recanalization of the occluded popliteal artery. High-quality trials assessing the effectiveness of thrombolytics in patients with TAO are needed.

Folate Supplementation

Folate therapy in TAO patients with increased homocysteine levels has been investigated in one RCT from Iran.³¹³ Single dose of folic acid (5 mg) and placebo were compared in 30 patients with TAO.³¹³ The authors concluded that a single dose of folic acid has a homocysteine-lowering effect but did not inhibit the risk of minor or major amputation rate.³¹³ Very low-certainty evidence suggests further well-designed clinical trials.²⁸⁸

Statins

There is increasing experimental evidence that the pleiotropic effects of statins may improve or restore endothelial function and decrease oxidative stress and vascular inflammation.^{314–316} However, the therapeutic role of statins in inflammation-induced thrombosis is still an unresolved issue.³¹⁷

Analgesia

Analgesia is often required in patients with rest pain, ischemic ulcers, and limb infection. Opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and neuronal block may provide symptomatic relief.

Regional sympathetic blockade

Guanethidine, an adrenergic neuron blocker that inhibits the presynaptic release and subsequent reuptake of noradrenaline from postganglionic sympathetic nerve endings, has been proposed for the treatment of TAO.^{318–321} Hannington-Kiff has described intravenous regional sympathetic blockade with guanethidine.³²² This “chemical sympathectomy” is based on multiple sessions of the intravenous regional sympathetic blockade with lidocaine and guanethidine using Bier’s arterial arrest.^{323,324} However, despite promising case reports in patients with ischemic rest pain and non-healing ulcerations, limitations regarding the use of this therapy still exist.³¹⁸

Spinal cord stimulation

There are increasing reports in the literature regarding the use of implantable spinal cord stimulators in patients with TAO.^{325–330} Electrical spinal cord stimulation relieves pain through several mechanisms, including preventing transmission of painful stimuli through the corresponding dermatomes, stimulation of the production of inhibitory neurotransmitters in the spinal cord, and inhibition of sympathetic vasoconstriction with consequent improvement in peripheral microcirculation.^{325,328,330} Spinal cord stimulation successfully addresses the neurogenic, but not the somatic, aspects of pain in patients with TAO.³²¹ Spinal cord stimulation can be attempted when other forms of therapy are ineffective.¹⁸⁸

Surgery

Lumbar or Thoracic Sympathectomy

In a randomized, multicenter study, the Turkish Buerger’s Disease Research Group compared the results of lumbar

sympathectomy ($n = 78$) to 28 days of intravenous iloprost ($n = 84$) in 162 patients with CLI and TAO.²⁹⁰ The primary endpoint of the study was complete healing without major amputations or pain at 4 and 24 weeks. Complete healing was achieved in 61.9% of the iloprost group and 41% of the lumbar sympathectomy group at 4 weeks ($P = 0.012$) and 85.3% versus 52.3%, respectively, at 24 weeks ($P < 0.001$).²⁹⁰ Kothari et al. recently reported that thoracoscopic dorsal sympathectomy reduces pain in patients with upper limb involvement in a recent case series of 25 TAO patients from India.³³¹

Distal Surgical Revascularization

The role of surgical revascularization in TAO is not clear. Revascularization is often not feasible because of the distribution of diffuse, segmental arterial involvement, and the distal nature of the disease.⁶⁹ Distal arterial spasm during dissection and poor-quality veins owing to phlebitis are other disease-specific handicaps. The arterial circulation of the lower extremity generally cannot serve as the distal anastomotic site for bypass surgery, resulting in suboptimal patency rates. However, if the patient has CLI, and a distal target vessel is present, bypass surgery using an autologous vein should be considered.^{332,333} Arterial bypasses of the larger vessels may be used in selected cases. In 1974, Inada and associates demonstrated that of their 236 patients with TAO, only 11 (4.6%) had lesions that were amenable to surgical revascularization,³³⁴ whereas a vasculitis database from Japan revealed that 15.5% of TAO patients underwent surgical revascularization.¹⁷² Dilege and associates reported that 36 of their 94 patients with TAO (38.3%) were deemed eligible for revascularization, but only 27 patients (28.7%) actually underwent revascularization procedures.³³⁵ In this study, any crural vessel with at least 10 cm of patency, preferably in continuation with the pedal arch or draining with a good collateral network, was considered appropriate for revascularization. The patency rates at 12, 24, and 36 months were 59.2%, 48%, and 33.3%, respectively. The limb salvage rate was, however, 92.5%. Bypass surgery was most frequently required below the trifurcation segment of the knee joint, with a cumulative patency rate of 54.6% at 5 years.³³⁶ In a retrospective review of 216 patients with TAO over a 10-year period, Sayin and colleagues reported that lumbar sympathectomy was performed in 85% and thoracic sympathectomy in 9.3% of TAO patients.³³⁷ Twenty-one patients (9.7%) underwent direct arterial reconstruction of varying types. The investigators noted that four of the five endarterectomized segments had occluded by the 7-year follow-up.³³⁷ Sasajima and associates showed that a strategy of aggressive distal bypass surgery using autologous disease-free vein grafts for TAO might provide acceptable primary and secondary patency rates.³³² The patency rates in the postoperative nonsmoking group were significantly higher than in the smoking group (66.8% versus 34.7%; $P < 0.05$).³³² Predictors of early graft failure were poor quality vein, an inadequate technique for anastomosis, inadequate tunneling, anastomosis to a diseased artery, arterial spasm, and vein graft intimal hyperplasia.³³² Late failures were due to disease progression, especially in smokers, vein graft intimal hyperplasia or aneurysm, atherosclerosis, and competition with the collateral flow.³³² Bozkurt and colleagues reported cumulative secondary patency rates of 57.9% for bypass grafts at a mean follow-up

of 5.4 years in 19 patients with Buerger disease.³³⁸ Cumulative patency was 70% (7 of 10) for saphenous vein grafts, 50% (3 of 6) for polytetrafluoroethylene grafts, and 33.3% (1 of 3) for composite grafts. Different distal bypass techniques and routes have been described to obtain better anatomical orientation and patency rates in patients with TAO.^{339–341} Collateral artery bypass is an option when the main arteries are affected by TAO.³⁴² Successful local flap transfers after distal bypass surgeries have been reported in selected cases.^{343–346} The prevalence of amputation and the primary and secondary patency rates after revascularization in patients with TAO are summarized in Table 139.6.

Pedicled Omental Graft

For foot salvage, paramalleolar arterial bypass grafts may be combined with microvascular free tissue transfer.³⁴³ Successful local flap transfers after distal bypass surgery have been reported in selected cases.^{343–346} Omental transfer to areas not amenable to arterial reconstruction has been proposed as a therapeutic option in TAO.^{347–353} In two retrospective series from India, complete healing was achieved in more than 80% of the patients, and limb salvage was 100% with pedicled omental graft.^{348,351} This surgical technique, however, has not been used in Europe or the United States.

Distal Venous Arterialization

Distal venous arterialization may be offered as a last surgical resort for limb salvage in the absence of graftable distal arteries.^{354–358} Distal venous arterialization can successfully salvage the critically ischemic lower limb with few serious complications. A recent meta-analysis showed that overall 1-year foot preservation was 71% (95% CI: 64%–77%) and 1-year secondary patency was 46% (95% CI: 39%–53%) after distal venous arterialization.³⁵⁵

Local Wound Care

In clinical practice, wound toilet, including limited surgical or ultrasound debridement and appropriate antibiotics, is often useful in the treatment of infected ischemic ulcerations.⁷ Caution is advised for excessive local debridement, which may widen ulcers.³⁵⁹ Topical agents for eliminating necrotic tissue and infection, maintaining a moist environment, and managing wound margin are the hallmarks for the treatment of ischemic ulcers associated with any vasculitis.³⁵⁹ Given the absence of a proven benefit and its high cost, hyperbaric oxygen therapy should be considered only in selected patients with ischemic ulcers, osteomyelitis, or necrotizing fasciitis who have not responded to other forms of treatment.^{56,90,360–365} Negative-pressure wound therapy, as continuous or intermittent vacuum-assisted settings, may have a role in the treatment debilitating complex chronic ulcers in patients with TAO.^{366–368}

Endovascular Treatment

Percutaneous subintimal angioplasty for limb salvage in patients with non-healing ulcers has been proposed.^{369–372} Extended endovascular management for tibial or foot artery obstruction was achieved in 17 patients with TAO and CLI with a technical success rate of 95%.³⁷³ Successful use of Silver-Hawk directional atherectomy in two TAO patients with

popliteal occlusions was recently reported; however, this endovascular procedure requires further validation by more extensive studies.³⁷⁴ In a retrospective case-control study from China, endovascular recanalization ($n = 35$, 43 limbs) and autogenous venous bypass ($n = 40$, 47 limbs) procedures were compared in TAO patients ($n = 75$, 90 limbs) who presented with CLI.³⁷⁵ The investigators showed that endovascular recanalization could be applied even in patients without runoff vessels with comparable amputation-free survival rates.³⁷⁵ Another recent retrospective, single-center, cohort study from the Republic of Korea demonstrated that endovascular therapy ($n = 44$; CLI, 86.4%) with TAO resulted in 83% major adverse limb event-free survival and 68% reintervention- and amputation-free survival at 3 years.³⁷⁶

Other Interventional Procedures

Immunoabsorption

Recent pilot studies demonstrated near-complete pain relief, increased maximum walking distance, and tissue perfusion after selective removal of circulating immunoglobulins and antibodies from the patient's plasma using immunoabsorption techniques.^{377,378} In one study, agonistic autoantibodies directed against G-protein coupled receptors were identified in 9 out of 11 patients. The authors concluded that elimination of agonistic autoantibodies by immunoabsorption might relieve immune-mediated vasospasm and improve microcirculation.³⁷⁹

Growth Factors

Basic fibroblast growth factor and vascular endothelial growth factor (VEGF) may play a role in patients with CLI due to Buerger disease. Isner and colleagues treated seven limbs in six patients with TAO (three men, three women; mean age, 33 years) in an open-label, dose-escalating, phase 1 clinical trial to document the efficacy and safety of gene transfer of naked plasmid DNA encoding VEGF (phVEGF165) via intramuscular injection in the treatment of CLI.³⁸⁰ Ulcers, which had not healed for more than 1 month before therapy, healed completely in 3 of 5 limbs after intramuscular phVEGF165 gene therapy. Nocturnal pain at rest was relieved in the remaining two patients, although both continued to have claudication. Two patients with advanced distal forefoot gangrene ultimately required below-knee amputation despite evidence of improved perfusion. This report suggests that angiogenesis induced by phVEGF165 gene transfer may provide an effective therapy for patients with advanced TAO that is unresponsive to standard interventions.³⁸⁰ Another study demonstrated higher VEGF plasma levels in patients with TAO than controls ($P = 0.008$), showing the existence of a natural defense mechanism for ischemia and new collateral formation.³⁸¹ A recent Phase I/IIa open-label four dose-escalation clinical study assessing the safety, tolerability, and efficacy of a single intramuscular administration of DVC1-0101 in patients with PAD also involved two patients with TAO.³⁸² DVC1-0101 is a new gene transfer vector based on a non-transmissible recombinant Sendai virus (rSeV) expressing the human fibroblast growth factor-2 (FGF-2) gene (rSeV/dF-hFGF2). The investigators

TABLE 139.6

Prevalence of Amputations, Primary and Secondary Patency Rates After Surgical and Endovascular Arterial Revascularization in Patients with Thromboangiitis Obliterans

Authors	Year	Study Type	Number of Patients	Number of Bypasses/Target Vessels	Primary Patency	Secondary Patency	Limb Salvage	Amputations
Surgical Revascularization								
Sayin ³³⁷	1993	R	21	21	62.5% at 5 y†		*	4 major
Sasajima ³³²	1997	R	61	71	49% at 5 y 43% at 10 y	63% at 5 y 56% at 10 y	59%	3 major 8 minor
Nakajima ³³⁶	1998	R	26		65% at 2 y†		*	*
Bozkurt ⁴⁰⁹	1998	P	14	14	57% at 8 y†		89%	*
Shindo ³⁴²	2002	R	8	10	*	*	*	*
Dilege ³³⁵	2002	P	27	24	59% at 1 y 48% at 2 y	33% at 3 y	93% at 3 y	2 major
Bozkurt ³³⁸	2004	P	19	20	*	57.9% at 5.4 y	90%	2 major
Ohta ²⁶³	2004	R	31	46	41% at 1 y 32% at 5 y 30% at 10 y	54% at 1 y 48% at 5 y 39% at 10 y	91% at 1 y 89% at 5 y 85% at 10 y	5 major (14%)
Ates ⁵²	2006	R	27	27	44.8% at 1 y† 37% at 5 y		*	12 (total)
Sugimoto ²⁷¹	2015	R	22	23	67% at 5 y† 45.6% at 10 y	*	90% at 20 y^ 69% at 20 y^AA	2 major
Ye ³⁷⁵	2017	R	40	47	71.1% at 1 y 60.4% at 3 y	80.9% at 1 y 68.7% at 3 y	93.2% at 1 y 90.6% at 3 y	4 major 6 minor
Endovascular Revascularization								
Graziani ³⁷³	2012	R	17	47 (36 below-knee)	*	*	100%	3 minor
Ye ³⁷⁵	2017	R	35	43	51.3% at 1 y 18.9% at 3 y	64.8% at 1 y 33.9% at 3 y	92.9% at 1 y 87.8% at 3 y	5 major 7 minor
Modaghegh ⁴¹⁰	2018	R	13	30	*	*	92.3% at 1 y	1 major 8 minor
Kim ³⁷⁶	2018	R	44	88	*	*	90.2% at 1 y 86.7% at 3 y 86.7% at 5 y	11.9% at 1 y 18.7% at 3 y 24.5% at 5 y
Firat ⁴¹¹	2019	R	28	40	84% at 1 y 78% at 2 y 75% at 3 y	87.5% at 1 y 87.5% at 2 y	96.8% at 1 y 96.8% at 2 y	1 major 4 minor

*Not mentioned

†Not stated primary or secondary

^Ex-smoker

^AAStill-smoker

P, prospective; R, retrospective; y, year.

Adapted from refs 15, 259.

concluded that DVC1-0101 was safe, effective and resulted in significant improvements of limb function.³⁸²

Stem Cell-Based Therapeutic Angiogenesis

Angioblasts isolated from peripheral blood or bone marrow-derived circulating progenitor cells (CPC) can be incorporated into sites of active angiogenesis, providing a key factor in re-endothelialization.³⁸³ Culture-expanded CPC transplantation in an animal model of limb ischemia improved neovascularization and blood flow recovery and reduced limb necrosis and autoamputation by 50% compared with controls.³⁸⁴ Preclinical,³⁸⁵ and clinical studies in patients with peripheral artery

disease and CLI,³⁸⁶ including TAO, suggest that the implantation of autologous bone marrow mononuclear cells,^{387–390} autologous peripheral blood stem cells,^{391,392} mesenchymal stem cells derived from human umbilical cord blood,³⁹³ autologous adipose tissue-derived stem cells,³⁹⁴ autologous whole bone marrow stem cells³⁹⁵ into ischemic limbs can restore limb function by increasing new collateral vessel formation.³⁹⁶ Our colleagues and we have also demonstrated that the implantation of autologous bone marrow mononuclear cells (ABMMNC) in the ischemic limbs of patients with TAO is associated with improved rest pain scores ($P < 0.0001$), peak walking time ($P < 0.0001$), quality of life ($P < 0.0083$), and augmentation of

collateral formation at 24 weeks in 78% of patients.^{388,397,398} Healing of ischemic ulcers was achieved in 83% of the study group (Fig. 139.9). For the study population, the 10-year amputation-free rate was 96% in ABMMNC-implanted limbs and 93% in saline-injected limbs.³⁹⁹ Subsequent studies and meta-analysis supported intramuscular bone marrow cell administration as a relatively safe, feasible, and potentially effective therapy in patients with CLI and TAO.^{396,400} Bone marrow-derived mononuclear cell therapy induced long-term improvement leading to an amputation-free rate of 91% (95% CI: 82%–100%) at 3 years in the Therapeutic Angiogenesis by Cell Transplantation (TACT) Trial.⁴⁰¹ A combined intra-arterial and intramuscular injections approach may maximize the chances of local deposition of stem cells in the ischemic limb.⁴⁰² However, a recent Cochrane systematic review by Caccione et al.⁴⁰³ included only one RCT⁴⁰⁴ ($n = 18$) comparing the implantation of stem cell derived from bone marrow with placebo and standard wound dressing care. They concluded that very low-quality evidence suggests there may be an effect of bone marrow-derived stem cells in the healing of ulcers.

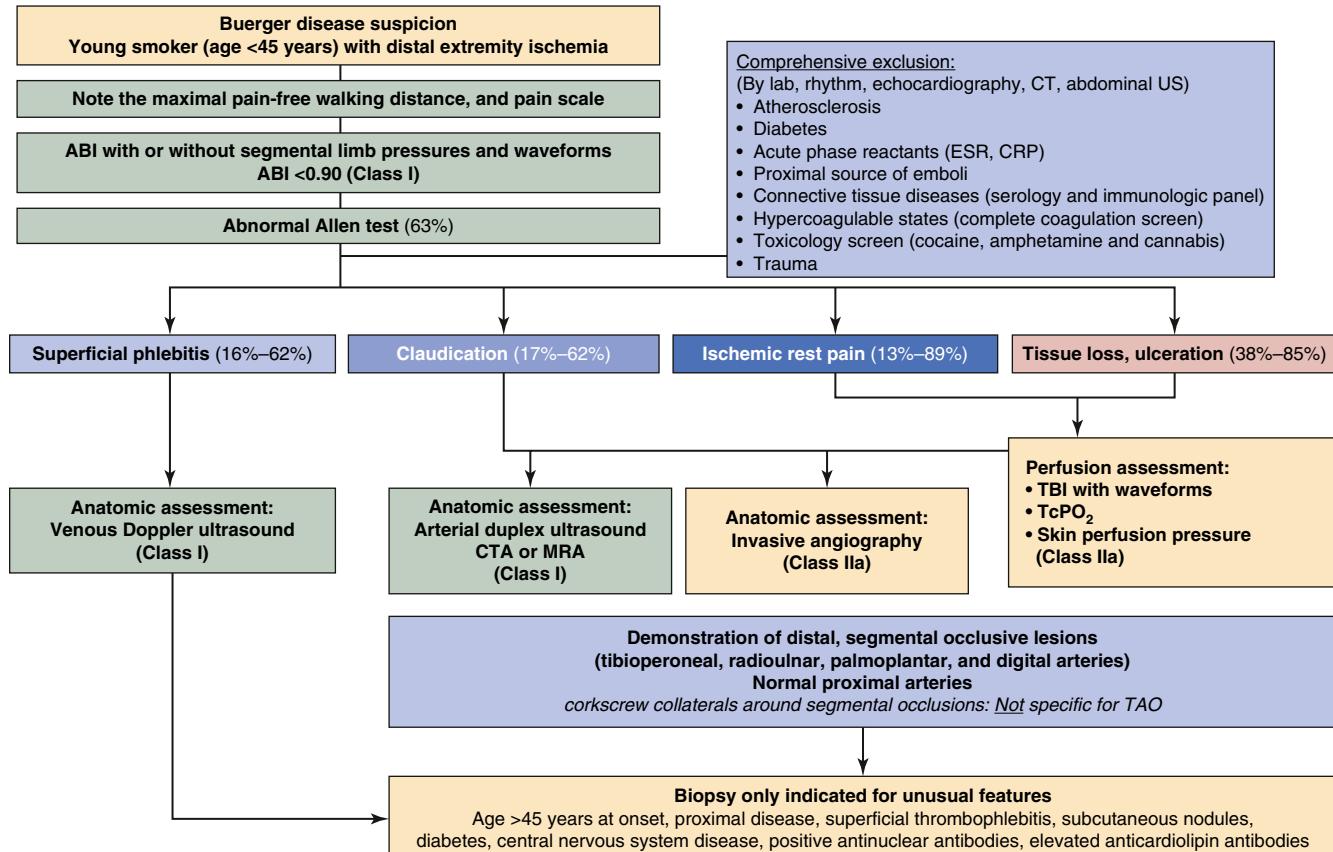
and improvement in the pain-free walking distance in patients with TAO.⁴⁰³

Inan and associates have suggested another method of stimulating angiogenesis by inserting intramedullary K-wires.⁴⁰⁵ Fenestration of the tibia at six sites with endothelial progenitor cell (EPC) mobilization from bone marrow using recombinant human granulocyte colony-stimulating factor was reported recently by Kim and associates in 27 patients (34 lower limbs) with Buerger disease.⁴⁰⁶ Over a mean follow-up period of 19 months, 13 of 17 limbs with nonhealing ulcers healed. This technique resulted in a similar degree of new vascular collateral network development⁴⁰⁶ compared with ABMMNC aspirated from the iliac crest and implanted into the intermetatarsal region, the gastrocnemius muscle, and the dorsum of the foot or forearm.³⁸⁸ Recently, functional impairment of EPCs was confirmed in TAO patients compared to healthy nonsmokers and smokers.⁴⁰⁷ Ongoing work is focused on understanding the mechanisms of therapeutic angiogenesis, including vascular stem cell niches, mobilization, homing, and vascular repair.⁴⁰⁸



Figure 139.9 Limb salvage after autologous bone marrow-derived mononuclear cell therapy. Preoperatively (left), this patient had a non-healing ischemic wound of the great toe and required high doses of narcotic analgesics. After surgical debridement (right), complete healing was achieved at 3 weeks and maintained at 24 months.

CHAPTER ALGORITHM



ACKNOWLEDGMENTS

We sincerely thank Drs. Shigehiko Shionoya and Jeffrey W. Olin, the authors of this chapter in previous editions, for their outstanding work, which has provided invaluable insights into Buerger disease, and Drs. Isinsu Kuzu and Suat Aytac of the Ankara University School of Medicine for their scientific assistance and the provision of pathology and radiology illustrations, and Kanat Akar for algorithm illustrations.

SELECTED KEY REFERENCES

Cacione DG, Macedo CR, do Carmo Novaes F, Baptista-Silva JC. Pharmacological treatment for Buerger's disease. *Cochrane Database Syst Rev*. 2020;5:CD011033.

This critical systematic review and meta-analysis assessed the effectiveness of any pharmacological agent (intravenous or oral) compared with placebo or any other pharmacological agent in patients with TAO. In this review, 5 RCTs were identified (n = 602) comparing prostacyclin analog with placebo, aspirin, or a prostaglandin analog, and folic acid with placebo.

Cooper LT, Tse TS, Mikhail MA, et al. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). *J Am Coll Cardiol*. 2004;44:2410–2411.

This study describes the time-dependent event rates for major or any amputation and death in a cohort of patients with TAO. In contrast with previous studies, the investigators report excessive late mortality in patients with TAO compared with the U.S. population. However, the risk of amputation in past smokers is eliminated by eight years after smoking cessation.

Durdur S, Akar AR, Arat M, et al. Autologous bone-marrow mononuclear cell implantation for patients with Rutherford grade II–III thromboangiitis obliterans. *J Vasc Surg*. 2006;44:732–739.

This is the first study investigating the use of autologous bone marrow mononuclear cell implantation for patients with Rutherford grade II–III thromboangiitis obliterans resulting in new vascular collateral networks across the affected arteries in 78.5% of the patients. Total healing of the most critical lesion was achieved in 83% of patients with ischemic ulcers. Relief of rest pain without the need for narcotic analgesics improved in all patients.

Isner JM, Baumgartner I, Rauh G, et al. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. *J Vasc Surg*. 1998;28:964–973.

The first report that documents the results of six patients with Buerger disease who were treated with gene therapy as part of a larger phase I clinical trial to document the safety and efficacy of intramuscular gene transfer of naked plasmid DNA-encoding vascular endothelial growth factor (phVEGF165) in the treatment of critical limb ischemia.

Kim DI, Kim MJ, Joh JH, et al. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. *Stem Cells*. 2006;24:1194–1200.

This intriguing study documents the angiogenesis facilitated by fenestration of the tibia bone and autologous whole bone marrow stem cell transplantation for Buerger disease.

Kobayashi M, Ito M, Nakagawa A, et al. Immunohistochemical analysis of arterial wall cellular infiltration in Buerger's disease (endarteritis obliterans). *J Vasc Surg*. 1999;29:451–458.

This original study describes important histological observations from 33 specimens of nine patients with TAO. The investigators concluded that TAO was a vasculitis (endarteritis) induced by an antigen in the intimal layer and subsequent activation of T cell-mediated cellular immunity and B cell-mediated humoral immunity associated with activation of macrophages or dendritic cells in the intima.

Kobayashi M, Sugimoto M, Komori K. Endarteritis obliterans in the pathogenesis of Buerger's disease from the pathological and immunohistochemical points of view. *Cir J*. 2014;78:2819–2826.

This review demonstrates the important pathological characteristics of arteries affected by TAO. The authors' observations support the activation of antigen-presenting cells by an unidentified antigen in the blood, resulting in an immunoreaction closely linked to Notch signaling pathway. The authors conclude that restriction of cellular and humoral immune reaction to the arterial intima defines TAO as an endarteritis.

Le Joncour A, Soudet S, Dupont A, et al. Long-term outcome and prognostic factors of complications in thromboangiitis obliterans (Buerger's disease): a multicenter study of 224 patients. *J Am Heart Assoc*. 2018;7:e010677.

An important study with the most extensive TAO series on the long-term outcomes from a Western country.

Mills SR JL. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003;16:179–189.

This review is another significant update on the clinical features and fundamental management principles of Buerger disease. The concept "No tobacco, no Buerger disease" is reintroduced.

Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of Buerger disease. *J Vasc Surg*. 2004;39:176–180.

This original investigation documents the natural course of TAO in Japan. The investigators report that occurrence or recurrence of necrotic lesions usually subsides after the age of 60, and arterial reconstruction is associated with poor long-term results, although it shortens the healing process of ischemic ulcers.

Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med*. 2000;343:864–869.

This landmark review summarizes the clinical features, pathogenesis, diagnostic criteria, and recommendations for the treatment of thromboangiitis obliterans and currently is still relevant.

Shionoya S. Diagnostic criteria of Buerger's disease. *Int J Cardiol*. 1998;66(Suppl 1):S243–S245.

The article outlines the need for well-defined, valid clinical diagnostic criteria for TAO, and essential clinical picture hallmarks.

The European TAO Study Group. Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomized, placebo-controlled trial. *Eur J Vasc Endovasc Surg*. 1998;15:300–307.

The first RCT comparing oral iloprost with placebo conducted in 22 centers in six European countries.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Buerger L. Thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene. *Am J Med Sci.* 1908;136:567–580.
2. Buerger L. Landmark publication from the American Journal of the Medical Sciences, ‘Thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene’. 1908. *Am J Med Sci.* 2009;337(4):274–284.
3. Olin JW. Thromboangiitis obliterans (Buerger’s disease). *N Engl J Med.* 2000;343(12):864–869.
4. Olin JW. Thromboangiitis obliterans. *Curr Opin Rheumatol.* 1994;6(1):44–49.
5. Olin JW, Young JR, Graor RA, et al. The changing clinical spectrum of thromboangiitis obliterans (Buerger’s disease). *Circulation.* 1990;82(5 suppl):IV3–IV8.
6. Piazza G, Creager MA. Thromboangiitis obliterans. *Circulation.* 2010;121(16):1858–1861.
7. Mills JL, Sr. Buerger’s disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg.* 2003;16(3):179–189.
8. Shionoya S. Diagnostic criteria of Buerger’s disease. *Int J Cardiol.* 1998;66(suppl 1):S243–S245.
9. Shionoya S. Buerger’s disease: diagnosis and management. *Cardiovasc Surg.* 1993;1(3):207–214.
10. Papa MZ, Rabi I, Adar R. A point scoring system for the clinical diagnosis of Buerger’s disease. *European J Vasc Endovasc Surg.* 1996;11(3):335–339.
11. Akar AR, Inan B. Thromboangiitis obliterans (Buerger disease). In: Sidawy AN, Perler BA, eds. *Rutherford’s Vascular Surgery and Endovascular Therapy.* 9th ed. Philadelphia: Elsevier; 2019:1809–1826.
12. Akar AR, Durdu S. Thromboangiitis obliterans. In: Cronenwett JL, Johnston KW, eds. *Rutherford’s Vascular Surgery.* 8th ed. Philadelphia: Elsevier, Saunders-Society for Vascular Surgery; 2014:1167–1186.
13. Akar AR, Durdu S. Thromboangiitis obliterans. In: Cronenwett JL, Johnston KW, eds. *Rutherford’s Vascular Surgery.* 7th ed. Philadelphia: Saunders, Elsevier-Society for Vascular Surgery; 2010:1169–1186.
14. Akar AR, Durdu S. Buerger’s disease. In: Hoffman GS, Weyand CM, Langford CA, Goronzy JJ, eds. *Inflammatory Diseases of Blood Vessels.* 2nd ed. Oxford: Blackwell Publishing; 2012:351–365.
15. Dargon PT, Landry GJ. Buerger’s disease. *Ann Vasc Surg.* 2012;26(6):871–880.
16. Qaja E, Muco E, Hashmi MF. Buerger Disease. In: StatPearls [Internet]. Treasure Island, FL: StatPearls; 2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK430858/>
17. Gallagher KA, Tracci MC, Scovell SD. Vascular arteritides in women. *J Vasc Surg.* 2013;57:27S–36S.
18. Lie JT. The rise and fall and resurgence of thromboangiitis obliterans (Buerger’s disease). *Acta Pathol Jpn.* 1989;39(3):153–158.
19. Mills JL, Porter JM. Buerger’s disease: a review and update. *Semin Vasc Surg.* 1993;6(1):14–23.
20. Kobayashi M, Ito M, Nakagawa A, et al. Immunohistochemical analysis of arterial wall cellular infiltration in Buerger’s disease (endarteritis obliterans). *J Vasc Surg.* 1999;29(3):451–458.
21. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheumat.* 2013;65(1):1–11.
22. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol.* 2013;17(5):603–606.
23. Puechal X, Fiessinger JN. Thromboangiitis obliterans or Buerger’s disease: challenges for the rheumatologist. *Rheumatology(Oxford).* 2007;46(2):192–199.
24. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(12):e726–e779.
25. Shionoya S. *Buerger’s disease: Pathology, diagnosis and treatment.* Nagoya: University of Nagoya Press; 1990.
26. von Winiwarter F. Ueber eine eigenthümliche Form von Endarteriitis und Endophlebitis mit Gangrän des Fusses. *Arch Klin Chir.* 1879;23:202–226.
27. Haga E. Über spontane Gangräne. *Arch Pathol Anat.* 1898;152:26–60.
28. Buerger L. The association of migrating thrombophlebitis with thrombo-angiitis. *Internat Clin.* 1909;19:84–105.
29. Buerger L. *The Circulatory Disturbances of the Extremities: Including Gangrene, Vasomotor, and Trophic Disorders.* Philadelphia: WB Saunders; 1924.
30. Allen EV, Brown GE. Thrombo-angiitis obliterans: A clinical study of 200 cases. *Ann Int Med.* 1928;1:535–549.
31. Gore I, Burrows S. A reconsideration of the pathogenesis of Buerger’s disease. *Am J Clin Pathol.* 1958;29(4):319–330.
32. Wessler S, Ming S, Gurewich V, Freiman DG. A critical evaluation of thromboangiitis obliterans. The case against Buerger’s disease. *N Engl J Med.* 1960;262:1149–1160.
33. Wessler S. Thromboangiitis obliterans: fact or fancy. *Circulation.* 1961;23:165–167.
34. Horwitz O. Buerger’s disease retrieved. *Ann Int Med.* 1961;55(2):341–344.
35. McKusick VA, Harris WS, Ottesen OE. Buerger’s disease, a distinct clinical and pathologic entity. *JAMA.* 1962;181:93–100.
36. Mcpherson JR, Juergens JL, Gifford Jr RW. Thromboangiitis obliterans and arteriosclerosis obliterans. Clinical and prognostic differences. *Ann Int Med.* 1963;59:288–296.
37. Abramson DI, Zayas AM, Canning JR, Edinburg JJ. Thromboangiitis obliterans: A true clinical entity. *Am J Cardiol.* 1963;12:107–118.
38. Szilagyi DE, Derusso FJ, Elliot Jr JP. Thromboangiitis obliterans. Clinico-angiographic correlations. *Arch Surg.* 1964;88:824–835.
39. Shionoya S. What is Buerger’s disease? *World J Surg.* 1983;7(4):544–551.
40. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 16-1989. A 36-year-old man with peripheral vascular disease. *N Engl J Med.* 1989;320(16):1068–1076.
41. Ansari A. Thromboangiitis obliterans: current perspectives and future directions. *Tex Heart Inst J.* 1990;17(2):112–117.
42. Rivera-Chavarría IJ, Brenes-Gutierrez JD. Thromboangiitis obliterans (Buerger’s disease). *Ann Med Surg (Lond).* 2016;7:79–82.
43. Nielubowicz J, Rosnowski A, Pruszynski B, et al. Natural history of Buerger’s disease. *J Cardiovasc Surg.* 1980;21(5):529–540.
44. Mills JL, Porter JM. Buerger’s disease (thromboangiitis obliterans). *Ann Vasc Surg.* 1991;5(6):570–572.
45. Cutler DA, Runge MS. 86 years of Buerger’s disease--what have we learned? *Am J Med Sci.* 1995;309(2):74–75.
46. Wysokinski WE, Kwiatkowska W, Sapien-Raczkowska B, et al. Sustained classic clinical spectrum of thromboangiitis obliterans (Buerger’s disease). *Angiology.* 2000;51(2):141–150.
47. Williams G. Recent views on Buerger’s disease. *J Clin Pathol.* 1969;22(5):573–578.
48. Cachovan M. Epidemiologic und geographisches Verteilungsmuster der Thromboangiitis obliterans Stuttgart. In: Heidrich H, ed. *Thromboangiitis obliterans Morbus Winiwarter-Buerger.* 1988:31–36.
49. Ishikawa K. In: Welfare MoHa, ed. *Annual report of the Buerger’s disease research committee of Ministry of Health and Welfare of Japan.* Tokyo: Japan; 1976:89–97.
50. Matsushita M, Nishikimi N, Sakurai T, Nimura Y. Decrease in prevalence of Buerger’s disease in Japan. *Surgery.* 1998;124(3):498–502.
51. Arkkila PE. Thromboangiitis obliterans (Buerger’s disease). *Orphanet J Rare Dis.* 2006;1:14.
52. Ates A, Yekeler I, Ceviz M, et al. One of the most frequent vascular diseases in northeastern of Turkey: Thromboangiitis obliterans or Buerger’s disease (experience with 344 cases). *Int J Cardiol.* 2006;111(1):147–153.
53. Horton B. The outlook in thromboangiitis obliterans. *JAMA.* 1938;111:2184–2189.
54. Lie JT. Thromboangiitis obliterans (Buerger’s disease) in women. *Medicine.* 1987;66(1):65–72.
55. Matsushita M, Kuzuya A, Kobayashi M, et al. Buerger’s disease in a 19-year-old woman. *J Vasc Surg.* 2003;38(1):175–179.

56. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33(suppl 1):S1–75.
57. Laslett LJ, Ikeda RM, Mason DT. Female adolescent Buerger's disease: objective documentation and therapeutic remission. *Am Heart J.* 1981;102(3 Pt 1):452–456.
58. Mills JL, Taylor LM Jr , Porter JM. Buerger's disease in the modern era. *Am J Surg.* 1987;154(1):123–129.
59. Malecki R, Zdrojowy K, Adamiec R. Thromboangiitis obliterans in the 21st century--a new face of disease. *Atherosclerosis.* 2009;206(2):328–334.
60. Jimenez-Ruiz CA, Dale LC, Astray MJ, et al. Smoking characteristics and cessation in patients with thromboangiitis obliterans. *Monaldi Arch Chest Dis.* 2006;65(4):217–221.
61. Casellas M, Perez A, Cabero L, Segura A, Puig dM, Selva OCR. Buerger's disease and antiphospholipid antibodies in pregnancy. *Ann Rheum Dis.* 1993;52(3):247–248.
62. Kikuchi N, Kanai M, Kita N, et al. Pregnancy complicated with Buerger's disease. *Int J Gynaecol Obstet.* 2006;94(1):62–66.
63. Young SG, Hanson FW, Kahn BB. Pregnancy in a young woman with Buerger's disease. A case report. *J Reprod Med.* 1983;28(10):694–696.
64. Zelikovsky A, Urca I, Kessler E. Thromboangiitis obliterans in a woman. Report of a case. *Angiology.* 1973;24(3):169–174.
65. Lie JT. Thromboangiitis obliterans (Buerger's disease) revisited. *Pathol Annu.* 1988;23(Pt 2):257–291.
66. Kobayashi M, Nishikimi N, Komori K. Current pathological and clinical aspects of Buerger's disease in Japan. *Ann Vasc Surg.* 2006;20(1):148–156.
67. Hida N, Ohta T. Current status of patients with Buerger disease in Japan. *Ann Vasc Dis.* 2013;6(3):617–623.
68. Aqel MB, Olin JW. Thromboangiitis obliterans (Buerger's disease). *Vasc Med.* 1997;2(1):61–66.
69. Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol.* 2006;18(1):18–24.
70. Papa MZ, Adar R. A critical look at thromboangiitis obliterans (Buerger's disease). *Perspect Vasc Surg.* 1992;5:1–21.
71. Rahman M, Chowdhury AS, Fukui T, et al. Association of thromboangiitis obliterans with cigarette and bidi smoking in Bangladesh: a case-control study. *Int J Epidemiol.* 2000;29(2):266–270.
72. Hill GL, Moeliono J, Tumewu F, et al. The Buerger syndrome in Java. A description of the clinical syndrome and some aspects of its aetiology. *Br J Surg.* 1973;60(8):606–613.
73. Hill GL, Smith AH. Buerger's disease in Indonesia: Clinical course and prognostic factors. *J Chronic Dis.* 1974;27(4):205–216.
74. Desbois AC, Cacoub P. Cannabis-associated arterial disease. *Ann Vasc Surg.* 2013;27(7):996–1005.
75. O'Dell JR, Linder J, Markin RS, Moore GF. Thromboangiitis obliterans (Buerger's disease) and smokeless tobacco. *Arthritis Rheum.* 1987;30(9):1054–1056.
76. Joyce JW. Buerger's disease (thromboangiitis obliterans). *Rheum Dis Clin North Am.* 1990;16(2):463–470.
77. Hill GL, Moeliono J, Tumewu F, Brataamadja D, Tohardi A. Asian cigarette" is an adverse prognostic factor in peripheral arterial disease. *Nature.* 1973;246(5434):492–493.
78. Grove WJ, Stansby GP. Buerger's disease and cigarette smoking in Bangladesh. *Ann R Coll Surg Engl.* 1992;74(2):115–117.
79. Kjeldsen K, Mozes M. Buerger's disease in Israel. Investigations on carboxyhemoglobin and serum cholesterol levels after smoking. *Acta Chir Scand.* 1969;135(6):495–498.
80. Boyd AM. The diagnosis and pathogenesis of obliterative vascular disease of the lower extremities. *Angiology.* 1950;1(5):373–390.
81. Dezellus P, Capron L, Fiessinger JN, Housset E. [Juvenile arteriopathy and nasal sympathomimetics]. *Nouv Presse Med.* 1982;11(29):2231.
82. Hagen B, Lohse S. Clinical and radiologic aspects of Buerger's disease. *Cardiovasc Intervent Radiol.* 1984;7(6):283–293.
83. Noel B. Thromboangiitis obliterans a new look for an old disease. *Int Cardiol.* 2001;78(2):199.
84. Watts RA, Scott DG. Epidemiology of the vasculitides. *Curr Opin Rheumatol.* 2003;15(1):11–16.
85. Fazeli B. Buerger's disease as an indicator of socioeconomic development in different societies, a cross-sectional descriptive study in the North-East of Iran. *Arch Med Sci.* 2010;6(3):343–347.
86. Disdier P, Swiader L, Jouglard J, et al. [Cannabis-induced arteritis vs. Leo Buerger disease. Nosologic discussion apropos of two new cases]. *Presse Med.* 1999;28(2):71–74.
87. Marder VJ, Mellingshoff IK. Cocaine and Buerger disease: is there a pathogenetic association? *Arch Intern Med.* 2000;160(13):2057–2060.
88. Noel B. Vascular complications of cocaine use. *Stroke.* 2002;33(7):1747–1748.
89. Noel B. Cocaine and arsenic-induced Raynaud's phenomenon. *Clin Rheumatol.* 2002;21(4):343–344.
90. Combemale P, Consort T, Denis-Thelis L, et al. Cannabis arteritis. *Br J Dermatol.* 2005;152(1):166–169.
91. Martin-Blondel G, Koskas F, Cacoub P, Sene D. Is thromboangiitis obliterans presentation influenced by cannabis addiction? *Ann Vasc Surg.* 2011;25(4):469–473.
92. Tseng CH, Chong CK, Chen CJ, Tai TY. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis.* 1996;120(1–2):125–133.
93. Tseng CH. Blackfoot disease and arsenic: a never-ending story. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2005;23(1):55–74.
94. Noel B. [Smoking and Buerger's disease: an arsenical controversy]. *J Mal Vasc.* 2001;26(4):265–266.
95. Noel B. Regarding "cannabis arteritis revisited--ten new case reports". *Angiology.* 2001;52(7):505–506.
96. Noel B. Buerger disease or arsenic intoxication? *Arch Intern Med.* 2001;161(7):1016.
97. Szuba A, Cooke JP. Thromboangiitis obliterans. An update on Buerger's disease. *West J Med.* 1998;168(4):255–260.
98. Roth GM, Shick RM. Effect of smoking on the cardiovascular system of man. *Circulation.* 1958;17(3):443–459.
99. Iwai T, Inoue Y, Umeda M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. *J Vasc Surg.* 2005;42(1):107–115.
100. Malecki R, Kluz J, Przedzicka-Dolyk J, Adamiec R. The pathogenesis and diagnosis of thromboangiitis obliterans: is it still a mystery? *Adv Clin Exp Med.* 2015;24(6):1085–1097.
101. Liew NC, Lee L, Hanipah ZN, et al. Pathogenesis and management of Buerger's disease. *Int J Lower Extremity Wounds.* 2015;14(3):231–235.
102. Harkavy J. Tobacco sensitivities in thromboangiitis obliterans, migratory phlebitis, and coronary artery disease. *Bull N Y Acad Med.* 1933;9:318–322.
103. Silbert S. Etiology of thromboangiitis obliterans. *JAMA.* 1945;129:5–9.
104. Matsushita M, Shionoya S, Matsumoto T. Urinary cotinine measurement in patients with Buerger's disease--effects of active and passive smoking on the disease process. *J Vasc Surg.* 1991;14(1):53–58.
105. Smolen JS, Youngchaiyud U, Weidinger P, et al. Autoimmunological aspects of thromboangiitis obliterans (Buerger's disease). *Clin Immunol Immunopathol.* 1978;11(2):168–177.
106. Adar R, Papa MZ, Halpern Z, et al. Cellular sensitivity to collagen in thromboangiitis obliterans. *N Engl J Med.* 1983;308(19):1113–1116.
107. Smolen JS, Weidinger P, Menzel EJ. Sensitivity to collagen in thromboangiitis obliterans. *N Engl J Med.* 1983;309(14):857–858.
108. Hada M, Sakihama T, Kamiya K, et al. Cellular and humoral immune responses to vascular components in thromboangiitis obliterans. *Angiology.* 1993;44(7):533–540.
109. Gulati SM, Singh KS, Thusoo TK, Saha K. Immunological studies in thromboangiitis obliterans (Buerger's disease). *J Surg Res.* 1979;27(5):287–293.
110. Gulati SM, Madhra K, Thusoo TK, et al. Autoantibodies in thromboangiitis obliterans (Buerger's disease). *Angiology.* 1982;33(10):642–651.

111. Roncon dA, Delgado L, Correia P, et al. Circulating immune complexes in Buerger's disease. Endarteritis obliterans in young men. *J Cardiovasc Surg.* 1989;30(5):821–825.
112. Papa MZ, Bass A, Adar R, et al. Autoimmune mechanisms in thromboangiitis obliterans (Buerger's disease): the role of tobacco antigen and the major histocompatibility complex. *Surgery.* 1992;111(5):527–531.
113. Halacheva K, Gulubova MV, Manolova I, Petkov D. Expression of ICAM-1, VCAM-1, E-selectin and TNF-alpha on the endothelium of femoral and iliac arteries in thromboangiitis obliterans. *Acta Histochem.* 2002;104(2):177–184.
114. Dellalibera-Joviliano R, Joviliano EE, Silva JS, Evora PR. Activation of cytokines corroborate with development of inflammation and autoimmunity in thromboangiitis obliterans patients. *Clin Exp Immunol.* 2012;170(1):28–35.
115. Slavov ES, Stanilova SA, Petkov DP, Dobreva ZG. Cytokine production in thromboangiitis obliterans patients: new evidence for an immune-mediated inflammatory disorder. *Clin Exp Rheumatol.* 2005;23(2):219–226.
116. Kong X, Yuan H, Wu X, et al. High-mobility-group box protein 1 A box reduces development of sodium laurate-induced thromboangiitis obliterans in rats. *J Vasc Surg.* 2013;57(1):194–204.
117. De Caridi G, Bitto A, Massara M, et al. Increased serum HMGB-1, ICAM-1 and Metalloproteinase-9 levels in Buerger's patients. *Curr Vasc Pharmacol.* 2016;14(4):382–387.
118. Vasugi Z, Danda D. Systemic lupus erythematosus with antiphospholipid antibody syndrome: A mimic of Buerger's disease. *J Postgrad Med.* 2006;52(2):132–133.
119. Maslowski L, McBane R, Alexewicz P, Wysokinski WE. Antiphospholipid antibodies in thromboangiitis obliterans. *Vasc Med.* 2002;7(4):259–264.
120. de Godoy JM, Braile DM, Godoy MF. Buerger's disease and anti-cardiolipin antibodies: a worse prognosis? *Clin Appl Thromb Hemost.* 2002;8(1):85–86.
121. Heper G, Kose S, Akkoc O, Amasyali B, Kilic A. Two female non-smoker Buerger's disease cases with anticardiolipin autoantibodies and a poor prognosis. *Int Heart J.* 2005;46(3):563–569.
122. Halacheva KS, Manolova IM, Petkov DP, Andreev AP. Study of anti-neutrophil cytoplasmic antibodies in patients with thromboangiitis obliterans (Buerger's disease). *Scand J Immunol.* 1998;48(5):544–550.
123. Eichhorn J, Sima D, Lindschau C, et al. Antientothelial cell antibodies in thromboangiitis obliterans. *Am J Med Sci.* 1998;315(1):17–23.
124. Schellong SM, Rautmann A, Gross WL, Alexander K. No ANCA in thromboangiitis obliterans (Buerger's disease). *Adv Exp Med Biol.* 1993;336:327–330.
125. Wysokinski WE, Kwiatkowska W, Maslowski L, et al. Buerger's disease in two brothers: iliac artery occlusion by thromboangiitis obliterans—case reports. *Angiology.* 1998;49(5):409–414.
126. Tashiro T. Epidemiological studies on Buerger's disease in Japan (in Japanese). *Gendai Iryo.* 1976;8:1231–1237.
127. Papa M, Bass A, Adar R, Halperin Z, et al. Autoimmune mechanisms in thromboangiitis obliterans (Buerger's disease): the role of tobacco antigen and the major histocompatibility complex. *Surgery.* 1992;111(5):527–531.
128. McLoughlin GA, Helsby CR, Evans CC, Chapman DM. Association of HLA-A9 and HLA-B5 with Buerger's disease. *Br Med J.* 1976;2(6045):1165–1166.
129. Aerabajnai W, Tsuchiya T, Kimura A, et al. HLA class II DNA typing in Buerger's disease. *Int J Cardiol.* 1996;54(suppl):S167–S172.
130. Kimura A, Kobayashi Y, Takahashi M, et al. MICA gene polymorphism in Takayasu's arteritis and Buerger's disease. *Int J Cardiol.* 1998;66(suppl 1):S107–S113.
131. Mehra NK, Jaini R. Immunogenetics of peripheral arteriopathies. *Clin Hemorheol Microcirc.* 2000;23(2–4):225–232.
132. Dehghani Firouzabadi F, Salimi J, Amirzargar A, et al. Human leukocyte antigen class I (A, B) and class II (DRB1) allele and haplotype frequencies in Iranian patients with Buerger's disease. *Immun Inflamm Dis.* 2020;8(3):434–440.
133. Glueck CJ, Haque M, Winarska M, et al. Stromelysin-1 5A/6A and eNOS T-786C polymorphisms, MTHFR C677T and A1298C mutations, and cigarette-cannabis smoking: a pilot, hypothesis-generating study of gene-environment pathophysiological associations with Buerger's disease. *Clin Appl Thromb Hemost.* 2006;12(4):427–439.
134. Shi ZF, Fang QB, Limu S, et al. Association Between Three SNPs and Thromboangiitis Obliterans in Xinjiang Uyghur Population. *Genet Test Mol Biomarkers.* 2016;20(2):55–62.
135. Shi Z-F, Fang Q-B, Limu S, et al. Association between three snps and thromboangiitis obliterans in Xinjiang Uyghur population. *Genetic Testing and Molecular Biomarkers.* 2016;20(2):55–62.
136. Brodmann M, Renner W, Stark G, et al. Prothrombotic risk factors in patients with thrombangitis obliterans. *Thromb Res.* 2000;99(5):483–486.
137. Avcu F, Akar E, Demirkilic U, et al. The role of prothrombotic mutations in patients with Buerger's disease. *Thromb Res.* 2000;100(3):143–147.
138. Demirbas MY, Gülsever M. Comparison of ADP-and collagen-induced platelet aggregation responses between patients with Buerger's disease and healthy individuals. *Turk Gogus Kalp Dama.* 2009;17(2):106–109.
139. Stammler F, Diehm C, Hsu E, et al. [The prevalence of hyperhomocysteinem in thromboangiitis obliterans. Does homocysteine play a role pathogenetically?]. *Dtsch Med Wochenschr.* 1996;121(46):1417–1423.
140. Mercie P, Baste JC, Sassoust G, et al. Factor V Leiden, mild hyperhomocyst(e)inemia and Buerger's disease. *Microvasc Res.* 1998;55(3):271–272.
141. Diehm C, Stammler F. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med.* 2001;344(3):230–231.
142. Di Micco P, Niglio A, Scudiero O, et al. A case of Buerger's disease associated with MTHFR C677T mutation homozygosity: a possible therapeutic support. *Nutr Metab Cardiovasc Dis.* 2004;14(4):225–226.
143. Caramaschi P, Biasi D, Carletto A, et al. Three cases of Buerger's disease associated with hyperhomocysteinem. *Clin Exp Rheumatol.* 2000;18(2):264–265.
144. Carr Jr ME, Hackney MH, Hines SJ, et al. Enhanced platelet force development despite drug-induced inhibition of platelet aggregation in patients with thromboangiitis obliterans—two case reports. *Vasc Endovascular Surg.* 2002;36(6):473–480.
145. Hus I, Sokolowska B, Walter-Croneck A, et al. Assessment of plasma prothrombotic factors in patients with Buerger's disease. *Blood Coagulat Fibrinolysis.* 2013;24(2):133–139.
146. Choudhury NA, Pietraszek MH, Hachiya T, et al. Plasminogen activators and plasminogen activator inhibitor 1 before and after venous occlusion of the upper limb in thromboangiitis obliterans (Buerger's disease). *Thromb Res.* 1992;66(4):321–329.
147. Chen YW, Iwai T, Umeda M, et al. Elevated IgG titers to periodontal pathogens related to Buerger disease. *Int J Cardiol.* 2007;122(1):79–81.
148. Chen YW, Nagasawa T, Wara-Aswpati N, et al. Association between periodontitis and anti-cardiolipin antibodies in Buerger disease. *J Clin Periodontol.* 2009;36(10):830–835.
149. Igari K, Inoue Y, Iwai T. The epidemiologic and clinical findings of patients with Buerger disease. *Ann Vasc Surg.* 2016;30:263–269.
150. Iwai T, Sato S, Kume H, et al. Clinical study of phlebitis migrans and incompetence of the leg's superficial vein in Buerger disease. *Ann Vasc Dis.* 2012;5(1):45–51.
151. Bartolo M, Rulli F, Raffi S. Buerger's disease: is it a rickettsiosis? *Angiology.* 1980;31(10):660–665.
152. Fazeli B, Ravari H, Ghazvini K. Rickettsia infection could be the missing piece of the Buerger's disease puzzle. *Int Angiol.* 2017;36(5):410–416.
153. Stvrtinova V, Mareschova K, Hasakova J. Thromboangiitis obliterans - what do we know 110 years after the description of the disease by Leo Buerger. *Bratislavské lekarske listy.* 2018;119(10):670.
154. Makita S, Nakamura M, Murakami H, et al. Impaired endothelium-dependent vasorelaxation in peripheral vasculature of patients with thromboangiitis obliterans (Buerger's disease). *Circulation.* 1996;94(suppl 9):II211–II215.

155. Azizi M, Boutouyrie P, Bura-Riviere A, et al. Thromboangiitis obliterans and endothelial function. *Eur Clin Investigat.* 2010;40(6):518–526.
156. Idei N, Nishioka K, Soga J, et al. Vascular function and circulating progenitor cells in thromboangiitis obliterans (Buerger's disease) and atherosclerosis obliterans. *Hypertension.* 2011;57(1):70–78.
157. Czarnacki M, Gacka M, Adamiec R. [A role of endothelin 1 in the pathogenesis of thromboangiitis obliterans (initial news)]. *Przeg Lek.* 2004;61(12):1346–1350.
158. Tanaka K. Pathology and pathogenesis of Buerger's disease. *Int J Cardiol.* 1998;66(suppl 1):S237–S242.
159. Kobayashi M, Sugimoto M, Komori K. Endarteritis obliterans in the pathogenesis of Buerger's disease from the pathological and immunohistochemical points of view. *Circ J.* 2014;78(12):2819–2826.
160. Shionoya S, Ban I, Nakata Y, et al. Diagnosis, pathology, and treatment of Buerger's disease. *Surgery.* 1974;75(5):695–700.
161. Lee T, Seo JW, Sumpio BE, Kim SJ. Immunobiologic analysis of arterial tissue in Buerger's disease. *Eur J Vasc Endovasc Surg.* 2003;25(5):451–457.
162. Kurata A, Machinami R, Schulz A, et al. Different immunophenotypes in Buerger's disease. *Pathol Int.* 2003;53(9):608–615.
163. Kim EJ, Cho BS, Lee TS, et al. Morphologic change of the internal elastic lamina in Buerger's disease. *J Korean Med Sci.* 2000;15(1):44–48.
164. Weinberg I, Jaff MR. Nonatherosclerotic arterial disorders of the lower extremities. *Circulation.* 2012;126(2):213–222.
165. Borner C, Heidrich H. Long-term follow-up of thromboangiitis obliterans. *VASA Zeitschrift für Gefasskrankheiten.* 1998;27(2):80–86.
166. Hirai M, Shinonoya S. Intermittent claudication in the foot and Buerger's disease. *Br J Surg.* 1978;65(3):210–213.
167. Uzun G, Mutluoglu M. Images in clinical medicine. Dependent rubor. *N Engl J Med.* 2011;364(26):e56.
168. Fazeli B, Modaghegh H, Ravrai H, Kazemzadeh G. Thrombophlebitis migrans as a footprint of Buerger's disease: a prospective-descriptive study in north-east of Iran. *Clin Rheumatol.* 2008;27(1):55–57.
169. Jimenez-Paredes CA, Canas-Davila CA, Sanchez A, et al. Buerger's disease at the 'San Juan De Dios' Hospital, Santa Fe De Bogota, Colombia. *Int J Cardiol.* 1998;66(suppl 1):S267–S272.
170. Hartmann P, Mohokum M, Schlattmann P. The association of Raynaud syndrome with thromboangiitis obliterans--a meta-analysis. *Angiology.* 2012;63(4):315–319.
171. Mishima Y. Thromboangiitis obliterans (Buerger's disease). *Int J Cardiol.* 1996;54(suppl):S155–S157.
172. Sasaki S, Sakuma M, Yasuda K. Current status of thromboangiitis obliterans (Buerger's disease) in Japan. *Int J Cardiol.* 2000;75(suppl 1):S175–S181.
173. Stone JH. Vasculitis: a collection of pearls and myths. *Rheum Dis Clin North Am.* 2007;33(4):691–739. v.
174. Chopra BS, Zakariah T, Sodhi JS, et al. Thromboangiitis obliterans: a clinical study with special emphasis on venous involvement. *Angiology.* 1976;27(2):126–132.
175. Laohapensang K, Rerkasem K, Kattipattanapong V. Decrease in the incidence of Buerger's disease recurrence in northern Thailand. *Surg Today.* 2005;35(12):1060–1065.
176. Modaghegh MH, Kazemzadeh GH, Ravari H, et al. Buerger's disease in the northeast of Iran: Epidemiology and clinical features. *Vascular.* 2015;23(5):519–524.
177. Ohta T, Shionoya S. Fate of the ischaemic limb in Buerger's disease. *Br J Surg.* 1988;75(3):259–262.
178. Hirsch AT, Haskal ZJ, Hertzler NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113(11):e463–e654.
179. Puechal X, Fiessinger JN, Kahan A, Menkes CJ. Rheumatic manifestations in patients with thromboangiitis obliterans (Buerger's disease). *J Rheumatol.* 1999;26(8):1764–1768.
180. Steib-Furno S, Bensoussan L, Parrado-Azulay J, Lafforgue P. Inflammatory joint disease and severe ischemia of the extremities revealing thromboangiitis obliterans in a female. *Joint Bone Spine.* 2005;72(1):69–72.
181. Quenneville JG, Gossard D. Subungual-splinter hemorrhage an early sign of thromboangiitis obliterans. *Angiology.* 1981;32(6):424–432.
182. Nuernberger E. Cases from the Osler medical service at Johns Hopkins university. *Am J Med.* 2002;112(1):70–71.
183. Farberow NL, Nehemkis AM. Indirect self-destructive behavior in patients with Buerger's disease. *J Pers Assess.* 1979;43(1):86–96.
184. Sasaki S, Sakuma M, Kunihara T, Yasuda K. Current trends in thromboangiitis obliterans (Buerger's disease) in women. *Am J Surg.* 1999;177(4):316–320.
185. Shionoya S. Buerger's disease (Thromboangiitis obliterans). In: Rutherford RB, ed. *Vascular surgery.* 3rd ed. Philadelphia: WB Saunders; 1989:207–217.
186. Hirai M, Shionoya S. Arterial obstruction of the upper limb in Buerger's disease: its incidence and primary lesion. *Br J Surg.* 1979;66(2):124–128.
187. Sasaki S, Sakuma M, Kunihara T, Yasuda K. Distribution of arterial involvement in thromboangiitis obliterans (Buerger's disease): results of a study conducted by the Intractable Vasculitis Syndromes Research Group in Japan. *Surg Today.* 2000;30(7):600–605.
188. Olin JW. Thromboangiitis obliterans (Buerger's disease). In: Rutherford RB, ed. *Vascular Surgery.* 6th ed. Philadelphia: Elsevier Saunders; 2005:404–419.
189. Herrington Jr JL, Grossman LA. Surgical lesions of the small and large intestine resulting from Buerger's disease. *Ann Surg.* 1968;168(6):1079–1087.
190. Wolf Jr EA, Sumner DS, Strandness Jr DE. Disease of the mesenteric circulation in patients with thromboangiitis obliterans. *Vasc Surg.* 1972;6(5):218–223.
191. Rosenberger A, Munk J, Schramek A, Ben Arieh J. The angiographic appearance of thromboangiitis obliterans (Buerger's disease) in the abdominal visceral vessels. *Br J Radiol.* 1973;46(545):337–343.
192. Guay A, Janower ML, Bain RW, McCready FJ. A case of Buerger's disease causing ischemic colitis with perforation in a young male. *Am J Med Sci.* 1976;271(2):239–244.
193. Sachs IL, Klima T, Frankel NB. Thromboangiitis obliterans of the transverse colon. *JAMA.* 1977;238(4):336–337.
194. Sobel RA, Ruebner BH. Buerger's disease involving the celiac artery. *Hum Pathol.* 1979;10(1):112–115.
195. Deitch EA, Sikkema WW. Intestinal manifestation of Buerger's disease: case report and literature review. *Am Surg.* 1981;47(7):326–328.
196. Soo KC, Hollinger-Vernea S, Miller G, et al. Buerger's disease of the sigmoid colon. *Aust NZ J Surg.* 1983;53(2):111–112.
197. Rosen N, Sommer I, Knobel B. Intestinal Buerger's disease. *Arch Pathol Lab Med.* 1985;109(10):962–963.
198. Iyer KR, Mair WS. Buerger's disease of the rectum: case report and literature review. *J R Coll Surg Edinb.* 1991;36(6):409–410.
199. Ito M, Nihei Z, Ichikawa W, Mishima Y. Intestinal ischemia resulting from Buerger's disease: report of a case. *Surg Today.* 1993;23(11):988–992.
200. Broide E, Scapa E, Peer A, et al. Buerger's disease presenting as acute small bowel ischemia. *Gastroenterology.* 1993;104(4):1192–1195.
201. Schellong SM, Bernhards J, Ensslen F, et al. Intestinal type of thromboangiitis obliterans (Buerger's disease). *J Intern Med.* 1994;235(1):69–73.
202. Sauvaget F, Debray M, Herve de Sigalony JP, et al. Colonic ischemia reveals thromboangiitis obliterans (Buerger's disease). *Gastroenterology.* 1996;110(3):900–903.
203. Lie JT. Visceral intestinal Buerger's disease. *Int J Cardiol.* 1998;66(suppl 1):S249–S256.
204. Iwai T. Buerger's disease with intestinal involvement. *Int J Cardiol.* 1998;66(suppl 1):S257–S263.

205. Hassoun Z, Lacrosse M, De Ronde T. Intestinal involvement in Buerger's disease. *J Clin Gastroenterol.* 2001;32(1):85–89.
206. Kobayashi M, Kurose K, Kobata T, et al. Ischemic intestinal involvement in a patient with Buerger disease: case report and literature review. *J Vasc Surg.* 2003;38(1):170–174.
207. Cho YP, Kwon YM, Kwon TW, Kim GE. Mesenteric Buerger's disease. *Ann Vasc Surg.* 2003;17(2):221–223.
208. Cho YP, Kang GH, Han MS, et al. Mesenteric involvement of acute-stage Buerger's disease as the initial clinical manifestation: report of a case. *Surg Today.* 2005;35(6):499–501.
209. Leung DK, Haskal ZJ. SIR 2006 film panel case: mesenteric involvement and bowel infarction due to Buerger disease. *J Vasc Interv Radiol.* 2006;17(7):1087–1089.
210. Lippmann HI. Cerebrovascular thrombosis in patients with Buerger's disease. *Circulation.* 1952;5(5):680–692.
211. Zulch KJ. The cerebral form of von Winiwarter-Buerger's disease: does it exist? *Angiology.* 1969;20(2):61–69.
212. Berlit P, Kessler C, Reuther R, Krause KH. New aspects of thromboangiitis obliterans (von Winiwarter-Buerger's disease). *Eur Neurol.* 1984;23(6):394–399.
213. Bozikas VP, Vlaikidis N, Petrikis P, et al. Schizophrenic-like symptoms in a patient with thrombo-angiitis obliterans (Winiwarter-Buerger's disease). *Int J Psychiatry Med.* 2001;31(3):341–346.
214. No YJ, Lee EM, Lee DH, Kim JS. Cerebral angiographic findings in thromboangiitis obliterans. *Neuroradiology.* 2005;47(12):912–915.
215. Ohno H, Matsuda Y, Takashiba K, et al. Acute myocardial infarction in Buerger's disease. *Am J Cardiol.* 1986;57(8):690–691.
216. Mautner GC, Mautner SL, Lin F, et al. Amounts of coronary arterial luminal narrowing and composition of the material causing the narrowing in Buerger's disease. *Am J Cardiol.* 1993;71(5):486–490.
217. Donatelli F, Triggiani M, Nascimbene S, et al. Thromboangiitis obliterans of coronary and internal thoracic arteries in a young woman. *J Thoracic Cardiovasc Surg.* 1997;113(4):800–802.
218. Hoppe B, Lu JT, Thistlewaite P, et al. Beyond peripheral arteries in Buerger's disease: angiographic considerations in thromboangiitis obliterans. *Catheter Cardiovasc Interv.* 2002;57(3):363–366.
219. Beçit N, Unlu Y, Kocak H, Ceviz M. Involvement of the coronary artery in a patient with thromboangiitis obliterans. A case report. *Heart Vessels.* 2002;16(5):201–203.
220. Hong TE, Faxon DP. Coronary artery disease in patients with Buerger's disease. *Rev Cardiovasc Med.* 2005;6(4):222–226.
221. Tamura A, Aso N, Kadota J. Corkscrew appearance in the right coronary artery in a patient with Buerger's disease. *Heart.* 2006;92(7):944.
222. Hsu PC, Lin TH, Su HM, et al. Frequent accelerated idioventricular rhythm in a young male of Buerger's disease with acute myocardial infarction. *Int J Cardiol.* 2008;127(2):e64–66.
223. Abe M, Kimura T, Furukawa Y, et al. Coronary Buerger's disease with a peripheral arterial aneurysm. *Eur Heart J.* 2007;28(8):928.
224. Mavioglu L, Mungan U, Ozeke O, et al. Buerger's disease (thromboangiitis obliterans) with an atypical presentation: a case report. *Turk Gogus Kalp Dama.* 2013;21(4):1039–1042.
225. Harten P, Muller-Huelsbeck S, Regensburger D, Loeffler H. Multiple organ manifestations in thromboangiitis obliterans (Buerger's disease). A case report. *Angiology.* 1996;47(4):419–425.
226. Calguneri M, Ozturk MA, Ay H, et al. Buerger's disease with multisystem involvement. A case report and a review of the literature. *Angiology.* 2004;55(3):325–328.
227. Hurelbrink CB, Barnett Y, Buckland ME, et al. Revisiting cerebral thromboangiitis obliterans. *J Neurol Sci.* 2012;317(1–2):141–145.
228. Lie JT. Thromboangiitis obliterans (Buerger's disease) in a saphenous vein arterial graft. *Hum Pathol.* 1987;18(4):402–404.
229. Lie JT, Michet Jr CJ. Thromboangiitis obliterans with eosinophilia (Buerger's disease) of the temporal arteries. *Hum Pathol.* 1988;19(5):598–602.
230. Bernardczykowa A, Zawilski J. [Fundus oculi changes in chronic ischemia of the lower extremities]. *Klin Oczna.* 1991;93(10–11):291–292.
231. Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. *Prog Retin Eye Res.* 2001;20(3):319–349.
232. Ohguro I, Ohguro H, Ohta T, Nakazawa M. A case of normal tension glaucoma associated with Buerger's disease. *Tohoku J Exp Med.* 2006;209(1):49–52.
233. Goktas S, Bedir S, Bozlar U, et al. Intrarenal arterial stenosis in a patient with thromboangiitis obliterans. *Int J Urol.* 2006;13(9):1243–1244.
234. Negredo E, Lopez-Conteras J, De Llobet JM, et al. Impotence as a cardinal sign in the thromboangiitis obliterans diagnosis. *Clin Rheumatol.* 1995;14(6):711–712.
235. Yavas US, Calisir C, Kaya T. Vasculogenic impotence as a symptom in late-onset Buerger's disease. *J Clin Ultrasound.* 2007;35(8):469–472.
236. Remy P, Jacquot C, Nochy D, et al. Buerger's disease associated with IgA nephropathy: report of two cases. *Br Med J (ClinResEd).* 1988;296(6623):683–684.
237. Takanashi T, Horigome R, Okuda Y, et al. Buerger's disease manifesting nodular erythema with livedo reticularis. *Intern Med.* 2007;46(21):1815–1819.
238. Yanez Siller FA, Bernal Vargas JG, Rodriguez Muguruza S, Olive Marques A. [Avascular necrosis of both femoral heads in a patient with thromboangiitis obliterans]. *Med Clin.* 2013;140(10):475–476.
239. Adar R, Papa MZ. The definition of Buerger's disease. *World J Surg.* 1984;8(3):423–424.
240. Adar R, Papa MZ, Schneiderman J. Thromboangiitis obliterans: an old disease in need of a new look. *Int J Cardiol.* 2000;75(Suppl 1):S167–S170.
241. Kroger K. Buerger's disease: What has the last decade taught us? *Eur J Intern Med.* 2006;17(4):227–234.
242. Laopongsang K, Rerkasem K, Kattipattanapong V. Seasonal variation of Buerger's disease in Northern part of Thailand. *Eur J Vasc Endovasc Surg.* 2004;28(4):418–420.
243. Tavakoli H, Rezaei J, Esfandiari K, et al. Buerger's disease: a 10-year experience in Tehran, Iran. *Clin Rheumatol.* 2008;27(3):369–371.
244. Gerhard-Herman M, Gardin JM, Jaff M, et al. Guidelines for noninvasive vascular laboratory testing: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. *Vasc Med.* 2006;11(3):183–200.
245. Fujii Y, Soga J, Hidaka T, et al. Color doppler flows of corkscrew collaterals in Thromboangiitis obliterans (Buerger's disease) using color duplex ultrasonography. *J Am Coll Cardiol.* 2011;57(25):2539.
246. Fujii Y, Nishioka K, Yoshizumi M, et al. Images in cardiovascular medicine. Corkscrew collaterals in thromboangiitis obliterans (Buerger's disease). *Circulation.* 2007;116(21):e539–e540.
247. Jargiello T, Wronski J, Drelich-Zbroja A, et al. Preliminary report on doppler quantification of peripheral vascular resistance in patients with thromboangiitis obliterans; the diagnostic value of high resistance index - HRI. *Pol J Radiol.* 2003;68(1):75–80.
248. Fujii Y, Fujimura N, Mikami S, et al. Flow-mediated vasodilation is augmented in a corkscrew collateral artery compared with that in a native artery in patients with thromboangiitis obliterans (Buerger disease). *J Vasc Surg.* 2011;54(6):1689–1697.
249. Nas OF, Kandemirli SG, Erdemli Gursel B, et al. Diagnostic utility of superb microvascular imaging in depiction of corkscrew collaterals in Buerger's disease. *J Clin Ultrasound.* 2021;49(2):129–134.
250. Sharifi A, Charjouei Moghadam M. CFD simulation of blood flow inside the corkscrew collaterals of the Buerger's disease. *Bioimpacts.* 2016;6(1):41–47.
251. Melillo E, Grigoratos C, Sanctis FD, et al. Noninvasive transcutaneous monitoring in long-term follow-up of patients with thromboangiitis obliterans treated with intravenous iloprost. *Angiology.* 2015;66(6):531–538.
252. Moreno-Arino M, Ortiz-Santamaría V, Deudero Infante A, et al. A classic mimicker of systemic vasculitis. *Reumatol Clin.* 2016;12(2):103–106.
253. Jaccard Y, Walther S, Anderson S, et al. Influence of secondary infection on amputation in chronic critical limb ischemia. *Eur J Vasc Endovasc Surg.* 2007;33(5):605–609.

254. Hackl G, Milosavljevic R, Belaj K, et al. The value of FDG-PET in the diagnosis of thromboangiitis obliterans-a case series. *Clin Rheumatol*. 2015;34(4):739–744.
255. Dimmick SJ, Goh AC, Cauzza E, et al. Imaging appearances of Buerger's disease complications in the upper and lower limbs. *Clin Radiol*. 2012;67(12):1207–1211.
256. Fujii Y, Soga J, Nakamura S, et al. Classification of corkscrew collaterals in thromboangiitis obliterans (Buerger's disease): relationship between corkscrew type and prevalence of ischemic ulcers. *Circ J*. 2010;74(8):1684–1688.
257. Suzuki S, Yamada I, Himeno Y. Angiographic findings in Buerger disease. *Int J Cardiol*. 1996;54(suppl):S189–S195.
258. Disdier P, Granel B, Serratrice J, et al. Cannabis arteritis revisited—ten new case reports. *Angiology*. 2001;52(1):1–5.
259. Lazarides MK, Georgiadis GS, Papas TT, Nikolopoulos ES. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds*. 2006;5(2):89–95.
260. Dean SM, Satiani B. Three cases of digital ischemia successfully treated with cilostazol. *Vasc Med*. 2001;6(4):245–248.
261. Nagashima T, Kamimura T, Nara H, et al. Images in cardiovascular medicine. Kimura's disease presenting as steroid-responsive thromboangiitis obliterans. *Circulation*. 2006;114(1):e10–e11.
262. Cooper LT, Tse TS, Mikhail MA, et al. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). *J Am Coll Cardiol*. 2004;44(12):2410–2411.
263. Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of Buerger disease. *J Vasc Surg*. 2004;39(1):176–180.
264. Karakoyun R, Koksoy C, Sener Z, et al. Comparison of quality of life in patients with peripheral arterial disease caused by atherosclerosis obliterans or Buerger's disease. *Cardiovasc J Africa*. 2014;25(3):124–129.
265. Cooper LT, Henderson SS, Ballman KV, et al. A prospective, case-control study of tobacco dependence in thromboangiitis obliterans (Buerger's Disease). *Angiology*. 2006;57(1):73–78.
266. Le Joncour A, Soudet S, Dupont A, et al. Long-term outcome and prognostic factors of complications in thromboangiitis obliterans (Buerger's disease): a multicenter study of 224 patients. *J Am Heart Assoc*. 2018;7(23):e010677.
267. Olin JW. Thromboangiitis obliterans: 110 years old and little progress made. *J Am Heart Assoc*. 2018;7(23):e011214.
268. Hooten WM, Bruns HK, Hays JT. Inpatient treatment of severe nicotine dependence in a patient with thromboangiitis obliterans (Buerger's disease). *Mayo Clin Proc*. 1998;73(6):529–532.
269. Lie JT. Thromboangiitis obliterans (Buerger's disease) and smokeless tobacco. *Arthritis Rheum*. 1988;31(6):812–813.
270. Sinclair NR, Laub DR. Thromboangiitis obliterans (Buerger's disease). *Eplasty*. 2015;15:ic22.
271. Sugimoto M, Miyachi H, Morimae H, et al. Fate of ischemic limbs in patients with Buerger's disease based on our 30-year experience: does smoking have a definitive impact on the late loss of limbs? *Surg Today*. 2015;45(4):466–470.
272. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med*. 2002;347(24):1941–1951.
273. Patru S, Marcu IR, Matei D, Bighea AC. The influence of physical exercise on smoking patients with peripheral arterial disease. *Curr Health Sci J*. 2018;44(1):34–38.
274. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA*. 1995;274(12):975–980.
275. Kawasaki T, Uemura T, Matsuo K, et al. The effect of different positions on lower limbs skin perfusion pressure. *Indian J Plast Surg*. 2013;46(3):508–512.
276. Sandri M, Adams V, Gielen S, et al. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation*. 2005;111(25):3391–3399.
277. Hirsch AT, Haskal ZJ, Hertzler NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease); endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113(11):e463–654.
278. Group JCSJW. Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). *Circ J*. 2014;78(8):2022–2093.
279. Papi M, Papi C. Vasculitic ulcers. *Int J Lower Extremity Wounds*. 2016;15(1):6–16.
280. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet*. 2005;366(9499):1809–1820.
281. Saha K, Chabra N, Gulati SM. Treatment of patients with thromboangiitis obliterans with cyclophosphamide. *Angiology*. 2001;52(6):399–407.
282. Naito AT, Minamino T, Tateno K, et al. Steroid-responsive thromboangiitis obliterans. *Lancet*. 2004;364(9439):1098.
283. Rirash F, Tingey PC, Harding SE, et al. Calcium channel blockers for primary and secondary Raynaud's phenomenon. *Cochrane Database Syst Rev*. 2017;12:CD000467.
284. Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomised, placebo-controlled trial. The European TAO Study Group. *Eur J Vasc Endovasc Surg*. 1998;15(4):300–307.
285. Mohler 3rd ER, Hiatt WR, Olin JW, et al. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I2 analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol*. 2003;41(10):1679–1686.
286. Vane J, Corin RE. Prostacyclin: a vascular mediator. *Eur J Vasc Endovasc Surg*. 2003;26(6):571–578.
287. Della BS, Molteni M, Mocellin C, et al. Novel mode of action of iloprost: in vitro down-regulation of endothelial cell adhesion molecules. *Prostaglandins Other Lipid Mediat*. 2001;65(2–3):73–83.
288. Cacione DG, Macedo CR, do Carmo Novaes F, Baptista-Silva JC. Pharmacological treatment for Buerger's disease. *Cochrane Database Syst Rev*. 2020;5:CD011033.
289. Fiessinger JN, Schafer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. The TAO Study. *Lancet*. 1990;335(8689):555–557.
290. Bozkurt AK, Koksal C, Demirbas MY, et al. A randomized trial of intravenous iloprost (a stable prostacyclin analogue) versus lumbar sympathectomy in the management of Buerger's disease. *Int Angiol*. 2006;25(2):162–168.
291. Spanos K, Georgiou E, Saleptsis V, et al. Effectiveness of intravenous ilomedin infusion and smoking cessation in the treatment of acutely symptomatic Buerger disease. *Angiology*. 2015;66(2):114–117.
292. Cacione DG, Baptista-Silva JC, Macedo CR. Pharmacological treatment for Buerger's disease. *Cochrane Database Syst Rev*. 2016;2:CD011033.
293. Swainston Harrison T, Plosker GL. *Limaprost. Drugs*. 2007;67(1):109–118; discussion 119–120.
294. Reilly MP, Mohler 3rd ER. Cilostazol: treatment of intermittent claudication. *Ann Pharmacother*. 2001;35(1):48–56.
295. Doganci S, Kaya E, Kadan M, et al. Additional cilostazol to iloprost trometamol improves six-month outcomes in critical limb ischemia patients with resting pain: a randomized-controlled trial. *Turk Gogus Kalp Dama*. 2013;21(1):42–48.
296. Song F, Ji B, Chen T. Cilostazol on the expression of ICAM-1, VCAM-1 and inflammatory factors in plasma in patients with thromboangiitis obliterans. *Exp Ther Med*. 2018;16(3):2349–2354.
297. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med*. 2000;109(7):523–530.
298. Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev*. 2014;10:CD003748.

299. Abeles AM, Nicolescu M, Pinchover Z, Abeles M. Thromboangiitis obliterans successfully treated with phosphodiesterase type 5 inhibitors. *Vascular.* 2014;22(4):313–316.
300. Broz P, Jaeger KA. Images in vascular medicine. Buerger's disease. *Vasc Med.* 2012;17(5):366–367.
301. Jimenez-Gallo D, Albaran-Planelles C, Arjona-Aguilera C, et al. Treatment of thromboangiitis obliterans (Buerger's disease) with high-potency vasodilators. *Dermatol Ther.* 2015;28(3):135–139.
302. Palomo-Arellano A, Cervigon-Gonzalez I, Torres-Iglesias LM. Effectiveness of bosentan in the treatment of ischemic lesions in a case of thromboangiitis obliterans (Buerger disease): a case report. *Dermatol Online J.* 2011;17(7):4.
303. Todoli Parra JA, Hernandez MM, Arrebola Lopez MA. Efficacy of bosentan in digital ischemic ulcers. *Ann Vasc Surg.* 2010;24(5):690 e691–694.
304. De Haro J, Florez A, Fernandez JL, Acin F. Treatment of Buerger disease (thromboangiitis obliterans) with bosentan: a case report. *BMJ Case Rep.* 2009;2009.
305. De Haro J, Acin F, Bleda S, et al. Treatment of thromboangiitis obliterans (Buerger's disease) with bosentan. *BMC Cardiovasc Disord.* 2012;12:5:bcr08.2008.0691.
306. De Haro J, Bleda S, Acin F. An open-label study on long-term outcomes of bosentan for treating ulcers in thromboangiitis obliterans (Buerger's disease). *Int J Cardiol.* 2014;177(2):529–531.
307. Narvaez J, Garcia-Gomez C, Alvarez L, et al. Efficacy of bosentan in patients with refractory thromboangiitis obliterans (Buerger disease): A case series and review of the literature. *Medicine.* 2016;95(48):e5511.
308. Lang EV, Bookstein JJ. Accelerated thrombolysis and angioplasty for hand ischemia in Buerger's disease. *Cardiovasc Intervent Radiol.* 1989;12(2):95–97.
309. Hussein EA, el Dorri A. Intra-arterial streptokinase as adjuvant therapy for complicated Buerger's disease: early trials. *Int Surg.* 1993;78(1):54–58.
310. Hodgson TJ, Gaines PA, Beard JD. Thrombolysis and angioplasty for acute lower limb ischemia in Buerger's disease. *Cardiovasc Intervent Radiol.* 1994;17(6):333–335.
311. Kubota Y, Kichikawa K, Uchida H, et al. Superselective urokinase infusion therapy for dorsalis pedis artery occlusion in Buerger's disease. *Cardiovasc Intervent Radiol.* 1997;20(5):380–382.
312. Ende N. Streptokinase and Buerger's disease. *Nature.* 1963;200:902–903.
313. Beigi AA, Hoghoughi MA, Eshaghian A, et al. The role of folic acid on the hyperhomocysteinemia in the Buerger's disease (thromboangiitis obliterans). *J Res Med Sci.* 2014;19(11):1034–1037.
314. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. *Arterioscler Thromb Vasc Biol.* 2001;21(11):1712–1719.
315. Calabro P, Yeh ET. The pleiotropic effects of statins. *Curr Opin Cardiol.* 2005;20(6):541–546.
316. Liao JK. Clinical implications for statin pleiotropy. *Curr Opin Lipidol.* 2005;16(6):624–629.
317. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. *Curr Pharmaceut Design.* 2012;18(11):1478–1493.
318. Olshwang D, Beer G, Magora F. Intravenous regional guanethidine treatment in peripheral vascular disease. *Angiology.* 1980;31(9):639–645.
319. Stumpflen A, Ahmadi A, Attender M, et al. Effects of transvenous regional guanethidine block in the treatment of critical finger ischemia. *Angiology.* 2000;51(2):115–122.
320. Paraskevas KI, Trigka AA, Samara M. Successful intravenous regional sympathetic blockade (Bier's Block) with guanethidine and lidocaine in a patient with advanced Buerger's Disease (thromboangiitis obliterans)—a case report. *Angiology.* 2005;56(4):493–496.
321. Paraskevas KI, Liapis CD, Briana DD, Mikhailidis DP. Thromboangiitis obliterans (Buerger's disease): searching for a therapeutic strategy. *Angiology.* 2007;58(1):75–84.
322. Hannington-Kiff JG. Intravenous regional sympathetic block with guanethidine. *Lancet.* 1974;1(7865):1019–1020.
323. Bier A. Ueber einen neuen Weg Localanästhesie an den Gliedmaassen zu erzeugen. *Arch Klin Chir.* 1908;86:1007–1016.
324. van Zundert A, Helmstadter A, Goerig M, Mortier E. Centennial of intravenous regional anesthesia. Bier's Block (1908–2008). *Reg Anesth Pain Med.* 2008;33(5):483–489.
325. Swigris JJ, Olin JW, Mekhail NA. Implantable spinal cord stimulator to treat the ischemic manifestations of thromboangiitis obliterans (Buerger's disease). *J Vasc Surg.* 1999;29(5):928–935.
326. Chierichetti F, Mambrini S, Bagliani A, Odero A. Treatment of Buerger's disease with electrical spinal cord stimulation--review of three cases. *Angiology.* 2002;53(3):341–347.
327. Pace AV, Saratzis N, Karokis D, et al. Spinal cord stimulation in Buerger's disease. *Ann Rheum Dis.* 2002;61(12):1114.
328. Manfredini R, Boari B, Gallerani M, et al. Thromboangiitis obliterans (Buerger disease) in a female mild smoker treated with spinal cord stimulation. *Am J Med Sci.* 2004;327(6):365–368.
329. Donas KP, Schulte S, Ktenidis K, Horsch S. The role of epidural spinal cord stimulation in the treatment of Buerger's disease. *J Vasc Surg.* 2005;41(5):830–836.
330. Boari B, Salmi R, Manfredini R. Buerger's disease: Spinal cord stimulation may represent a useful tool for delaying amputation in young patients. *Eur J Intern Med.* 2007;18(3):259.
331. Kothari R, Sharma D, Thakur DS, et al. Thoracoscopic dorsal sympathectomy for upper limb Buerger's disease. *JSLS.* 2014;18(2):273–276.
332. Sasajima T, Kubo Y, Inaba M, et al. Role of infrainguinal bypass in Buerger's disease: an eighteen-year experience. *Eur J Vasc Endovasc Surg.* 1997;13(2):186–192.
333. De Caridi G, Massara M, Villari S, et al. Extreme distal bypass to improve wound healing in Buerger's disease. *Int Wound J.* 2016;13(1):97–100.
334. Inada K, Iwashima Y, Okada A, Matsumoto K. Nonatherosclerotic segmental arterial occlusion of the extremity. *Arch Surg.* 1974;108(5):663–667.
335. Dilegi S, Aksoy M, Kayabali M, et al. Vascular reconstruction in Buerger's disease: is it feasible? *Surg Today.* 2002;32(12):1042–1047.
336. Nakajima N. The change in concept and surgical treatment on Buerger's disease--personal experience and review. *Int J Cardiol.* 1998;66(suppl 1):S273–S280.
337. Sayin A, Bozkurt AK, Tuzun H, et al. Surgical treatment of Buerger's disease: experience with 216 patients. *Cardiovasc Surg.* 1993;1(4):377–380.
338. Bozkurt AK, Besirli K, Koksal C, et al. Surgical treatment of Buerger's disease. *Vascular.* 2004;12(3):192–197.
339. Dardik H, Orozco V. Regarding "New routine alternative for proximal anterior tibial artery bypass in patients with Buerger disease. *J Vasc Surg.* 2012;56(2):590; author reply 591.
340. Lee T, Ra HD, Park YJ, Park HS, Kim SJ. New routing alternative for proximal anterior tibial artery bypass in patients with Buerger disease. *J Vasc Surg.* 2011;54(6):1839–1841.
341. Belkin M, Knox J, Donaldson MC, et al. Infrainguinal arterial reconstruction with nonreversed greater saphenous vein. *J Vasc Surg.* 1996;24(6):957–962.
342. Shindo S, Matsumoto H, Ogata K, et al. Arterial reconstruction in Buerger's disease: by-pass to disease-free collaterals. *Int Angiol.* 2002;21(3):228–232.
343. Briggs SE, Banis Jr JC, Kaebnick H, et al. Distal revascularization and microvascular free tissue transfer: an alternative to amputation in ischemic lesions of the lower extremity. *J Vasc Surg.* 1985;2(6):806–811.
344. Chang H, Hasegawa T, Moteki K, Ishitobi K. A challenging treatment for an ischaemic ulcer in a patient with Buerger's disease: vascular reconstruction and local flap coverage. *Br J Plast Surg.* 2001;54(1):76–79.
345. Van Landuyt K, Monstrey S, Tonnard P, Vermassen F. Free flap coverage of a gangrenous forefoot in a patient with Buerger's disease: a case report. *Ann Plast Surg.* 1996;36(2):154–157.
346. Ikeda K, Yotsuyanagi T, Arai K, et al. Combined revascularization and free-tissue transfer for limb salvage in a Buerger disease patient. *Ann Vasc Surg.* 2012;26(3):422.e5–8.
347. Maurya SD, Singhal S, Gupta HC, et al. Pedicled omental grafts in the revascularization of ischemic lower limbs in Buerger's disease. *Int Surg.* 1985;70(3):253–255.

348. Singh I, Ramteke VK. The role of omental transfer in Buerger's disease: New Delhi's experience. *Aust NZ J Surg.* 1996;66(6):372–376.
349. Bhargava JS, Makker A, Bhargava K, Shaunik AV, Sharda A, Kumar PS. Pedicled omental transfer for ischaemic limbs—a 5-year experience. *J Indian Med Assoc.* 1997;95(4):100–102.
350. Talwar S, Jain S, Porwal R, et al. Free versus pedicled omental grafts for limb salvage in Buerger's disease. *Aust NZ J Surg.* 1998;68(1):38–40.
351. Talwar S, Jain S, Porwal R, et al. Pedicled omental transfer for limb salvage in Buerger's disease. *Int J Cardiol.* 2000;72(2):127–132.
352. Talwar S, Prasad P. Single-stage lumbar sympathectomy and omentopexy: a new surgical approach towards patients with Buerger's disease. *Trop Doct.* 2001;31(2):73–75.
353. Talwar S, Choudhary SK. Omentopexy for limb salvage in Buerger's disease: indications, technique and results. *J Postgrad Med.* 2001;47(2):137–142.
354. Taylor RS, Belli AM, Jacob S. Distal venous arterialisation for salvage of critically ischaemic inoperable limbs. *Lancet.* 1999;354(9194):1962–1965.
355. Lu XW, Idu MM, Ubbink DT, Legemate DA. Meta-analysis of the clinical effectiveness of venous arterialization for salvage of critically ischaemic limbs. *Eur J Vasc Endovasc Surg.* 2006;31(5):493–499.
356. Pokrovsky AV, Dan VN, Chupin AV, Kalinin AA. Arterialization of the hand venous system in patients with critical ischemia and thromboangiitis obliterans. *Angiol Sosud Khr.* 2007;13(2):105–111.
357. Lengua F, Nuss JM, Lechner R, Kunlin J. Arterialization of the venous network of the foot through a bypass in severe arteriopathic ischemia. *J Cardiovasc Surg.* 1984;25(4):357–360.
358. Sasajima T, Azuma N, Uchida H, et al. Combined distal venous arterialization and free flap for patients with extensive tissue loss. *Ann Vasc Surg.* 2010;24(3):373–381.
359. Fujimoto M, Asano Y, Ishii T, et al. The wound/burn guidelines - 4: Guidelines for the management of skin ulcers associated with connective tissue disease/vasculitis. *J Dermatol.* 2016;43(7):729–757.
360. Hirn M, Niinikoski J. Hyperbaric oxygen in the treatment of clostridial gas gangrene. *Ann Chir Gynaecol.* 1988;77(1):37–40.
361. Saito S, Nishikawa K, Obata H, Goto F. Autologous bone marrow transplantation and hyperbaric oxygen therapy for patients with thromboangiitis obliterans. *Angiology.* 2007;58(4):429–434.
362. Matsubara J. [Results of treatments for critical limb ischemia: effectiveness and indications]. *Nippon Geka Gakkai Zashi.* 2007;108(4):181–185.
363. Johnson JA, Enzenauer RJ. Inflammatory arthritis associated with thromboangiitis obliterans. *J Clin Rheumatol.* 2003;9(1):37–40.
364. Sims JR, Hanson EL. Images in clinical medicine. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med.* 1998;339(10):672.
365. Maudsley RH, Hopkinson WI, Horne T, Williams KG. Buerger's disease. *Lancet.* 1964;2(7371):1245–1246.
366. Canter HI, Isci E, Erk Y. Vacuum-assisted wound closure for the management of a foot ulcer due to Buerger's disease. *J Plast Reconstr Aesthet Surg.* 2009;62(2):250–253.
367. Canter HI, Isci E, Erk Y. Vacuum-assisted wound closure for the management of a foot ulcer due to Buerger's disease. *J Plast Reconstr Aesthet Surg.* 2009;62(2):250–253.
368. Skurikhina LA. [Treatment under altered barometric pressure (barotherapy, vacuum therapy, hyperbaric oxygenation)]. *Vopr Kurortol Fizioter Lech Fiz Kult.* 1976;(3):83–89.
369. Reekers JA, Bolia A. Percutaneous intentional extraluminal (subintimal) recanalization: how to do it yourself. *Eur J Radiol.* 1998;28(3):192–198.
370. Reekers JA. Percutaneous intentional extraluminal (subintimal) revascularization (PIER) for critical lower limb ischemia: too good to be true? *J Endovasc Ther.* 2002;9(4):419–421.
371. Reekers JA. The feasibility of a percutaneous temporary pedal bypass. *Eur J Vasc Endovasc Surg.* 2007;34(1):50–52.
372. Ingle H, Nasim A, Bolia A, et al. Subintimal angioplasty of isolated infragenicular vessels in lower limb ischemia: long-term results. *J Endovasc Ther.* 2002;9(4):411–416.
373. Graziani L, Morelli L, Parini F, et al. Clinical outcome after extended endovascular recanalization in Buerger's disease in 20 consecutive cases. *Ann Vasc Surg.* 2012;26(3):387–395.
374. Yuan L, Li Z, Bao J, Jing Z. Endovascular SilverHawk directional atherectomy for thromboangiitis obliterans with occlusion of the popliteal artery. *Ann Vasc Surg.* 2014;28(4):1037.e11–14.
375. Ye K, Shi H, Qin J, et al. Outcomes of endovascular recanalization versus autogenous venous bypass for thromboangiitis obliterans patients with critical limb ischemia due to tibiofibular arterial occlusion. *J Vasc Surg.* 2017;66(4):1133–1142.e1.
376. Kim DH, Ko YG, Ahn CM, et al. Immediate and late outcomes of endovascular therapy for lower extremity arteries in Buerger disease. *J Vasc Surg.* 2018;67(6):1769–1777.
377. Baumann G, Stangl V, Klein-Weigel P, et al. Successful treatment of thromboangiitis obliterans (Buerger's disease) with immunoabsorption: results of a pilot study. *Clin Res Cardiol.* 2011;100(8):683–690.
378. Klein-Weigel PF, Koning C, Hartwig A, et al. [Immunoabsorption in thromboangiitis obliterans - a promising therapeutic option. Results of a consecutive patient cohort treated in clinical routine care]. *Zentralbl Chir.* 2012;137(5):460–465.
379. Klein-Weigel PF, Bimmler M, Hempel P, et al. G-protein coupled receptor auto-antibodies in thromboangiitis obliterans (Buerger's disease) and their removal by immunoabsorption. *Vasa Eur J Vasc Med.* 2014;43(5):347–352.
380. Isner JM, Baumgartner I, Rauh G, et al. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. *J Vasc Surg.* 1998;28(6):964–973.
381. Brodmann M, Renner W, Stark G, Seinost G, Pilger E. Vascular endothelial growth factor expression in patients suffering from thromboangiitis obliterans. *Int J Cardiol.* 2001;80(2–3):185–186.
382. Yonemitsu Y, Matsumoto T, Itoh H, et al. DVC1-0101 to treat peripheral arterial disease: a phase I/IIa open-label dose-escalation clinical trial. *Mol Ther.* 2013;21(3):707–714.
383. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997;275(5302):964–967.
384. Kalka C, Masuda H, Takahashi T, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. *Proc Natl Acad Sci USA.* 2000;97(7):3422–3427.
385. Iba O, Matsubara H, Nozawa Y, et al. Angiogenesis by implantation of peripheral blood mononuclear cells and platelets into ischemic limbs. *Circulation.* 2002;106(15):2019–2025.
386. Tateishi-Yuyama E, Matsubara H, Murohara T, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet.* 2002;360(9331):427–435.
387. Taguchi A, Ohtani M, Soma T, et al. Therapeutic angiogenesis by autologous bone-marrow transplantation in a general hospital setting. *Eur J Vasc Endovasc Surg.* 2003;25(3):276–278.
388. Durdu S, Akar AR, Arat M, et al. Autologous bone-marrow mononuclear cell implantation for patients with Rutherford grade II–III thromboangiitis obliterans. *J Vasc Surg.* 2006;44(4):732–739.
389. Miyamoto K, Nishigami K, Nagaya N, et al. Unblinded pilot study of autologous transplantation of bone marrow mononuclear cells in patients with thromboangiitis obliterans. *Circulation.* 2006;114(24):2679–2684.
390. Saito Y, Sasaki K, Katsuda Y, et al. Effect of autologous bone-marrow cell transplantation on ischemic ulcer in patients with Buerger's disease. *Circ J.* 2007;71(8):1187–1192.
391. Wan J, Yang Y, Ma ZH, et al. Autologous peripheral blood stem cell transplantation to treat thromboangiitis obliterans: preliminary results. *Eur Rev Med Pharmacol Sci.* 2016;20(3):509–513.
392. Ishida A, Ohya Y, Sakuda H, et al. Autologous peripheral blood mononuclear cell implantation for patients with peripheral arterial disease improves limb ischemia. *Circ J.* 2005;69(10):1260–1265.
393. Kim SW, Han H, Chae GT, et al. Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model. *Stem Cells.* 2006;24(6):1620–1626.

394. Lee HC, An SG, Lee HW, et al. Safety and effect of adipose tissue-derived stem cell implantation in patients with critical limb ischemia: a pilot study. *Circ J.* 2012;76(7):1750–1760.
395. Heo S-H, Park Y-S, Kang E-S, et al. Early results of clinical application of autologous whole bone marrow stem cell transplantation for critical limb ischemia with Buerger's disease. *Scient Rep.* 2016;6:19690.
396. Lawall H, Bramlage P, Amann B. Treatment of peripheral arterial disease using stem and progenitor cell therapy. *J Vasc Surg.* 2011;53(2):445–453.
397. Akar R, Durdu S, Arat M, et al. Therapeutic angiogenesis by autologous transplantation of bone-marrow mononuclear cells for Buerger's patients with retractable limb ischaemia. Preliminary results. *Turkish J Haematol.* 2004;00:01–02.
398. Akar AR, Durdu S, Baran C. Letter by Akar et al Regarding Article, "Effect of Autologous Bone-Marrow Cell Transplantation on Ischemic Ulcer in Patients With Buerger's Disease. *Circ J.* 2008;72(4):684.
399. Baran C, Durdu S, Ozcinar E, et al. Long-term follow-up of patients with Buerger's disease after autologous stem cell therapy. *Anatol J Cardiol.* 2019;21(3):155–162.
400. Idei N, Soga J, Hata T, et al. Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in patients with critical limb ischemia: a comparison of atherosclerotic peripheral arterial disease and Buerger disease. *Circ Cardiovasc Interv.* 2011;4(1):15–25.
401. Matoba S, Tatsumi T, Murohara T, et al. Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia. *Am Heart J.* 2008;156(5):1010–1018.
402. Blum A, Balkan W, Hare JM. Advances in cell-based therapy for peripheral vascular disease. *Atherosclerosis.* 2012;223(2):269–277.
403. Cacione DG, do Carmo Novaes F, Moreno DH. Stem cell therapy for treatment of thromboangiitis obliterans (Buerger's disease). *Cochrane Database Syst Rev.* 2018;10:CD012794.
404. Dash NR, Dash SN, Routray P, et al. Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. *Rejuvenat Res.* 2009;12(5):359–366.
405. Inan M, Alat I, Kutlu R, et al. Successful treatment of Buerger's Disease with intramedullary K-wire: the results of the first 11 extremities. *Eur J Vasc Endovasc Surg.* 2005;29(3):277–280.
406. Kim DI, Kim MJ, Joh JH, et al. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. *Stem Cells.* 2006;24(5):1194–1200.
407. Hewing B, Stangl V, Stangl K, et al. Circulating angiogenic factors in patients with thromboangiitis obliterans. *PloS One.* 2012;7(4):e34717.
408. Akar AR, Durdu S, Corapcioglu T, Ozyurda U. Regenerative medicine for cardiovascular disorders. New milestones: Adult stem cells. *Artificial Organs.* 2006;30(4):213–232.
409. Bozkurt AK, Tuzun H, Sayin AG, et al. The role of polytetrafluoroethylene graft material in Buerger's disease. *Int J Angiol.* 1998;7(3):188–190.
410. Modaghegh MS, Hafezi S. Endovascular treatment of thromboangiitis obliterans (Buerger's disease). *Vasc Endovasc Surg.* 2018;52(2):124–130.
411. Firat A, Igus B. Endovascular recanalization of thromboangiitis obliterans (Buerger's disease) in twenty-eight consecutive patients and combined antegrade-retrograde intervention in eight patients. *Cardiovasc Interv Radiol.* 2019;42(6):820–828.

Takayasu Arteritis

BRYAN A. EHLERT

INTRODUCTION 1843

EPIDEMIOLOGY 1843

PATHOGENESIS 1844

Etiology 1844

Pathology 1844

CLINICAL PRESENTATION 1844

DIAGNOSTIC EVALUATION 1848

Diagnostic Criteria 1848

Laboratory Markers 1848

Radiologic Evaluation 1849

CLASSIFICATION 1851

MEDICAL TREATMENT 1851

REFRACTORY THERAPY 1852

INDICATIONS FOR AND RESULTS OF REVASCULARIZATION PROCEDURES 1853

Endovascular Treatment 1853

Open Surgical Treatment 1854

Direct Comparison of Endovascular and Open Surgical Treatment 1855

SPECIAL CONSIDERATIONS 1855

Pregnant Patients 1855

Pediatric Patients 1855

PROGNOSIS 1856

CHAPTER ALGORITHM 1856

INTRODUCTION

Takayasu's arteritis is an immune arteritis causing inflammation of the aorta, its major branches, and pulmonary arteries. It is predominantly a disease of young women, with onset typically in the second or third decade of life.¹ The disease is more common among Asians, although all ethnicities can be affected. The annual incidence in North America is approximately 2.6 per million people.²

The first description of a patient with Takayasu arteritis (TA) may have occurred as early as the 18th century. Morgagni found large-vessel aneurysms and stenoses at autopsy in a 40-year-old woman in 1761.³ In 1830 Yamamoto described a 45-year-old man who originally presented with complaints of fever and developed pulselessness in the radial arteries 1 year later.⁴ TA is named after Japanese ophthalmologist Mikito Takayasu, who presented his findings of arteriovenous anastomoses of the ocular papilla in a 21-year-old woman with sudden vision loss in 1908.⁴ Two other ophthalmologists at the same meeting presented similar findings in patients with absent radial pulses.⁵ The term *Takayasu arteritis* was first coined in 1939 by Yasuzo Shinmi when reporting on a patient with comparable symptoms and physical findings.⁶ In 1975 the research committee of the Japanese Department of Health and Welfare officially proposed adopting the term *Takayasu arteritis* for the disease.

Although TA is a chronic disease, it is characterized by a waxing and waning course. Symptoms range from fever, myalgias, and loss of appetite to cerebral, visceral, and extremity ischemia.⁷ This variation in presentation frequently leads to a delay in diagnosis.

EPIDEMIOLOGY

TA most commonly affects patients from East Asia, and the incidence varies by geographic location. The estimated incidence in Japan is approximately 150 new cases per year,⁷ and postmortem studies reveal a prevalence of 1 in 3000 patients.⁸ The incidence in India is 200 to 300 per million,⁹ whereas the incidence in Sweden is 0.8 per million, with a prevalence of 0.64 per 100,000.¹⁰ In Birmingham, England, the incidence is 0.2 per million.⁹ Finally, a population-based study in Olmstead County, Minnesota, found an incidence of 2.6 per million.²

TA affects women 6 to 8 times more frequently than men, although this distribution may depend on the region being studied. Authors from India have found female to male ratios of 4:1,¹¹ whereas others from China have reported ratios of 3:1.¹² The median age at diagnosis in a cohort of 60 patients from the National Institutes of Health (NIH) was 25 years.¹³ Although the detection of TA in some patients after age 40 years may be related to delay in diagnosis, it is now understood that a significant number of patients do not develop symptoms

until later in life. When the results from most major studies are examined, the majority of patients develop symptoms between the ages of 20 and 40 years, with no trend by region.^{13–19}

PATHOGENESIS

Etiology

A genetic predisposition to the disease has been suggested because of the predilection for patients of Asian descent, especially those with a Japanese background,²⁰ and the occasional familial clustering of the disease.²¹ HLA-Bw52 occurs in approximately 44% of Japanese patients with TA, compared with 13% in the general Japanese population.²² Furthermore, the haplotype of Bw52-Dw12 confers a greater likelihood of an active inflammatory state and rapid disease progression.²³ Other studies have found increased susceptibility in patients with gene mutations in the HLA-A, -D, and -DR regions.^{24,25} In a group of North American patients with TA, there was no significant association between any HLA antigen and disease severity or complications.²⁶ In fact, there was a negative association between TA and the HLA-DR1 antigen, suggesting a possible protection against disease development. Further studies examining the genetic factors associated with TA must be performed because consistent associations are lacking.²⁷

Immune-mediated mechanisms, including both antibody- and cell-mediated mechanisms, have also been suggested as a cause of TA. TA has been associated with rheumatoid arthritis,²⁸ systemic lupus erythematosus,²⁹ inflammatory bowel disease,³⁰ and glomerulonephritis.³¹ All these conditions have autoimmune mechanisms associated with their pathology, which suggests a common mechanism with TA. Numerous studies have suggested a link between TA and *Mycobacterium tuberculosis* (TB) due to the granulomatous nature of the two disease processes. Despite the high prevalence of TB in TA patients, a definitive causal relationship has not been identified.³²

Cell-mediated mechanisms of endothelial damage have been implicated in TA. Gamma/delta T cells in patients with TA are reactive to Hsp60 and exhibit cytotoxicity to aortic endothelial cells, suggesting a role in the pathogenesis of TA.³³ This mechanism occurs via increased production of interferon gamma and is distinct from other similar rheumatologic disorders.³⁴

Antibody-mediated mechanisms of TA have been advocated based on elevated levels of antiaortic endothelial cell antibodies. These lead to the induction of endothelial adhesion molecules, cytokines, and apoptosis.³⁵ Levels of antiaortic endothelial cell antibodies are 20 times greater in patients with TA compared with healthy controls³⁶ and with patients with other autoimmune disorders.³⁷

The fact that TA is commonly found in women of childbearing age suggests that sex hormones may play a role in its development. Studies of patients with TA compared with healthy controls have shown elevated urinary estrogens.³⁸ Furthermore, the association of Klinefelter syndrome in patients with TA may implicate elevated estrogens in the disease.³⁹

Many causative factors have been implicated in TA, but none is found consistently. The cause of TA is likely multifactorial, and further studies are necessary to elucidate the associations among the various suggested mechanisms.

Pathology

Histologic examination of inflammatory lesions of TA reveals a panarteritis of all three layers of the vessel wall, with skip areas along the length of the vessel (Fig. 140.1).⁴⁰ These lesions can range from acute exudative inflammation to chronic, nonspecific productive inflammation to various types of granulomatous inflammation.⁴¹ Active inflammatory lesions begin in the vasa vasorum, extend through the media and adventitia, and terminate in a diffuse or nodular fibrosis. Smooth muscle cells and fibroblasts invade the intima and produce excessive ground substance. Occasionally, intimal thickening of the peripheral branches of inflamed arteries may lead to end-organ ischemia.

Immunohistochemical examination of postoperative aortic specimens with active inflammation has shown replacement of the muscular and elastic layers of the media and adventitia by dense fibrous tissue.⁴² In certain patients, inflammatory nodules of numerous T cells and B cells colocalized with dendritic cells have been observed in the deep portion of the intima and adventitia. This colocalization suggests that interactions between dendritic cells and lymphocytes may be important in the pathogenesis of TA.

In the chronic phase of TA, inflammation leads to thickening of the entire vessel wall. The vessel lumen narrows owing to proliferation of the intima, destruction of the elastic fibers of the media, and fibrosis of the adventitia.⁴³

Aneurysmal disease may also be associated with TA, although it is less frequent than stenotic disease. It has been hypothesized that aneurysmal disease occurs when destruction of the elastic component of the media occurs before fibrosis of the adventitia, leading to a weakened vessel wall.⁴⁴

CLINICAL PRESENTATION

TA was first thought to progress in three phases. The first phase was characterized by an inflammatory period with constitutional symptoms such as fever, headache, weight loss, myalgia, and arthralgia. The second phase was characterized by vessel inflammation with symptoms of vessel pain and tenderness, or carotidynia. The third and final phase, called the “burned-out” phase, was characterized by vessel fibrosis or aneurysmal degeneration. In this phase, patients presented with the classic signs of ischemia or aneurysm. It is now understood that although most patients with TA experience these three phases, many do not; and patients with TA can endure very diverse courses. In a group of North American patients, 10% were asymptomatic at presentation, 57% never had any constitutional symptoms, and only 33% developed systemic symptoms.¹³ Some TA patients present with inflammatory and fibrotic changes simultaneously, further emphasizing the diverse nature of this disease.⁷

It is likely that the nonspecific nature of constitutional complaints leads to the delay in diagnosis that is common in patients with TA. A median delay of 1 year before diagnosis in a group of North American patients has been reported, similar to the 10 to 15.5 months reported in other studies.^{13,20} Approximately 90% of patients see more than one medical doctor, with a mean of five doctors, before obtaining the correct diagnosis of TA.⁴³

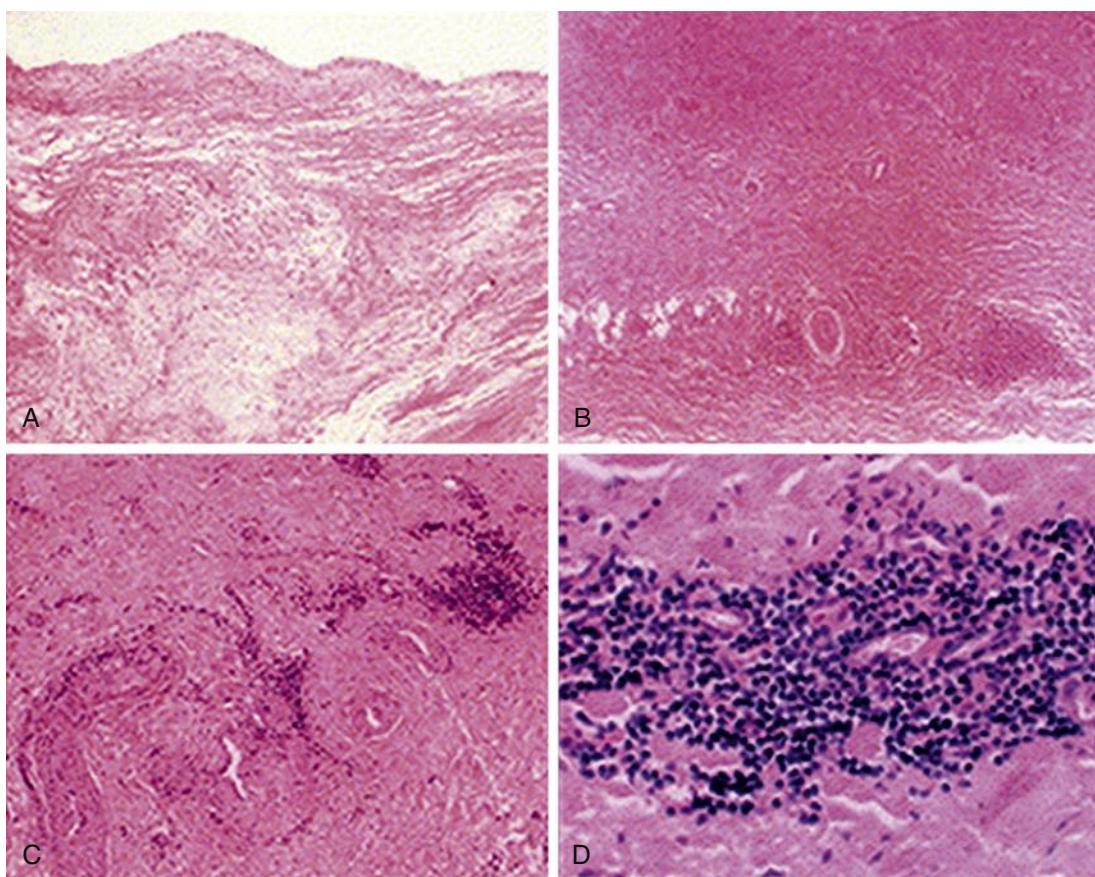


Figure 140.1 Histologic Findings in Takayasu Arteritis. (A) Aortic cusp with intimal fibrosis and myxoid degenerative changes in media without inflammatory cells. (B) Aortic wall with fibrosis of media and infiltration of inflammatory cells around vasa vasorum. (C and D) Inflammatory cell infiltrate consists of predominantly mononuclear lymphocytes. (From Song JK, et al. Echocardiographic and clinical characteristics of aortic regurgitation because of systemic vasculitis. *J Am Soc Echocardiogr.* 2003;16:850–857.)

TABLE 140.1 Major Clinical Features of Takayasu Arteritis in Different Geographic Regions

Major Clinical Feature	PERCENTAGE OF PATIENTS (%)				
	United States	Mexico	India	Korea	Japan
Bruit	80	94	71	37	—
Claudication	70	29	20	21	13
Diminished or absent pulses	60	96	—	55	62
Musculoskeletal symptoms	53	53	31	—	—
Asymmetrical blood pressure	47	—	—	—	—
Constitutional symptoms	43	78	16	34	27
Headache	42	57	22	60	31
Lightheadedness or dizziness	35	—	44	36	40
Hypertension	33	72	76	40	33
Carotidynia	32	—	4	2	21

Modified from Kerr GS: Takayasu's arteritis. *Rheum Dis Clin North Am* 1995;21:1041–1058.

Physical examination may help in diagnosis but is not particularly sensitive. However, normal physical exam findings should not be thought to exclude the presence of arterial disease.

The clinical presentation of patients with TA varies by geographic region (Table 140.1).⁷ The most frequent finding in

patients from North America and Italy were carotid bruits,^{13,20} versus absent pulses in Mexico⁴⁵ and hypertension in India.⁴⁶

Overall, arterial involvement is often symmetric in paired arteries and contiguous in the aorta.⁴⁷ Cerebrovascular signs and symptoms are common because of the frequency of aortic

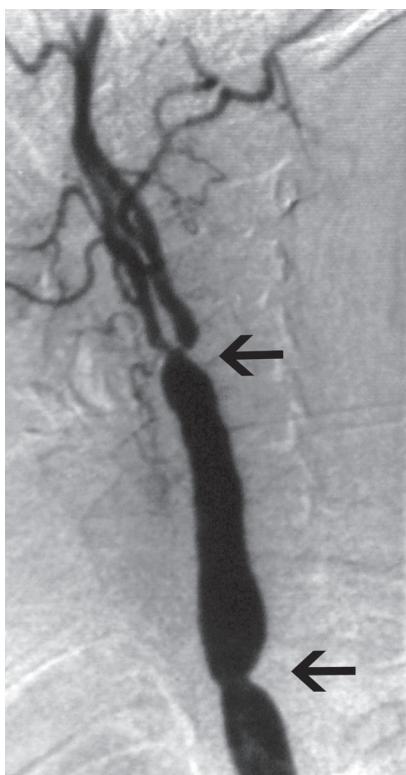


Figure 140.2 Selective carotid angiogram of a 34-year-old woman with symptoms of cerebral ischemia. Note the stenoses of both the common carotid artery and the carotid bifurcation (arrows).

arch and branch involvement. Approximately 32% of patients present with carotidynia.¹³ Many patients report syncope or presyncope at some point during the disease course. Ischemic symptoms of stroke, transient ischemic attack, or amaurosis fugax occur in 5% to 20% of patients.⁴⁸ Visual disturbances occur in up to 30% of patients and are statistically associated with vertebral and common carotid artery involvement (Fig. 140.2).¹³ The retinal disease pattern described by Takayasu also leads to visual disturbances due to central retinal hypoperfusion.⁴⁹

Upper extremity involvement is common in patients with TA. Diminished or absent pulses occur in 53% to 98% of patients.^{13,50} Claudication is more frequent in the upper extremities than the lower extremities and occurs in approximately 62% of patients.¹³ This may be because the left subclavian artery is more commonly affected by TA than other arteries (Fig. 140.3).^{13,20} It has been hypothesized that subclavian steal syndrome is rare in patients with TA because the subclavian artery is involved both proximal and distal to the origin of the vertebral artery. More recent studies have shown that this may not always be true, with angiography demonstrating isolated disease in the proximal subclavian artery 80% of the time.⁴⁷

Cardiac manifestations of TA are common. Coronary artery involvement occurs in 6% to 16% of patients with TA and may lead to ischemic symptoms or congestive heart failure.⁵⁰ Aortic valve regurgitation occurs in 12% to 24% of patients and is generally caused by dilation of the aortic root.²⁰ Aortic valve regurgitation seems to be more common in TA patients from India.²² Mitral valve regurgitation occurs in 3% to 11%

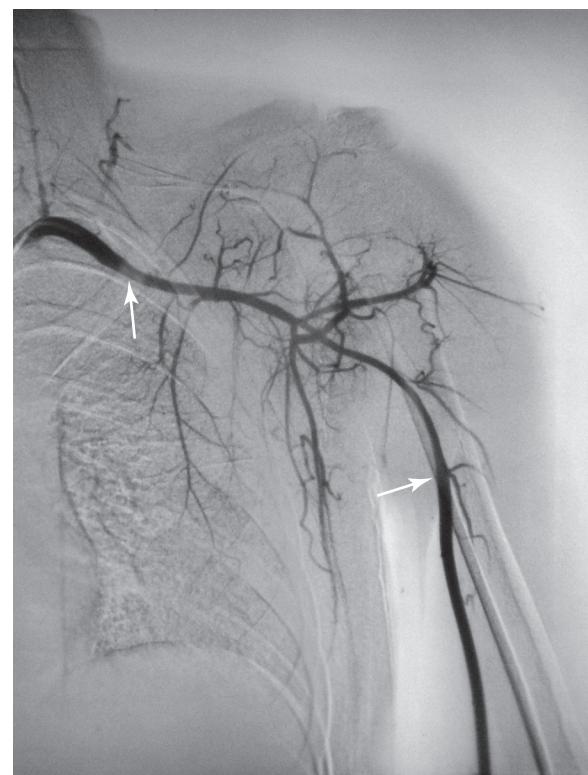


Figure 140.3 Selective left subclavian angiogram of a 26-year-old woman with claudication of the left upper extremity. Note the long, tapered stenosis of the left subclavian and axillary arteries (arrows).

of patients.^{7,51} The cause of mitral valve regurgitation is unclear but is thought to be independent of aortic regurgitation.⁵² Pulmonary artery involvement with TA may be underdiagnosed. In studies in which pulmonary angiography was performed, up to 70% of patients had evidence of disease.^{53,54} These patients most often present with symptoms of pulmonary hypertension. Finally, diffuse vascular involvement of the myocardium has been reported in the absence of coronary stenosis or aortic valve regurgitation. Patients present with symptoms of congestive heart failure, and biopsies of the myocardium show diffuse myocarditis.⁵⁵

Hypertension is one of the most common presenting signs in patients with TA and occurs in 33% to 60% of patients.^{12,13} Bilateral stenosis of the subclavian arteries occurs in up to 92% of patients with TA and can mask hypertension.¹³ Therefore blood pressure measurements of both upper and lower extremities should be performed in any patient suspected of having TA. Renal artery stenosis is a significant cause of hypertension in patients with TA. Involvement of the renal arteries occurs in approximately 20% to 50% of patients.^{51,56} The stenoses are frequently bilateral and involve the ostia of the vessels (Fig. 140.4).⁵¹ Hypertension in the absence of renal artery stenosis occurs in 5% to 30% of patients.^{13,20} Causes of hypertension in this group of patients include middle aortic syndrome, reduced compliance of the aorta, and dysfunction of the carotid baroreceptors (Fig. 140.5).^{57,58} Sen and colleagues first reported on 16 patients with middle aortic syndrome in 1963.⁵⁹ All patients presented with hypertension, and more than half of them had decreased or absent lower extremity pulses. In a 1991

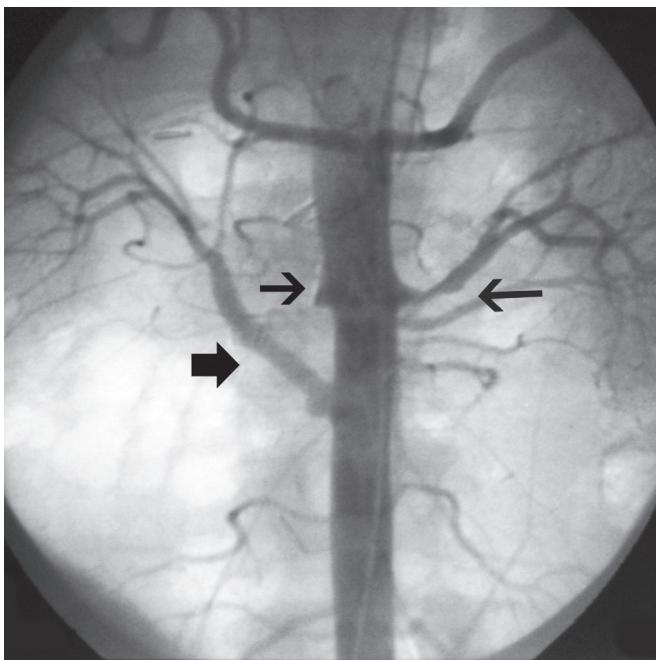


Figure 140.4 Abdominal aortogram of a 48-year-old hypertensive woman with known Takayasu arteritis. Note the short-segment left renal artery stenosis (long arrow), right renal artery occlusion (small arrow), and right aortorenal artery bypass (broad arrow).



Figure 140.5 Abdominal aortogram of a 37-year-old hypertensive woman. Note the long, tapered stenosis of the infrarenal aorta (arrow) and sparing of the distal aorta and iliac arteries.

report from the Japanese Ministry of Health and Welfare, middle aortic syndrome occurred in 16% of surgically treated patients with TA.⁶⁰ Long-segment narrowing of the descending thoracic or abdominal aorta is characteristic, and interscapular or abdominal bruits are frequently heard on auscultation.



Figure 140.6 Aortic arch angiogram depicting extensive aneurysmal disease of the arch vessels of a 54-year-old man.

According to one report, the majority of patients with middle aortic syndrome die by age 35 if left untreated.⁶¹ Middle aortic syndrome is not unique to TA and may be due to congenital hypoplasia, von Recklinghausen disease, fibromuscular dysplasia, and tuberculosis.^{62–64}

Visceral arterial involvement occurs in 3% to 31% of patients with TA.^{20,51} Despite these findings, symptoms of mesenteric ischemia are rare. Aortic endarterectomy for visceral ischemia has been performed, with mixed results. It is controversial in patients with TA because the inflammatory lesions typically involve all three layers of the arterial wall, making the procedure difficult.^{65,66}

Lower extremity ischemic symptoms occur in 24% to 32% of patients and, as stated previously, are less common than upper extremity symptoms.^{13,50} Iliac artery disease is seen in approximately 20% of patients undergoing angiography.^{13,20} Angiographic data suggest that claudication of the lower extremities may be related to abdominal aortic involvement because stenotic disease of the femoral, popliteal, and tibial arteries is rare.²⁰

Aneurysmal disease in patients with TA varies by geographic location. In South Africa, up to 71% of patients underwent surgery for aneurysmal disease.⁶⁷ In a study of Thai patients, 60% of patients had aneurysms, with the abdominal aorta being the most common location, followed by the subclavian artery and the thoracic aorta.⁶¹ In North America, 27% of patients had aneurysms, with the aortic arch being the most common site, followed by the abdominal aorta (Fig. 140.6).¹³ Elsewhere, 13.7% of patients in India and 7% of patients in Italy had aneurysms on angiography.^{20,51} A study from Japan

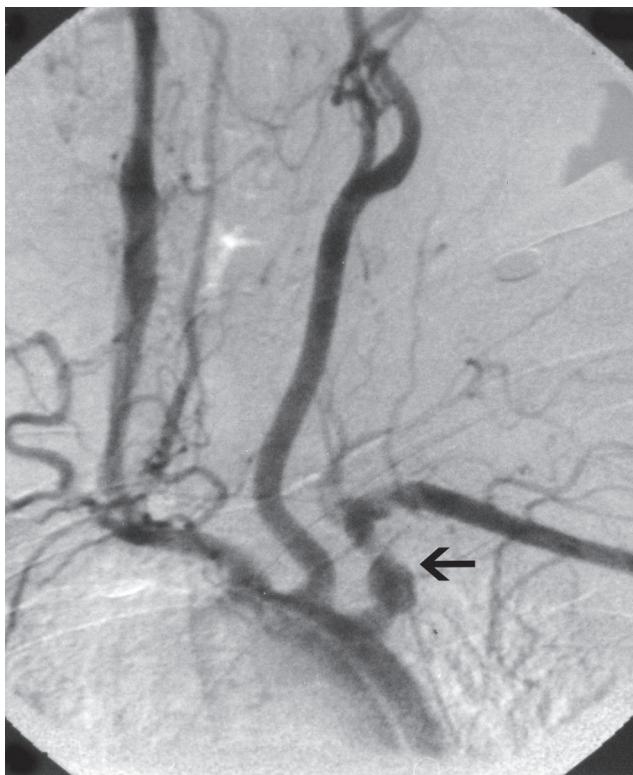


Figure 140.7 Aortic arch angiogram of a 33-year-old woman with left upper extremity claudication. Note the left subclavian aneurysm and concomitant distal stenosis (arrow).

reported 32% of patients with aneurysmal disease and noted that the aneurysms were frequently multiple and associated with stenotic lesions (Fig. 140.7).⁶⁸ In most series the incidence of aneurysm rupture is low compared with that of noninflammatory aneurysms.⁶⁹

Patients with TA may present with nonischemic symptoms. Raynaud phenomenon has been reported in approximately 8% to 14% of patients.²⁰ Skin changes have been reported in 8% to 25% of patients.^{13,50} These cutaneous manifestations of TA range from erythema nodosum to pyoderma gangrenosum to a lupus-like malar flush.^{70,71}

DIAGNOSTIC EVALUATION

Diagnostic Criteria

Because TA affects patients in myriad ways, there have been many proposed diagnostic criteria. The first diagnostic criteria were set forth by Ishikawa, based on a cohort of 96 Japanese patients with TA and 12 patients with other diseases of the aorta.¹⁶ These criteria included an obligatory age less than 40 years. The Ishikawa criteria identified 96% of young patients and 80% of older patients with active disease but, unfortunately, only 67% of young patients and 64% of older patients with inactive disease.

In 1990 the American College of Rheumatology created new diagnostic criteria based on a North American group of patients with TA (Table 140.2).⁷² It removed Ishikawa age criterion because 13% of patients developed the disease after age 40.¹³ The presence of at least three of the six criteria from the

TABLE 140.2

American College of Rheumatology 1990 Diagnostic Criteria for Takayasu Arteritis

Criteria	Definition
Age at disease onset in years	Symptoms or findings of Takayasu arteritis at <40 years
Extremity claudication	Lower or upper extremity muscle fatigue during exercise
Diminished brachial artery pulse	Unilateral or bilateral
Blood pressure difference >10 mmHg	Measured systolic blood pressure between upper extremities
Bruit over subclavian arteries or aorta	One or both subclavian arteries or aorta
Angiographic abnormalities	Narrowing or occlusion of the aorta, primary branches, or large arteries in proximal extremities; must not be secondary to atherosclerosis, fibromuscular dysplasia, or other causes; usually focal or segmental

Modified from Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum*. 1990;33:1129–1134.

traditional classification demonstrated a sensitivity of 90.5% and a specificity of 97.8%. The same group also created a classification tree with five of these six criteria, omitting claudication of an extremity. The classification tree demonstrated a sensitivity of 92.1% and a specificity of 97.0%.

In 1996 Sharma and associates devised a third set of diagnostic criteria. The Ishikawa criteria were modified in an effort to improve early diagnosis and to take into account geographic and racial variations (Table 140.3).^{73,74} The presence of two major criteria, one major criterion and two minor criteria, or four minor criteria was found to have a sensitivity of 92.5% and a specificity of 95% in a group of Indian patients and 96% sensitivity and 96% specificity in a group of Japanese patients.

Although there is no global consensus on the best diagnostic criteria, it is generally agreed that the diagnosis of TA should not be made without ruling out all other vasculitides, vascular infections, fibromuscular dysplasia, and idiopathic inflammatory syndromes.⁷⁵

Laboratory Markers

TA is not associated with any specific laboratory abnormality but is characterized by generalized inflammatory markers. Patients are frequently anemic, with hematocrits in the 20s or 30s.⁴³ The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most common markers used. At presentation, approximately 72% of patients with TA have an elevated ESR.⁷ However, the ESR is very nonspecific; 56% of patients have an elevated ESR with disease remission, and 28% have a normal ESR with clinically active disease.

Investigators have begun to examine the role of other laboratory markers in TA, including serum interleukin-6 (IL-6) and regulated upon activation, normal T-cell expressed, and presumably secreted (RANTES). IL-6 enhances T-cell cytotoxicity

TABLE 140.3 Modified Diagnostic Criteria for Takayasu Arteritis

Criteria	Definition
Three Major Criteria	
Left mid-subclavian artery lesion	Severe stenosis or occlusion present in midportion from 1 cm proximal to the left vertebral artery origin to a point 3 cm distal to the origin
Right mid-subclavian artery lesion	Severe stenosis or occlusion in midportion from the right vertebral artery origin to a point 3 cm distal to the origin
Characteristic signs and symptoms of at least 1 month in duration	Includes limb claudication, pulselessness or pulse difference in the limbs, unobtainable or significant blood pressure difference (>10 mmHg systolic difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea, or palpitations
Ten Minor Criteria	
Elevated erythrocyte sedimentation rate	Unexplained persistent erythrocyte sedimentation rate >20 mm/h at diagnosis or presence of evidence in patient history
Carotidynia	Unilateral or bilateral tenderness of the common carotid artery on palpation; must differentiate from neck muscle tenderness
Hypertension	Persistent elevation of blood pressure above 140/90 mmHg (brachial) or 160/90 mmHg (popliteal)
Aortic regurgitation or annulo-aortic ectasia	By auscultation, echocardiography, or angiography
Pulmonary artery disease	Lobar or segmental artery occlusion or equivalent; stenosis, aneurysm, luminal irregularity, or any combination of these findings in pulmonary trunk or pulmonary arteries
Left mid-common carotid artery lesion	Severe stenosis or occlusion in midportion, 5 cm in length from a point 2 cm distal to the origin
Distal brachiocephalic trunk lesion	Severe stenosis or occlusion in distal third
Descending aortic lesion	Narrowing, dilatation or aneurysm, luminal irregularity, or combination of these findings involving the thoracic aorta; tortuosity alone is insufficient
Abdominal aortic lesion	Narrowing, dilatation or aneurysm, luminal irregularity, or combination of these findings involving the abdominal aorta; tortuosity alone is insufficient
Coronary artery lesion	Narrowing, dilatation or aneurysm, luminal irregularity, or combination of these findings before the age of 30 years in the absence of atherosclerotic risk factors, such as hyperlipidemia or diabetes mellitus

Modified from Sharma BK, et al: Diagnostic criteria for Takayasu arteritis. *Int J Cardiol.* 1996;54(Suppl):S141–S147.

and natural killer cell activity,^{76,77} whereas RANTES is a selective chemoattractant for most mononuclear cell types implicated in TA.⁷⁸ A recent study showed increased levels of IL-6 and RANTES in patients with TA.⁷⁹ Furthermore, both IL-6 and RANTES paralleled disease activity.

Other investigators have examined matrix metalloproteinases (MMPs) in patients with TA.⁸⁰ MMP-2 levels were elevated in patients with TA compared with controls, although no correlation was found between serum MMP-2 and disease activity. MMP-3 and MMP-9 levels in patients with active disease were elevated compared with those in controls and patients in disease remission, and a positive correlation was found between MMP-3 or MMP-9 level and disease activity.

While multiple studies addressing serologic biomarkers have attempted to identify better diagnostic parameters, the 2018 European League Against Rheumatism (EULAR) systematic literature review found that ESR and CRP remain the most efficacious studies currently available.⁸¹

Radiologic Evaluation

Although histopathologic examination of arterial specimens provides the most accurate determination of disease, radiologic

evaluation can provide a more extensive assessment of pathology. In the past, digital subtraction angiography of all possibly affected arteries was considered the only reliable radiologic method of evaluating patients with TA.⁸²

More recently, noninvasive methods such as ultrasound, computed tomographic angiography (CTA), and magnetic resonance imaging (MRI) have been used to assess the mural changes of the arterial wall seen in TA before the development of stenotic or aneurysmal disease.⁸³ Duplex ultrasound has been useful for evaluating the carotid arteries in patients with TA. Active disease is characterized by prominent wall thickening with a maintained outer diameter, whereas inactive disease is characterized by mild wall thickening with a decreased outer diameter (Fig. 140.8).⁸⁴ A comparison of duplex ultrasound and arteriography of the carotid arteries reveals that the two closely correlate in terms of disease assessment and that ultrasonographic mural thickness is a more sensitive indicator of early, latent inflammation.⁸⁵

MRI has now replaced conventional angiography as the consensus “gold standard” imaging modality for diagnosing TA in the updated EULAR imaging recommendations.⁸⁶ MRI is noninvasive and reduces exposure to radiation and contrast while allowing for the evaluation of mural inflammation and/

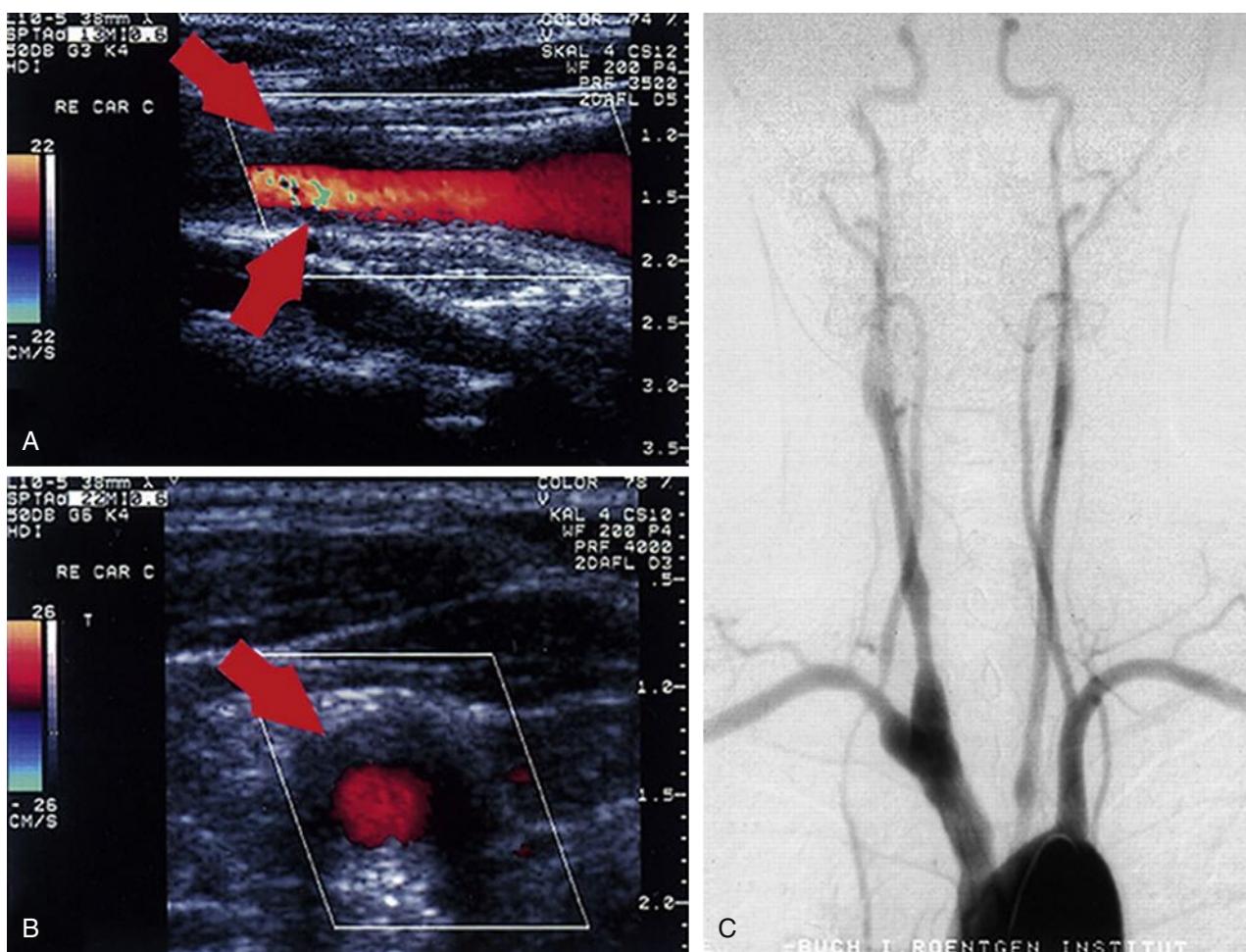


Figure 140.8 Patient with Early Takayasu Arteritis. (A and B) Ultrasound images: longitudinal plane (A) and transverse plane (B) of the right common carotid artery with the typical morphologic appearance of Takayasu arteritis indicated by arrows. (C) Angiography of the branches of the aortic arch, confirming the ultrasound diagnosis and revealing narrowing of up to 40% as well as post-stenotic dilations at the right common carotid artery, the left proximal common carotid artery, the proximal right subclavian artery, and the proximal right vertebral artery. (From Schmidt WA, et al. Diagnosis of early Takayasu arteritis with sonography. *Rheumatology (Oxford)*. 2002;41:496–502.)

or luminal irregularities. Given the young age at diagnosis of TA, the lack of radiation exposure is preferred in this population. Spin-echo MRA depicts early arterial wall thickening similar to CTA.⁸⁷ Significant enhancement of the aorta and carotid arteries may be seen before the development of stenoses, and greater contrast enhancement in the aortic wall as compared with myocardium correlates positively with disease activity (Fig. 140.9). T2-weighted images may show bright signal correlating with vessel wall inflammation and edema.⁸⁸ MR does have limitations: although MRA accurately depicts approximately 98% of arterial involvement in TA, 2% of stenotic arteries are overestimated as occluded.⁸⁹ Furthermore, vessel wall edema can be found in up to 56% of patients who are in clinical remission.⁹⁰ The new intravascular contrast agent gadofosveset trisodium (MS-325) shows promise in the use of MR for the detection of TA, and more specifically for differentiation between active and inactive disease.⁹¹

Findings on CTA may include high density and calcifications of the aortic wall on pre-contrast images, a thickened wall with enhancements in the arterial and venous phases, and a

low-attenuation ring in the venous phase (Fig. 140.10).⁹² CTA is also useful to assess the extent of disease involvement. In one study the extent assessed by mural change was wider than that assessed by luminal change in 61% of patients.⁹³ Skip lesions were seen in 16% of patients, although contiguous arterial involvement was more common (81%). Finally, CTA revealed the coexistence of active and inactive lesions in 11% of patients. A comparison of CTA with conventional angiography showed that the two correlated in 71% of patients, but CTA depicted more extensive disease, owing to its ability to assess mural inflammation.⁹⁴

The inflammation associated with TA has led investigators to evaluate the role of positron emission tomography (PET). Quantification of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake can be used to evaluate active vascular inflammation before the development of hemodynamically significant stenoses.⁹⁵ It may be useful not only in identifying disease activity but also in accurately monitoring treatment efficacy (Fig. 140.11). In one study, ¹⁸F-FDG PET had a 92% sensitivity, 100% specificity, and negative and positive predictive values of 85% and 100%,

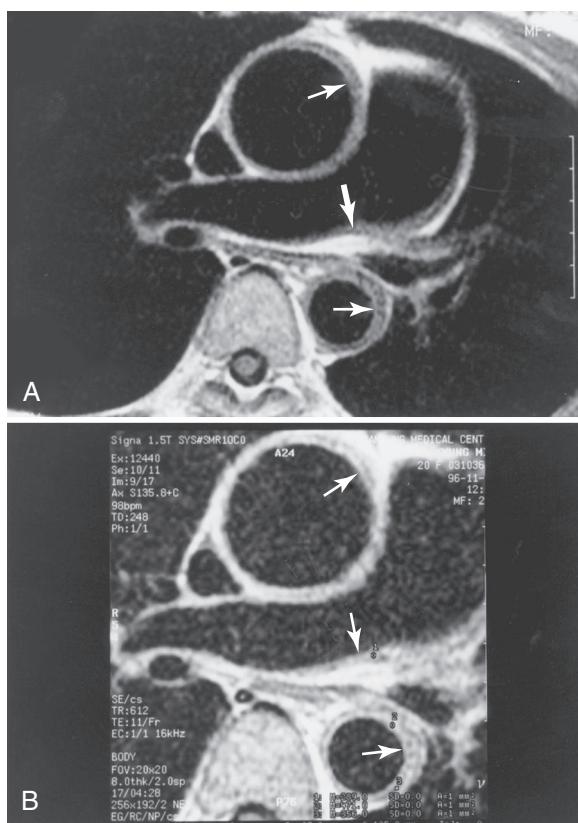


Figure 140.9 Clinically Active Takayasu Arteritis in a 25-Year-Old Woman. (A) A T1-weighted axial magnetic resonance image before contrast media injection shows diffuse and concentric mural thickening of the thoracic aorta (thin arrows) and mild mural thickening of the right pulmonary artery (thicker arrow). (B) Immediately after contrast media injection, a T1-weighted axial image shows enhancement in the thickened aortic and pulmonary arterial walls (arrows), which suggests increased vascularization in the inflamed vessel walls. (From Choe YH, et al. Magnetic resonance imaging diagnosis of Takayasu arteritis. *Int J Cardiol*. 1998;66(Suppl 1):S175–S179.)

respectively, in disease activity assessment.⁹⁶ PET provides further value in identifying alternative causes of illness in patients whose initial symptoms are nonspecific.⁸⁶ Overall, ¹⁸F-FDG PET strongly correlates with the response to medical therapy and may prove useful for managing patients whose serum inflammatory markers remain elevated despite inactive disease.

Although no longer the “gold standard” for the diagnosis of TA, angiography depicts the extent of disease and can be utilized at the time of endovascular interventions⁹⁷ (see Figs. 140.2–140.7). Comparison of direct aortic blood pressure measurement at the time of angiography to measurements in the upper and lower extremities is important considering the nature of stenotic lesions and their interference with extremity cuff pressures. Furthermore, the classification of TA is based on arteriographic findings and correlates with clinical manifestations and prognosis.⁴³

CLASSIFICATION

The classification of TA was originally proposed by Ueno in 1967.⁹⁸ He divided TA into three types based on aortic involvement (Table 140.4). Lupi-Herrera added a type IV to this

classification for pulmonary artery involvement.²³ Nasu and others described a variation on Ueno’s classification based on the distribution of aortic disease.^{8,15,99} In 1994 a new classification was proposed at the Tokyo International Conference on Takayasu’s Arteritis that divided TA into six patterns of disease.¹⁰⁰ A “C” or “P” was added if a patient had coronary or pulmonary artery involvement, respectively.

Classification of disease activity is important in determining response to treatment but has not been uniform throughout the literature. Because steroids play a major role in the treatment of TA, certain authors have relied on steroid use as the sole determinant of active disease. This definition is ultimately too narrow and may equate patients in remission and off steroids with patients acutely presenting with active disease and not yet on steroids.¹⁰¹ The NIH followed 60 patients between 1970 and 1990, with an average age at disease onset of 25 years.¹³ Active disease was defined as new onset or worsening of two or more features of TA (Box 140.1). These included systemic manifestations, elevated ESR, signs of vascular disease, and typical angiographic findings. Researchers at the Mayo Clinic have used a similar definition of two or more features of TA but have substituted elevated CRP and active inflammation at the time of operation and in the pathologic specimen.¹⁰² These criteria may be more stringent, but they make the diagnosis of active disease difficult without open surgical operation.

MEDICAL TREATMENT

Approximately 12% to 20% of patients diagnosed with TA have a self-limited, monophasic illness and may not need immunosuppressive therapy.^{20,80} All other patients typically require some regimen of immunosuppression to control disease activity. Glucocorticoids (GC) are the first-line agents for patients with TA and are begun at a dose of 40–60 mg/day prednisolone equivalent.¹⁰³ If there is improvement in disease activity, the prednisolone dose may be tapered to a target dose of 15–20 mg/day within 2–3 months and after 1 year maintained at ≤10 mg/day. The clinical response to oral glucocorticoids is varied and ranges from 20% to 100%.^{23,104} Determining clinical response is complicated by the difficulty of assessing disease activity based on laboratory markers and symptoms alone. In the NIH cohort, oral GC induced remission in 60% of patients at least once.¹³ In the 40% who did not achieve disease remission with oral GC, the addition of other cytotoxic agents induced remission in another 40%.

Relapse is common even in patients who achieve remission on oral GC and is seen in 45% to 96% of patients.^{13,52} Alternative immunosuppressive agents are typically added in 40% to 73% of patients who relapse or who never achieve remission.^{19,52} As a result, the updated 2018 EULAR recommendations include the addition of non-biological disease-modifying agents in all patients with TA. These agents include methotrexate, cyclophosphamide, azathioprine, or mycophenolate mofetil.

Although the results of immunosuppressive regimens are promising, limitations of therapy still exist in larger series of patients. In the Cleveland Clinic cohort, only 28% of patients

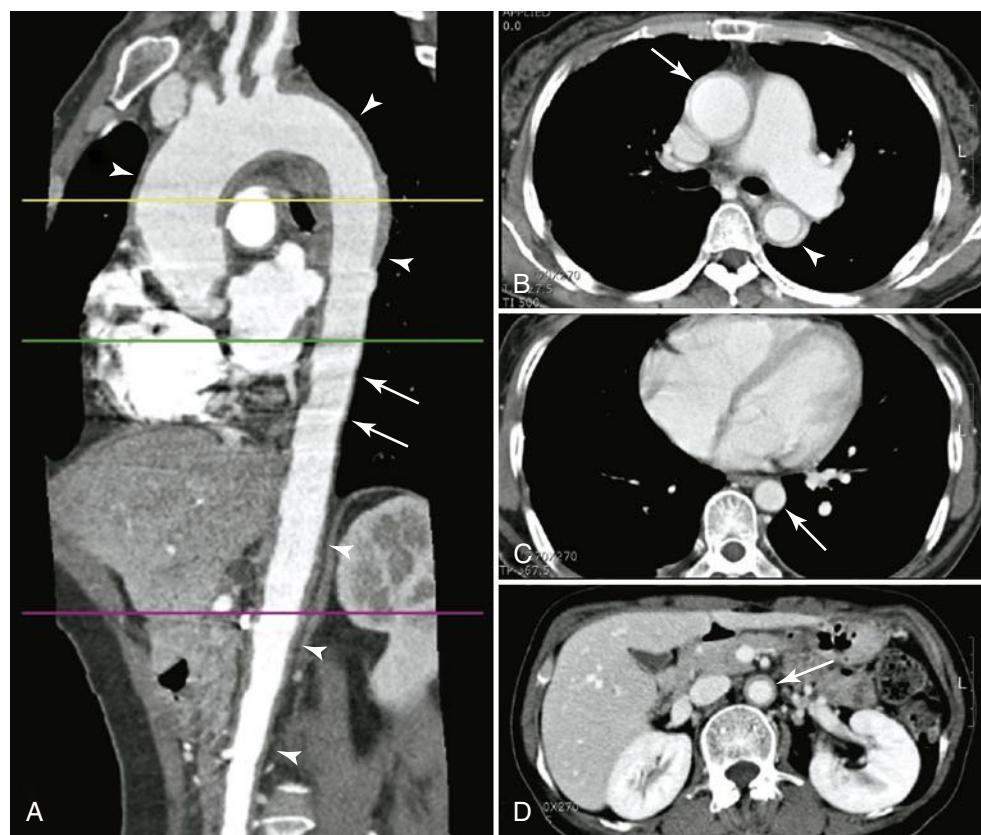


Figure 140.10 Takayasu Arteritis Involving the Aorta with a Skipped Segment in a 50-Year-Old Woman. (A) Multiplanar reformation image shows wall thickening (arrowheads) of ascending thoracic aorta, aortic arch, proximal descending thoracic aorta, and abdominal aorta. No wall thickening of distal descending thoracic aorta is noted. Motion artifact (pulsation artifact) was not observed in the thickened segment, such as the aortic arch and abdominal aorta, because of stiffness of the involved aorta but was observed in the distal descending thoracic aorta (arrows) owing to pulsation of the noninvolved segment. (B) Computed tomography (CT) scan at the proximal descending thoracic aorta shows diffuse wall thickening and inner low-attenuation ring of ascending (arrow) and descending thoracic aorta (arrowhead). (C) CT scan at the distal descending thoracic aorta (arrow) shows no wall thickening of aorta. (D) CT scan at the abdominal aorta shows diffuse wall thickening and inner low-attenuation ring of abdominal aorta (arrow). (From Chung JW, et al. Patterns of aortic involvement in Takayasu arteritis and its clinical implications: evaluation with spiral computed tomography angiography. *J Vasc Surg.* 2007;45:906–914.)

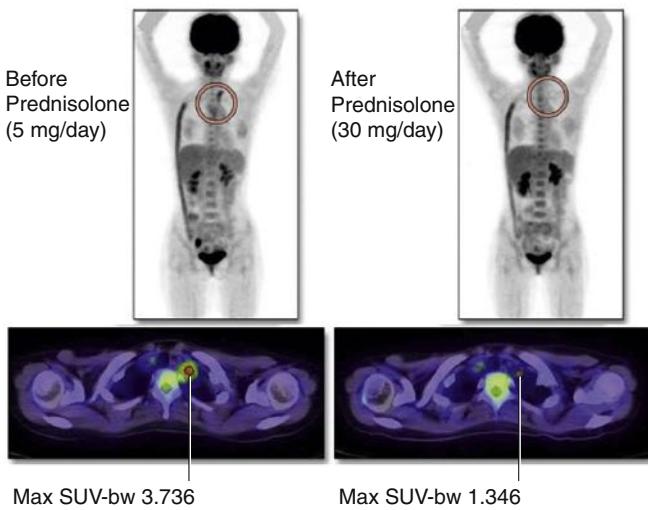


Figure 140.11 A 23-year-old woman with Takayasu arteritis was taking corticosteroids at a dose of 5 mg/day. The erythrocyte sedimentation rate was 18 mm/h, but she had left arm pain with slight elevation of the C-reactive protein level up to 1.1 mg/dL. The ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography imaging showed uptake in the left subclavian artery, and the maximum standardized uptake value (max SUV) was elevated (left). After the dose of prednisolone was increased to 30 mg/day, the uptake disappeared, and max SUV decreased (right). Strong ¹⁸F-fluorodeoxyglucose uptake on her right side is uptake due to an artificial graft from the right axial artery to the right external iliac artery. (From Tezuka D, et al. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. *JACC Cardiovasc Imaging.* 2012;5:422–429.)

had sustained remission,⁵² and 23% of patients in the NIH cohort had continuous disease regardless of therapy.¹³ These results, along with the hypothesis that autoimmunity contributes to the disease, have led investigators to examine the role of immunomodulating medications for the treatment of TA.

REFRACTORY THERAPY

Immunomodulating medications have been used with some success in patients unable to achieve remission on standard drug therapies. Long-term data from the Cleveland Clinic on patients treated with anti-TNF therapy found that remission was achieved and prednisone was discontinued in 60% of patients and tapered to less than 10 mg/day in an additional 28%.¹⁰²

Anti-IL-6 therapy (tocilizumab) has also been used successfully to induce remission and decrease the need for steroid therapy.^{103,104} When comparing anti-TNF agents to tocilizumab, there were no significant differences in efficacy between therapies. A randomized, double-blind trial in Japan demonstrated a trend towards improved time to relapse in patients treated with tocilizumab compared to placebo.¹⁰⁵ More recently, B-cell depletion strategies using rituximab have also been used successfully in patients refractory to other immunosuppressive therapies.¹⁰⁶ The 2018 EULAR recommendations further support the utilization of tocilizumab or anti-TNF agents in cases of refractory disease to conventional therapy.¹⁰³

INDICATIONS FOR AND RESULTS OF REVASCULARIZATION PROCEDURES

The need for surgical procedures in patients with TA varies by geographic region. Approximately 50% of patients from the United States and Italy need surgery,^{7,20,52} whereas only 10% to 12% of patients in Japan and India undergo surgical intervention.^{21,51} If possible, surgery should be performed when

TABLE 140.4

Angiographic Classification Systems for Takayasu Arteritis Based on Vessel Involvement

UENO Classification

Type I	Aortic arch and its branches
Type II	Descending thoracic and abdominal aorta and their branches
Type III	Combination of types I and II
Type IV	Any of the above with pulmonary artery involvement (Lupi-Herrera modification)

NASU Classification

Type I	Aortic arch branches alone
Type II	Aortic root, arch and its branches
Type III	Subdiaphragmatic aorta
Type IV	Entire aorta and its branches

1994 Tokyo International Conference on Takayasu's Arteritis Classification

Type I	Aortic arch branches alone
Type IIa	Ascending aorta, arch and its branches
Type IIb	Ascending aorta, arch and its branches, and descending thoracic aorta
Type III	Descending thoracic and abdominal aorta and their branches
Type IV	Abdominal aorta and its branches
Type V	Entire aorta and its branches

Modified from Rigberg DA, et al. Takayasu's disease: non-specific aortoarteritis. In: Rutherford RB, ed. *Vascular Surgery*, 6th ed. Philadelphia: Elsevier; 2005:419.

disease activity is minimal.⁵⁴ In fact, one study showed a decrease in the 5-year patency rate from 88% to 53% when bypass was performed in patients with active disease.¹⁰⁷ Another study found that patients with active disease were more likely to require revision or develop progressive symptomatic disease at another site.¹⁰² In a group of 42 patients with TA, the rate of bypass revision or disease progression at 5 years was 0% in patients with quiescent disease not on steroids, 10% in patients with quiescent disease on steroids, 57% in patients with active disease on steroids, and 67% in patients with active disease not on steroids. Again, disease activity assessment is not perfect, and surgical specimens show active disease in up to 44% of patients who were thought to be in remission.⁷

General indications for surgical revascularization include hypertension in the setting of renal artery stenosis, lifestyle-limiting extremity ischemia, cerebral ischemia or greater than 70% symptomatic stenosis of cerebral vessels, moderate (grade II New York Heart Association) aortic regurgitation, cardiac ischemia in the setting of proven coronary artery stenosis, severe aortic coarctation, or progressive aneurysmal enlargement and dissecting aneurysm.¹⁸

Endovascular Treatment

Initial reports of percutaneous vascular interventions in patients with TA were promising. Sharma reported 1-year success rates for percutaneous transluminal angioplasty (PTA) of the renal arteries and the abdominal aorta of 80% and 100%, respectively.¹⁰⁸ Others reported initial success rates in 74% of patients.¹⁰⁹ In a report of subclavian artery PTA, initial success rates were 88% for stenotic lesions and 67% for total occlusions. On mean 4-year follow-up, restenosis occurred in 20% of patients.¹¹⁰

Despite these results, long-term evaluation of percutaneous interventions is less encouraging. In a study of 20 patients treated with PTA, the initial success rates of PTA for renal artery stenosis and middle aortic syndrome were 83% and 100%, respectively, but the 5-year patency rate was 33.3% for each.¹¹¹ In a study of Korean patients, patency rates decreased from 90% at 1 year to 50% at 10 years.¹¹² Stable disease activity and treatment with GC and immunosuppressive agents were found to aid in the maintenance of arterial patency.

BOX 140.1 Definition of Active Disease in Takayasu Arteritis

National Institutes of Health

Systemic features such as fever, musculoskeletal symptoms (no other cause identified)
Elevated ESR
Features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, carotidynia, asymmetrical blood pressure
Typical angiographic features

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Modified from Kerr GS, et al. Takayasu arteritis. *Ann Intern Med*. 1994;120:919–929; and Fields CE, et al. Takayasu's arteritis: operative results and influence of disease activity. *J Vasc Surg*. 2006;43:64–71.

Mayo Clinic

Systemic features such as fever, myalgia, or arthralgia
Elevation of serum markers such as ESR or CRP
Active inflammation in a pathologic specimen taken from diseased arteries
Acute inflammation of the artery and surrounding soft tissue at the time of operation
Active disease defined by new onset or worsening of two or more features

In the NIH cohort, 11 patients underwent a total of 20 endovascular interventions: 8 subclavian, 7 renal, 4 iliofemoral, and 1 thoracic aorta angioplasty.¹³ The initial success rate was 56%; it was only 33% on the second attempt. Restenosis was frequent and occurred within 3 to 13 months. In the Cleveland Clinic cohort, 20 patients underwent PTA: 8 renal, 4 subclavian, 2 iliofemoral, 2 carotid, 2 axillary, 1 abdominal aorta, and 1 coronary angioplasty.⁵² Restenosis was common and occurred in 78% of patients. Thirteen of those patients required reintervention, and 6 required subsequent bypass.

PTA's poor long-term results in patients with TA may be explained by the fibrotic and noncompliant nature of diseased vessels. Many authors have reported the need for higher balloon pressures to achieve success.¹¹³ Other impediments to successful angioplasty include the fact that stenoses in TA are often long, and PTA results have been poor for eccentric stenoses and diffuse aortic disease.¹⁰²

With developments in the technology of endovascular devices, the long-term results of percutaneous interventions in TA are beginning to show some improvement. Although the number of patients reported is small, stent grafts have been found to have better patency rates in the treatment of TA than PTA or bare metal stents.¹¹⁴ In this retrospective study, none of the stent grafts occluded or became severely stenosed during follow-up ranging from 2 to 6 years, as compared with bare metal stents that had a higher rate of in-stent restenosis.

Open Surgical Treatment

Open vascular surgical intervention has been a mainstay in the treatment of complications associated with TA. The majority of vascular lesions associated with TA cause ischemic symptoms and are best managed with bypass grafts.

Common carotid bypass is typically performed for stroke prevention and is one of the most common procedures performed for ischemic disease.¹³ Unlike atherosclerotic carotid disease, the lesions of TA are longer, poorly amenable to endarterectomy, and cause symptoms through thrombosis rather than embolism. Endarterectomy in patients with TA is more difficult because of the transmural nature of the inflammation and the difficulty in determining the correct plane of dissection.¹¹⁵ In the Cleveland Clinic cohort, two-thirds of endarterectomy and patch angioplasty procedures failed.⁵³ Carotid bypass in patients with TA should originate from the aortic arch rather than an aortic branch artery because the arch is typically less involved with disease compared with its branches.¹

Upper extremity bypass for subclavian and axillary lesions is one of the most common surgical procedures performed in patients with TA. In the NIH and Cleveland Clinic cohorts, upper extremity bypass was performed in 17% and 11%, respectively.^{13,52} Again, the aortic arch may be preferred for inflow, owing to its less common involvement.

Coronary artery revascularization is frequently necessary because of ostial narrowing and subsequent ischemia. Excellent results have been obtained with bypass surgery. Aortic regurgitation may present along with coronary artery disease in up to 45% of patients, necessitating concomitant aortic valve replacement.¹¹⁶

Renal artery revascularization is commonly performed after failed endovascular therapy and may be more beneficial as a first-line therapy in patients who have disease beyond the ostia.¹¹⁷ Inflow is typically taken from the aorta but may be limited to the visceral vessels if the abdominal aorta is significantly diseased. An autologous conduit is preferred, owing to the lower complication rate.¹³ In one of the largest series of renal revascularization for TA-induced renal artery stenosis, 27 patients underwent 40 interventions: 32 aortorenal bypasses, 2 repeat implantations, 4 nephrectomies, and 2 transluminal angioplasties.¹¹⁸ These interventions significantly decreased both the mean arterial blood pressure and the number of antihypertensive medications, and they increased the mean glomerular filtration rate. The 5-year primary and secondary patency rates were 79% and 89%, respectively.

Open surgical treatment remains the gold standard for the treatment of middle aortic syndrome. Endovascular repair of middle aortic syndrome has been attempted, with successful initial results, but 5-year patency rates were approximately 33%.¹¹⁹ This has led other investigators to examine aortic stenting. Again, initial success rates were excellent, but long-term results are lacking.^{120,121} Patch aortoplasty has been performed in the past, but it has the same complications related to endarterectomy for carotid revascularization. Definitive repair typically consists of aorto-aortic bypass, owing to the long length and calcification of the affected segment.¹²² Inflow should be taken from the suprarenal aorta because the infrarenal aorta is frequently involved with disease (Fig. 140.12). The



Figure 140.12 Angiogram of a 46-year-old woman who originally presented with hypertension and lower extremity claudication. Note the occlusion of the infrarenal aorta consistent with middle aortic syndrome (small arrow) and the bypass from the thoracic aorta to the left external iliac artery (large arrow).

iliac arteries are commonly used as a distal target because the distal aorta is usually spared. Open surgical revascularization can lead to a greater than 75% improvement in hypertension, with 50% of patients no longer requiring antihypertensive medications.¹²³ Postoperative event-free survival is greatest in those who experience resolution of hypertension.

Revascularization of the visceral arteries may occasionally be necessary in patients with chronic mesenteric ischemia. Although some reports have recommended bypass or endarterectomy even in asymptomatic patients,¹²⁴ reports from North America suggest that only the rare patient with TA and symptoms of chronic mesenteric ischemia should undergo mesenteric bypass.^{13,52}

Few reports of endovascular aneurysm repair exist in the literature, and the majority of patients have undergone open aneurysm repair. The fact that the incidence of rupture is lower for TA-related aneurysms must be weighed against the fact that these patients develop aneurysms at such a young age.¹ Therefore aneurysm repair is typically performed for the same indications as in patients with non-TA aneurysms.

Certain authors have hypothesized that patients with TA are at increased risk for anastomotic aneurysms due to vessel wall inflammation. In a large study of 103 patients with TA treated surgically, over 40 years with 259 anastomoses, the anastomotic aneurysm rate was 12%.¹²⁵ The investigators found that the incidence of anastomotic aneurysms was increased only after operations for aneurysmal lesions and not in patients with systemic inflammation or on steroids.

Overall results suggest that open surgical treatment of TA can be performed with minimal morbidity and mortality.¹⁰² In the NIH cohort, 30% of the bypasses resulted in complications, including 24% restenosis and 4% thrombosis,¹³ whereas 36% of the bypasses in the Cleveland Clinic cohort had restenosis or occlusion.⁵² Reports from Japan have shown similar results. In a series of 106 patients followed up to 40 years, the 10-year cumulative patency rates of carotid, subclavian, aorto-aortic, renal, and mesenteric revascularizations were 88%, 64%, 100%, 68%, and 67%, respectively.¹²⁶ Overall 20-year survival was 74%. Early death occurred in 12% of patients (0% after 1980). Late death occurred in 31% of patients and was most frequently due to congestive heart failure.

Direct Comparison of Endovascular and Open Surgical Treatment

Due to the low incidence of TA, few studies have compared endovascular therapy and open surgery. However, one large retrospective multicenter study examined the outcomes of 79 patients with TA, of whom 63% were treated with an open surgical procedure and 34% with endovascular intervention, including angioplasty and/or stenting.¹²⁷ Follow-up ranged from 2 to 11 years. Surgical intervention was associated with a 38% vascular complication rate compared with 50% for endovascular intervention. Biologic inflammation, as manifested by elevated ESR, CRP, and serum fibrinogen levels at the time of intervention, was independently associated with complications after intervention.

Analysis of outcomes in patients with symptomatic supra-aortic arterial occlusive disease has also shown the superiority of open surgical treatment in long-term outcomes. Kim et al. compared endovascular intervention with angioplasty and bare metal stent placement to open surgical treatment with bypass for short (<5 cm) occlusive lesions.¹²⁸ Restenosis was observed in 53% of patients in the endovascular group and 13% of patients in the bypass group. However, serious early postoperative complications, such as intracerebral hemorrhage or cardiac tamponade, were more common in the surgical bypass group.

A more recent meta-analysis including 770 patients with 1363 lesions showed patients treated with endovascular interventions were more likely to incur restenosis (odds ratio 5.18; $P < 0.001$).¹²⁹ These findings were found independent of disease state and impacted by lesion location. Subgroup analysis identified higher restenosis rates following endovascular intervention when coronary, supra-aortic branches or renal arteries were treated. As seen in other studies, stroke was more common in open revascularizations, particularly in those with supra-aortic branch involvement; however, mortality and other complications were equivocal between populations.

Patients who undergo revascularization for symptomatic TA lesions should be carefully followed because they are likely to develop symptoms requiring intervention in another vascular bed or revision of the original procedure. A study from UCLA of 40 patients with TA who underwent revascularization from 1980 to 2009 (60 bypass procedures and 4 endovascular interventions) showed that during a mean follow-up of 6.4 years, 40% of patients exhibited progression of TA requiring intervention.¹⁰⁶

SPECIAL CONSIDERATIONS

Pregnant Patients

Because TA is most commonly a disease of women of child-bearing age, many authors have examined the effects of TA on pregnancy. In the NIH cohort, five women became pregnant, and all delivered healthy children without complications related to the delivery.¹³ One patient in this group had an exacerbation of TA-related symptoms. Similarly, the Cleveland Clinic cohort reported one spontaneous abortion in four pregnancies. All three children brought to term were healthy.

Overall, prognostic indicators of poor maternal and fetal outcome include hypertension, aneurysmal disease, cardiac failure, and extent of disease.⁷ Interestingly, the state of pregnancy may alter TA physiology, as evidenced by improvement in inflammatory markers and hemodynamic parameters.¹³⁰ Pregnancy itself has not been found to have an adverse effect on the state of TA.¹³¹

Pediatric Patients

The youngest patient ever diagnosed with TA was 7 months old.¹¹⁵ This patient presented with an aneurysm of the right common iliac artery and an iliocaval fistula. Overall, patients presenting with TA before age 20 years represent approximately

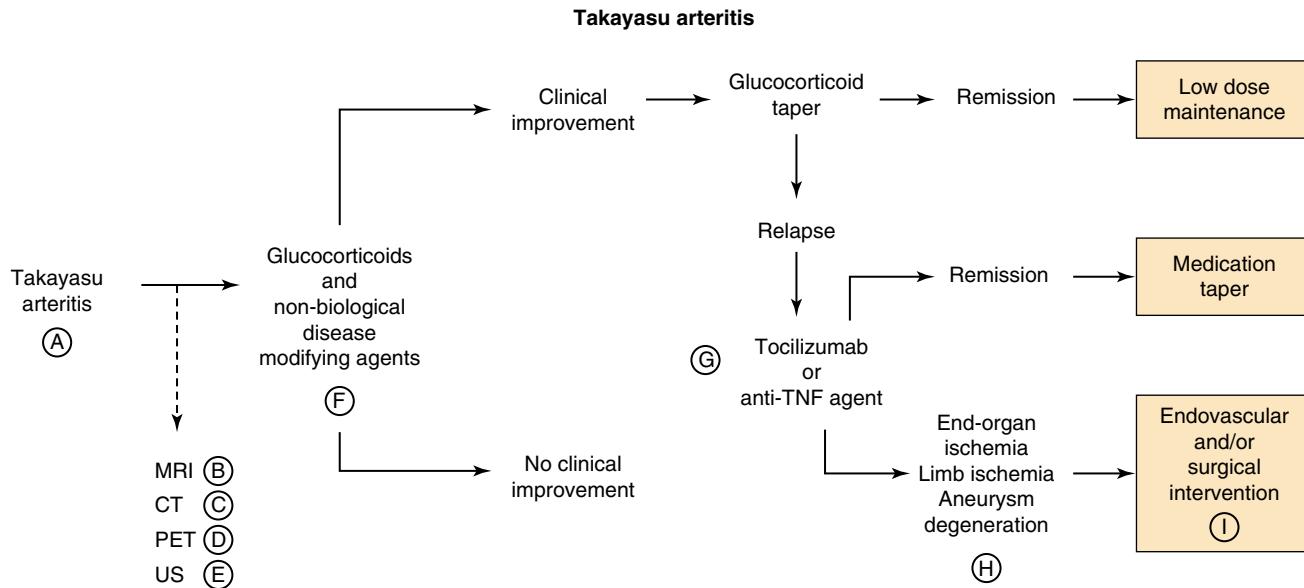
13% to 77% of reported cases.^{13,23,53} The propensity for non-specific systemic symptoms makes diagnosis difficult, although it is unclear whether the development of TA before age 20 actually leads to a delay in diagnosis. The thoracic and abdominal aorta are most commonly involved, and ischemic symptoms are less frequent.⁷

One of the largest series of children diagnosed with TA comes from China and reviews the presenting signs and symptoms, and outcomes of treatment of pediatric patients with TA.¹³² Fourteen children, with a mean age of 10, were diagnosed with TA in the 12-year-long review. Median time to diagnosis after onset of symptoms was 2 months. The most common presenting symptom was hypertension (in 93%), and most patients had an abnormal pulse exam. Medical treatment was successful in 50% of patients. Imaging may show arterial stenosis, dissection, or aneurysm.¹³³

PROGNOSIS

The overall prognosis of patients with TA is guarded. The effects of TA extend into all aspects of patients' lives, especially given the fact that the disease develops at such an early age and progresses despite both medical and surgical therapy. Relapse is common and occurs in 29% to 90% of patients.^{19,52} The 2018 EULAR recommendations identified the presence of major complications, older age, progressive disease course and a weaker inflammatory response to be associated with worse prognosis.⁸¹ The overall survival rate in 120 patients 15 years after the diagnosis of TA was 83%.²¹ For patients with both a major complication and a progressive disease course, survival decreased to 43% at 15 years. Congestive heart failure is the most common cause of death in patients with TA across geographic regions.^{21–23}

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

- Fields CE, Bower TC, Cooper LT, et al. Takayasu's arteritis: operative results and influence of disease activity. *J Vasc Surg.* 2006;43:64–71.
- Short- and long-term operative results in 42 patients with TA and the effect of disease activity on outcome.*
- Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* 2020;79(1):19–30.
- Most up-to-date consensus recommendation document regarding diagnosis and management.*
- Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. *Circulation.* 1994;90:1855–1860.
- Long-term outcome and prognostic factors in 120 patients with TA, with the proposal of a new prognostic classification system.*

Jung JH, Lee YH, Song GG, et al. Endovascular versus open surgical intervention in patients with Takayasu's Arteritis: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2018;55(6):888–899.

Large-volume meta-analysis comparing open vs. endovascular treatment outcomes.

Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med.* 1994;120:919–929.

NIH cohort of 60 patients with TA.

Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. *Curr Opin Rheumatol.* 2005;17:16–24.

General review of the medical and surgical therapy of TA.

Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheum.* 2007;56:1000–1009.

Cleveland Clinic cohort of 75 patients compared with other published series of TA patients.

Miyata T, Sato O, Koyama H, et al. Long-term survival after surgical treatment of patients with Takayasu's arteritis. *Circulation*. 2003;108:1474–1480.

Outcome over 40 years in 106 patients with TA who underwent surgical intervention.

Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol*. 1996;54(suppl):S141–S147.

Rationale for the diagnostic criteria for TA and a comparison of the sensitivity and specificity of other diagnostic criteria.

Unizony S, Stone JH, Stone JR. New treatment strategies in large-vessel vasculitis. *Curr Opin Rheumatol*. 2012;24:1–7.

New immunomodulators in the treatment of TA.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Giordano JM. Surgical treatment of Takayasu's disease. *Cleve Clin J Med.* 2002;69(suppl 2):SII146–SII148.
2. Hall S, Barr W, Lie JT, et al. Takayasu arteritis: a study of 32 North American patients. *Medicine (Baltimore).* 1985;64:89–99.
3. DiGiacomo V. A case of Takayasu's disease occurred over 200 years ago. *Angiology.* 1984;35:750–754.
4. Numano F. The story of Takayasu arteritis. *Rheumatology (Oxford).* 2002;41:103–106.
5. Numano F. Introductory remarks for this special issue on Takayasu arteritis. *Heart Vessels Suppl.* 1992;7:3–5.
6. Shimmi Y. A case of Takayasu's arteritis. *Sogo Gannka.* 1942;36:1404–1410.
7. Kerr GS. Takayasu's arteritis. *Rheum Dis Clin North Am.* 1995;21:1041–1058.
8. Nasu T. Takayasu's truncoarteritis in Japan. A statistical observation of 76 autopsy cases. *Pathol Microbiol (Basel).* 1975;43:140–146.
9. González-Gay MA, García-Porrúa C. Epidemiology of the vasculitides. *Rheum Dis Clin North Am.* 2001;27:729–749.
10. Waern AU, Andersson P, Hemmingsson A. Takayasu's arteritis: a hospital-region based study on occurrence, treatment and prognosis. *Angiology.* 1983;34:311–320.
11. Kumar S, Subramanyan R, Mandalam KR, et al. Aneurysmal form of aortoarteritis (Takayasu's disease): analysis of thirty cases. *Clin Radiol.* 1990;42:342–347.
12. Zheng D, Fan D, Liu L. Takayasu arteritis in China: a report of 530 cases. *Heart Vessels Suppl.* 1992;7:32–36.
13. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med.* 1994;120:919–929.
14. Nakao K, Ikeda M, Kimata S, et al. Takayasu's arteritis. Clinical report of eighty-four cases and immunological studies of seven cases. *Circulation.* 1967;35:1141–1155.
15. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. *J Am Coll Cardiol.* 1988;12:964–972.
16. Zheng DY, Liu LS, Fan DJ. Clinical studies in 500 patients with aortoarteritis. *Chin Med J.* 1990;103:536–540.
17. Liang P, Tan-Ong M, Hoffman GS. Takayasu's arteritis: vascular interventions and outcomes. *J Rheumatol.* 2004;31:102–106.
18. Park MC, Lee SW, Park YB, et al. Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. *Scand J Rheumatol.* 2005;34:284–292.
19. Vanoli M, Daina E, Salvarani C, et al. Takayasu's arteritis: a study of 104 Italian patients. *Arthritis Rheum.* 2005;53:100–107.
20. Numano F. Hereditary factors of Takayasu arteritis. *Heart Vessels Suppl.* 1992;7:68–72.
21. Jeeva I, Sajid J, Ali O, et al. Atypical Takayasu arteritis: a family with five affected siblings. *Med Sci Monit.* 2007;13:CS101–CS105.
22. Isohisa I, Numano F, Maezawa H, et al. HLA-Bw52 in Takayasu disease. *Tissue Antigens.* 1978;12:246–248.
23. Numano F, Ohta N, Sasazuki T. HLA and clinical manifestations in Takayasu disease. *Jpn Circ J.* 1982;46:184–189.
24. Lee SW, Kwon OJ, Park MC, et al. HLA alleles in Korean patients with Takayasu arteritis. *Clin Exp Rheumatol.* 2007;25(1 suppl 44):S18–S22.
25. Girona E, Yamamoto-Furusho JK, Cutiño T, et al. HLA-DR6 (possibly DRB1*1301) is associated with susceptibility to Takayasu arteritis in Mexicans. *Heart Vessels.* 1996;11:277–280.
26. Khraishi MM, Gladman DD, Dagenais P, et al. HLA antigens in North American patients with Takayasu arteritis. *Arthritis Rheum.* 1992;35:573–575.
27. Numano F, Kobayashi Y, Maruyama Y, et al. Takayasu arteritis: clinical characteristics and the role of genetic factors in its pathogenesis. *Vasc Med.* 1996;1:227–233.
28. Korkmaz C, Zubayoglu I, Kaya T, et al. Takayasu's arteritis associated with rheumatoid arthritis: a case report and review of the literature. *Rheumatology.* 2001;40:1420–1422.
29. Saxe PA, Altman RD. Takayasu's arteritis syndrome associated with systemic lupus erythematosus. *Semin Arthritis Rheum.* 1992;21:295–305.
30. Reny JL, Paul JF, Lefèvre C, et al. Association of Takayasu's arteritis and Crohn's disease. Results of a study on 44 Takayasu patients and review of the literature. *Ann Med Intern.* 2003;154:85–90.
31. Lai KN, Chan KW, Ho CP. Glomerulonephritis associated with Takayasu's arteritis: report of three cases and review of literature. *Am J Kidney Dis.* 1986;7:197–204.
32. Pedreira ALS, Santiago MB. Association between Takayasu arteritis and latent or active Mycobacterium tuberculosis infection: a systematic review. *Clin Rheumatol.* 2020;39(4):1019–1026.
33. Chauhan SK, Singh M, Nityanand S. Reactivity of gamma/delta T cells to human 60-kd heat-shock protein and their cytotoxicity to aortic endothelial cells in Takayasu arteritis. *Arthritis Rheum.* 2007;56:2798–2802.
34. Chauhan SK, Tripathy NK, Sinha N, et al. T-cell receptor repertoire of circulating gamma delta T-cells in Takayasu's arteritis. *Clin Immunol.* 2006;118:243–249.
35. Chauhan SK, Tripathy NK, Nityanand S. Antigenic targets and pathogenicity of anti-aortic endothelial cell antibodies in Takayasu arteritis. *Arthritis Rheum.* 2006;54:2326–2333.
36. Eichhorn J, Sima D, Thiele B, et al. Anti-endothelial cell antibodies in Takayasu arteritis. *Circulation.* 1996;94:2396–2401.
37. Dhingra R, Talwar KK, Chopra P, et al. An enzyme linked immunosorbent assay for detection of anti-aorta antibodies in Takayasu arteritis patients. *Int J Cardiol.* 1993;40:237–242.
38. Numano F, Shimamoto T. Hypersecretion of estrogen in Takayasu's disease. *Am Heart J.* 1971;81:591–596.
39. Berginer VM, Paran E, Hirsch M, et al. Klinefelter's and Takayasu's syndromes in one patient—a pure coincidence? *Angiology.* 1983;34:170–175.
40. Maffei S, Di Renzo M, Bova G, et al. Takayasu's arteritis: a review of the literature. *Intern Emerg Med.* 2006;1:105–112.
41. Hotchi M. Pathological studies on Takayasu arteritis. *Heart Vessels Suppl.* 1992;7:11–17.
42. Inder SJ, Bobryshev YV, Cherian SM, et al. Immunophenotypic analysis of the aortic wall in Takayasu's arteritis: involvement of lymphocytes, dendritic cells and granulocytes in immuno-inflammatory reactions. *Cardiovasc Surg.* 2000;8:141–148.
43. Abularragge CJ, Slidell MB, Sidawy AN, et al. Quality of life of patients with Takayasu's arteritis. *J Vasc Surg.* 2008;47:131–137.
44. Numano F, Kishi Y, Tanaka A, et al. Inflammation and atherosclerosis. Atherosclerotic lesions in Takayasu arteritis. *Ann N Y Acad Sci.* 2000;902:65–76.
45. Dabague J, Reyes PA. Takayasu arteritis in Mexico: a 38-year clinical perspective through literature review. *Int J Cardiol.* 1996;54(suppl):S103–S109.
46. Jain S, Kumari S, Ganguly NK, et al. Current status of Takayasu arteritis in India. *Int J Cardiol.* 1996;54(suppl):S111–S116.
47. Yamato M, Lecky JW, Hiramatsu K, et al. Takayasu arteritis: radiographic and angiographic findings in 59 patients. *Radiology.* 1986;161:329–334.
48. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheum.* 2007;56:1000–1009.
49. Ueda H, Morooka S, Ito I, et al. Clinical observation of 52 cases of aortitis syndrome. *Jpn Heart J.* 1969;10:277–288.
50. Cipriano PR, Silverman JF, Perlroth MG, et al. Coronary arterial narrowing in Takayasu's aortitis. *Am J Cardiol.* 1977;39:744–750.
51. Morooka S, Tanaka S, Ohya T, et al. Mitral regurgitation associated with aortitis syndrome. *Jpn Heart J.* 1983;24:471–480.
52. Gupta SK, Khanna MN, Lahiri TK, et al. Involvement of cardiac valves in Takayasu's arteritis. Report of seven cases. *Indian Heart J.* 1980;32:147–155.
53. Yamada I, Shibuya H, Matsubara O, et al. Pulmonary artery disease in Takayasu's arteritis: angiographic findings. *AJR Am J Roentgenol.* 1992;159:263–269.

54. Sharma S, Kamalakar T, Rajani M, et al. The incidence and patterns of pulmonary artery involvement in Takayasu's arteritis. *Clin Radiol.* 1990;42:177–181.
55. Talwar KK, Chopra P, Narula J, et al. Myocardial involvement and its response to immunosuppressive therapy in nonspecific aortoarteritis (Takayasu's disease)—a study by endomyocardial biopsy. *Int J Cardiol.* 1988;21:323–334.
56. Suwanwela N, Piaychon C. Takayasu arteritis in Thailand: clinical and imaging features. *Int J Cardiol.* 1996;54(suppl):S117–S134.
57. Sharma BK, Sagar S, Chugh KS, et al. Spectrum of renovascular hypertension in the young in north India: a hospital based study on occurrence and clinical features. *Angiology.* 1985;36:370–378.
58. Chugh KS, Jain S, Sakhuja V, et al. Renovascular hypertension due to Takayasu's arteritis among Indian patients. *QJM.* 1992;85:833–843.
59. Sen PK, Kinare SG, Engineer SD, et al. The middle aortic syndrome. *Br Heart J.* 1963;25:610–618.
60. Katsumura T. In: *A report on the diagnostic criteria and therapeutic strategy of aortitis syndrome.* In: 1991 Annual Report of the Intractable Arteritis Research Committee of Japan Organized by the Ministry of Health and Welfare, Tokyo, Japan; 1991:9–12.
61. Cohen JR, Birnbaum E. Coarctation of the abdominal aorta. *J Vasc Surg.* 1988;8:160–164.
62. Connolly JE, Wilson SE, Lawrence PL, et al. Middle aortic syndrome: distal thoracic and abdominal coarctation, a disorder with multiple etiologies. *J Am Coll Surg.* 2002;194:774–781.
63. Uwabe K, Okada O, Harada M. Ascending to descending aorta bypass for middle aortic syndrome. *Circ J.* 2007;71:1162–1163.
64. Janzen J, Vuong PN, Rothenberger-Janzen K. Takayasu's arteritis and fibromuscular dysplasia as causes of acquired atypical coarctation of the aorta: retrospective analysis of seven cases. *Heart Vessels.* 1999;14:277–282.
65. Esato K, Noma F, Kurata S, et al. Mesenteric infarction in Takayasu's arteritis treated by thromboendarterectomy and intestinal resection. *Jpn J Surg.* 1982;12:130–134.
66. Nussaume O, Bouttier S, Duchatelle JP, et al. Mesenteric infarction in Takayasu's disease. *Ann Vasc Surg.* 1990;4:117–121.
67. Robbs JV, Abdool-Carrim AT, Kadwa AM. Arterial reconstruction for non-specific arteritis (Takayasu's disease): medium to long term results. *Eur J Vasc Surg.* 1994;8:401–407.
68. Matsumura K, Hirano T, Takeda K, et al. Incidence of aneurysms in Takayasu's arteritis. *Angiology.* 1991;42:308–315.
69. Weaver FA, Yellin AE, Campen DH, et al. Surgical procedures in the management of Takayasu's arteritis. *J Vasc Surg.* 1990;12:429–437.
70. Francès C, Boisnic S, Blétry O, et al. Cutaneous manifestations of Takayasu arteritis. A retrospective study of 80 cases. *Dermatologica.* 1990;181:266–272.
71. Perniciaro CV, Winkelmann RK, Hunder GG. Cutaneous manifestations of Takayasu's arteritis. A clinicopathologic correlation. *J Am Acad Dermatol.* 1987;17:998–1005.
72. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* 1990;33:1129–1134.
73. Sharma BK, Siveski-Iliskovic N, Singal PK. Takayasu arteritis may be underdiagnosed in North America. *Can J Cardiol.* 1995;11:311–316.
74. Sharma BK, Jain S, Suri S, et al. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol.* 1996;54(suppl):S141–S147.
75. Hoffman GS. Takayasu arteritis: lessons from the American National Institutes of Health experience. *Int J Cardiol.* 1996;54(suppl):S99–S102.
76. Takai Y, Wong GG, Clark SC, et al. B cell stimulatory factor-2 is involved in the differentiation of cytotoxic T lymphocytes. *J Immunol.* 1988;140:508–512.
77. Okada M, Kitahara M, Kishimoto S, et al. IL-6/BSF-2 functions as a killer helper factor in the in vitro induction of cytotoxic T cells. *J Immunol.* 1988;141:1543–1549.
78. Schall TJ, Bacon K, Toy KJ, et al. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature.* 1990;347:669–671.
79. Noris M, Daina E, Gamba S, et al. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? *Circulation.* 1990;100:55–60.
80. Matsuyama A, Sakai N, Ishigami M, et al. Matrix metalloproteinases as novel disease markers in Takayasu arteritis. *Circulation.* 2003;108:1469–1473.
81. Agueda AF, Monti S, Luqmani RA, et al. Management of Takayasu arteritis: a systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. *RMD Open.* 2019;5(2):e001020.
82. Grollman Jr JH, Hanafee W. The roentgen diagnosis of Takayasu's Arteritis. *Radiology.* 1964;83:387–395.
83. Park JH, Chung JW, Im JG, et al. Takayasu arteritis: evaluation of mural changes in the aorta and pulmonary artery with CT angiography. *Radiology.* 1995;196:89–93.
84. Park SH, Chung JW, Lee JW, et al. Carotid artery involvement in Takayasu's arteritis: evaluation of the activity by ultrasonography. *J Ultrasound Med.* 2001;20:371–378.
85. Taniguchi N, Itoh K, Honda M, et al. Comparative ultrasonographic and angiographic study of carotid arterial lesions in Takayasu's arteritis. *Angiology.* 1997;48:9–20.
86. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* 2018;77(5):636–643.
87. Choe YH, Kim DK, Koh EM, et al. Takayasu arteritis: diagnosis with MR imaging and MR angiography in acute and chronic active stages. *J Magn Reson Imaging.* 1999;10:751–757.
88. Choe YH, Lee WR. Magnetic resonance imaging diagnosis of Takayasu arteritis. *Int J Cardiol.* 1998;66(suppl 1):S175–S179.
89. Yamada I, Nakagawa T, Himeno Y, et al. Takayasu arteritis: diagnosis with breath-hold contrast-enhanced three-dimensional MR angiography. *J Magn Reson Imaging.* 2000;11:481–487.
90. Tso E, Flamm SD, White RD, et al. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. *Arthritis Rheum.* 2002;46:1634–1642.
91. Papa M, De Cobelli F, Baldissera E, et al. Takayasu arteritis: intravascular contrast medium for MR angiography in the evaluation of disease activity. *AJR Am J Roentgenol.* 2012;198(3):W279–W284.
92. Kim SY, Park JH, Chung JW, et al. Follow-up CT evaluation of the mural changes in active Takayasu arteritis. *Korean J Radiol.* 2007;8:286–294.
93. Chung JW, Kim HC, Choi YH, et al. Patterns of aortic involvement in Takayasu arteritis and its clinical implications: evaluation with spiral computed tomography angiography. *J Vasc Surg.* 2007;45:906–914.
94. Park JH, Chung JW, Lee KW, et al. CT angiography of Takayasu arteritis: comparison with conventional angiography. *J Vasc Interv Radiol.* 1997;8:393–400.
95. Meave A, Soto ME, Reyes PA, et al. Pre-pulseless Takayasu's arteritis evaluated with 18F-FDG positron emission tomography and gadolinium-enhanced magnetic resonance angiography. *Tex Heart Inst J.* 2007;34:466–469.
96. Webb M, Chambers A, Al-Nahhas A, et al. The role of 18F-FDG PET in characterising disease activity in Takayasu arteritis. *Eur J Nucl Med Mol Imaging.* 2004;31:627–634.
97. Lande A, Rossi P. The value of total aortography in the diagnosis of Takayasu's arteritis. *Radiology.* 1975;114:287–297.
98. Ueno A, Awane Y, Wakabayashi A, et al. Successfully operated obliterative brachiocephalic arteritis (Takayasu) associated with the elongated coarctation. *Jpn Heart J.* 1967;8:538–544.
99. Ishikawa K. Natural history and classification of occlusive thromboangiopathy (Takayasu's disease). *Circulation.* 1978;57:27–35.
100. Hata A, Noda M, Moriwaki R, et al. Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol.* 1996;54(suppl):S155–S163.
101. Fields CE, Bower TC, Cooper LT, et al. Takayasu's arteritis: operative results and influence of disease activity. *J Vasc Surg.* 2006;43:64–71.
102. Sharma S, Shrivastava S, Kothari SS, et al. Influence of angiographic morphology on the acute and longer-term outcome of percutaneous transluminal angioplasty in patients with aortic stenosis due to nonspecific aortitis. *Cardiovasc Interv Radiol.* 1994;17:147–151.

103. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* 2020;79(1):19–30.
104. Fraga A, Mintz G, Valle L, et al. Takayasu's arteritis: frequency of systemic manifestations (study of 22 patients) and favorable response to maintenance steroid therapy with adrenocorticosteroids (12 patients). *Arthritis Rheum.* 1972;15:617–624.
105. Nakaoaka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomized, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis.* 2018;77(3):348–354.
106. Ham SW, Kumar SR, Rowe VL, et al. Disease progression after initial surgical intervention for Takayasu arteritis. *J Vasc Surg.* 2011;54(5):1345–1351.
107. Pajari R, Hekali P, Harjola PT. Treatment of Takayasu's arteritis: an analysis of 29 operated patients. *Thorac Cardiovasc Surg.* 1986;34:176–181.
108. Sharma S, Rajani M, Kaul U, et al. Initial experience with percutaneous transluminal angioplasty in the management of Takayasu's arteritis. *Br J Radiol.* 1990;63:517–522.
109. Kumar S, Mandalam KR, Rao VR, et al. Percutaneous transluminal angioplasty in nonspecific aortoarteritis (Takayasu's disease): experience of 16 cases. *Cardiovasc Interv Radiol.* 1989;12:321–325.
110. Tyagi S, Verma PK, Gambhir DS, et al. Early and long-term results of subclavian angioplasty in aortoarteritis (Takayasu disease): comparison with atherosclerosis. *Cardiovasc Interv Radiol.* 1998;21:219–224.
111. Fava MP, Foradori GB, García CB, et al. Percutaneous transluminal angioplasty in patients with Takayasu arteritis: five-year experience. *J Vasc Interv Radiol.* 1993;4:649–652.
112. Park MC, Lee SW, Park YB, et al. Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. *Rheumatology (Oxford).* 2006;45:600–605.
113. Crotch MF. The socioeconomic impact of vasculitis. *Curr Opin Rheumatol.* 2000;12:20–23.
114. Qureshi MA, Martin Z, Greenberg RK. Endovascular management of patients with Takayasu arteritis: stents versus stent grafts. *Semin Vasc Surg.* 2011;24(1):44–52.
115. Gronemeyer PS, deMello DE. Takayasu's disease with aneurysm of right common iliac artery and iliocaval fistula in a young infant: case report and review of the literature. *Pediatrics.* 1982;69:626–631.
116. Amano J, Suzuki A. Coronary artery involvement in Takayasu's arteritis. Collective review and guideline for surgical treatment. *J Thorac Cardiovasc Surg.* 1991;102:554–560.
117. Maksimowicz-McKinnon K, Hoffman GS. Takayasu arteritis: what is the long-term prognosis? *Rheum Dis Clin North Am.* 2007;33:777–786.
118. Weaver FA, Kumar SR, Yellin AE, et al. Renal revascularization in Takayasu arteritis-induced renal artery stenosis. *J Vasc Surg.* 2004;39:749–757.
119. Ware Jr JE, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide.* Lincoln, RI: Quality Metric Incorporated; 2000.
120. Keith DS, Markey B, Schiedler M. Successful long-term stenting of an atypical descending aortic coarctation. *J Vasc Surg.* 2002;35:166–167.
121. Perrone-Filardi P, Costanzo P, Cesario P, et al. Long abdominal aortic stenosis: a rare presentation of Takayasu arteritis treated with percutaneous stent implantation. *J Thorac Cardiovasc Surg.* 2007;133:1647–1648.
122. Heinemann MK, Ziemer G, Wahlers T, et al. Extraanatomic thoracic aortic bypass grafts: indications, techniques, and results. *Eur J Cardiothorac Surg.* 1997;11:169–175.
123. Taketani T, Miyata T, Morota T, et al. Surgical treatment of atypical aortic coarctation complicating Takayasu's arteritis—experience with 33 cases over 44 years. *J Vasc Surg.* 2005;41:597–601.
124. Pokrovsky AV, Tsereshkin DM, Golosovskaya MA. Pathology of non-specific aortoarteritis. *Angiology.* 1980;31:549–557.
125. Miyata T, Sato O, Deguchi J, et al. Anastomotic aneurysms after surgical treatment of Takayasu's arteritis: a 40-year experience. *J Vasc Surg.* 1998;27:438–445.
126. Miyata T, Sato O, Koyama H, et al. Long-term survival after surgical treatment of patients with Takayasu's arteritis. *Circulation.* 2003;108:1474–1480.
127. Saadoun D, Lambert M, Mirault T, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. *Circulation.* 2012;125(6):813–819.
128. Kim YW, Kim DI, Park YJ, et al. Surgical bypass vs. endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis. *J Vasc Surg.* 2012;55(3):693–700.
129. Jung JH, Lee YH, Song GG, et al. Endovascular versus open surgical intervention in patients with Takayasu's Arteritis: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2018;55(6):888–899.
130. Matsumura A, Morikawa R, Numano F. Pregnancy in Takayasu arteritis from the view of internal medicine. *Heart Vessels Suppl.* 1992;7:120–124.
131. Aso T, Abe S, Yaguchi T. Clinical gynecologic features of pregnancy in Takayasu arteritis. *Heart Vessels Suppl.* 1992;7:125–132.
132. Zhu WH, Shen LG, Neubauer H. Clinical characteristics, interdisciplinary treatment and follow up of 14 children with Takayasu arteritis. *World J Pediatr.* 2010;6(4):342–347.
133. Katsicas MM, Pompozi K, Ryssouw R, et al. Takayasu arteritis in children. *Argentine Arch Pediatr.* 2012;110(3):251–255.

Aneurysms Caused by Connective Tissue Abnormalities

REBECCA A. SORBER and JAMES H. BLACK III

MARFAN SYNDROME	1859	Differential Diagnosis	1866
Epidemiology and Natural History	1859	Selection of Treatment	1867
Pathogenesis	1859	True Aneurysms	1868
Role of Fibrillin	1859	Vascular Complications	1868
Interaction with Transforming Growth Factor	1860	Nonvascular Complications	1868
Clinical Manifestations and Diagnostic Evaluation	1860	Medical Treatment	1868
Diagnostic Criteria	1860	Surgical Treatment	1868
GHENT CRITERIA	1860	Endovascular Treatment	1870
Differential Diagnosis	1861	LOEYS-DIETZ SYNDROME	1870
Surveillance	1862	Epidemiology	1872
Aortic Disease	1862	Clinical Evaluation	1872
Prevention	1862	Common Manifestations	1872
Medical Treatment	1862	Differential Diagnosis	1872
Surgical Treatment	1863	Selection of Treatment	1873
Descending Thoracic and Thoracoabdominal		Medical Treatment	1873
Aorta	1863	Surgical Treatment	1873
Endovascular Treatment	1864	FAMILIAL THORACIC AORTIC ANEURYSM AND	
VASCULAR-TYPE EHRLERS-DANLOS		DISSECTION	1874
SYNDROME	1864	Pathogenesis	1874
Epidemiology and Natural History	1866	Clinical Manifestations	1875
Pathogenesis	1866	Selection of Treatment	1875
Clinical Evaluation	1866	CHAPTER ALGORITHM	1876
Common Manifestations	1866		

The primary structural proteins of connective tissue are collagen and elastin, which vary in type and amount within each of the body's tissues; those constitutive of blood vessels are listed in Table 141.1. A *connective tissue disease* is a genetic disease in which the primary target is either collagen or elastin protein assembly, disruption of which leads to an inherent predisposition to degeneration, loss of structural integrity, and consequent aneurysm formation or spontaneous vascular dissection and rupture. Although inflammation may affect these proteins and induce structural damage in some patients, such

conditions often imply some element of autoimmune disorder and are termed *collagen vascular diseases* or *mixed connective tissue diseases*. Such conditions and arteriopathies related to the vascular tree, which are considered in Chapter 138 (Vasculitis and Other Uncommon Arteriopathies), may have genetic profiles that predispose to their development. Although clustering of aneurysms in multiple affected family members within these arteriopathies may indicate some element of an inheritance pattern, there are often greatly varying levels of expression and penetrance, and no defined genetic test is available to

TABLE 141.1 Structural Elements of Blood Vessels

Structural Proteins	Approximate Amount (% Dry Wt)	Function
Type I collagen	20–40	Fibrillar network
Type III collagen	20–40	Thin fibrils
Elastin, fibrillin	20–40	Elasticity
Type IV collagen, laminin	<5	Basal lamina
Types V and VI collagen	<2	Function unclear
Proteoglycans (>30 types)	<3	Resiliency

assist treatment. Herein we seek to define the common connective tissue diseases affecting the arterial tree, which have a studied natural history, a defined basis for genetic inheritance, and sufficiently understood pathophysiologic mechanisms to guide treatment paradigms. These “heritable disorders of connective tissue”¹ have severe vascular manifestations, and most commonly include Marfan syndrome (MFS), the vascular type of Ehlers–Danlos syndrome (EDS IV or vEDS), Loeys–Dietz syndrome (LDS), and familial thoracic aortic aneurysm and dissection (TAAD).

MARFAN SYNDROME

Antoine Bernard-Jean Marfan, a professor of pediatrics in Paris, in 1896 encountered a 5-year-old girl with congenital deformation of all four limbs.² By the time she was 11 years old, thoracolumbar kyphoscoliosis, pectus carinatum, and signs of tuberculosis had developed.³ She died at age 16 from infection, and no autopsy was performed to document any vascular involvement. The first description of aortic pathology in MFS was published in 1943, a year after Marfan’s death.⁴ Although he correctly identified the many Mendelian features of the condition that would eventually bear his name, the pleiotropic disorder has benefited from decades of further description of clinical manifestations, molecular pathogenesis, and emerging therapeutic options.

Epidemiology and Natural History

The incidence of MFS is about 2 to 3 per 10,000 individuals, but this estimate relies on proper recognition of all affected and genetically predisposed individuals.⁵ A population-based study in Scotland found an incidence of 1 in 9802 live births,⁶ although this number would underestimate the true incidence inasmuch as the features of MFS, particularly the skeletal ones, become more apparent with growth. Furthermore, even though the disorder is passed as a dominant Mendelian trait, about 25% of cases are due to sporadic *de novo* mutations.⁷ The disease has no gender predisposition. Its incidence is increased in athletes, particularly in basketball and volleyball players, because the characteristic tall stature with long-bone overgrowth (dolichostenomelia) confers a competitive advantage. In a

screening study of 415 high-school basketball and volleyball athletes performed with standard echocardiography, four (1%) of these subjects exhibited aortic root enlargement greater than 4.6 cm, and MFS was diagnosed in two.⁸

The life span of individuals with MFS was significantly shortened before the widespread use and successful refinement of aortic root surgery. Before the adoption of thresholds for aortic root replacement, the cause of death was cardiovascular (aortic rupture, aortic dissection, or valvular disease) in 90% of cases at a mean of 38 years old.⁹ A report in the 1970s on the life expectancy of patients with MFS described longevity as only two-thirds that of unaffected individuals, with life-table mortality curves deviating in infancy.⁹ However, a later assessment of longevity in patients with MFS describes a nearly normal life expectancy as a result of improvement and refinement in diagnosis and treatment, particularly of the cardiovascular manifestations of the disorder.¹⁰

Pathogenesis

As early as 1955 it was suggested that the basic structural defect in MFS was localized to the elastic fiber,¹¹ with skin and aorta from affected patients showing decreased elastin content and fragmentation of elastic fibers.^{12,13} Yet the elastin gene and molecule were poor targets to explain the clinical manifestations of MFS in tissues that are devoid of elastin, such as bone and the ciliary zonules in the eye. Further histochemical analysis demonstrated that the amorphous fragmented elastin tissues were surrounded by a rod-like material with a distinct staining pattern and distinguishable susceptibility to enzymatic digestion.^{14,15} These so-called microfibrils are 10 to 14 nm in diameter and are constituents of all connective tissue.¹⁵ Sakai et al.¹⁶ first identified fibrillin-1 (FBN1) as the principal component of the extracellular matrix microfibril, present in all tissues with the phenotypic manifestations of MFS. Additional linkage analysis mapped the MFS locus to 15q21.1.¹⁷ The mutation is passed in an autosomal dominant manner with complete penetrance, so 50% of the offspring of an affected individual can inherit a genetic predisposition to the disorder.⁵

Role of Fibrillin

The *FBN1* gene encodes a large, 350-kD glycoprotein that is highly conserved among different species, thus suggesting its critical homeostatic importance.^{18,19} These models demonstrated that normal FBN1 molecules are not needed to assemble an elastic fiber; rather, microfibrils are required to maintain normal elastic fibers during postnatal life. If proper connections among elastic fibers and vascular smooth muscle cells are not suitably maintained, aortic wall homeostasis is perturbed, and inflammation as well as calcification and structural weakening of elastic fibers may ensue. This pathology has been observed in large muscular arteries from patients with MFS,²⁰ leading to appreciation of the classic lesion of cystic medial necrosis in large arteries of individuals with MFS. Verhoeff–van Gieson staining of elastic fibers in the aorta demonstrates classic lamellar disorganization in MFS secondary to errant elastic fiber maintenance (Fig. 141.1).

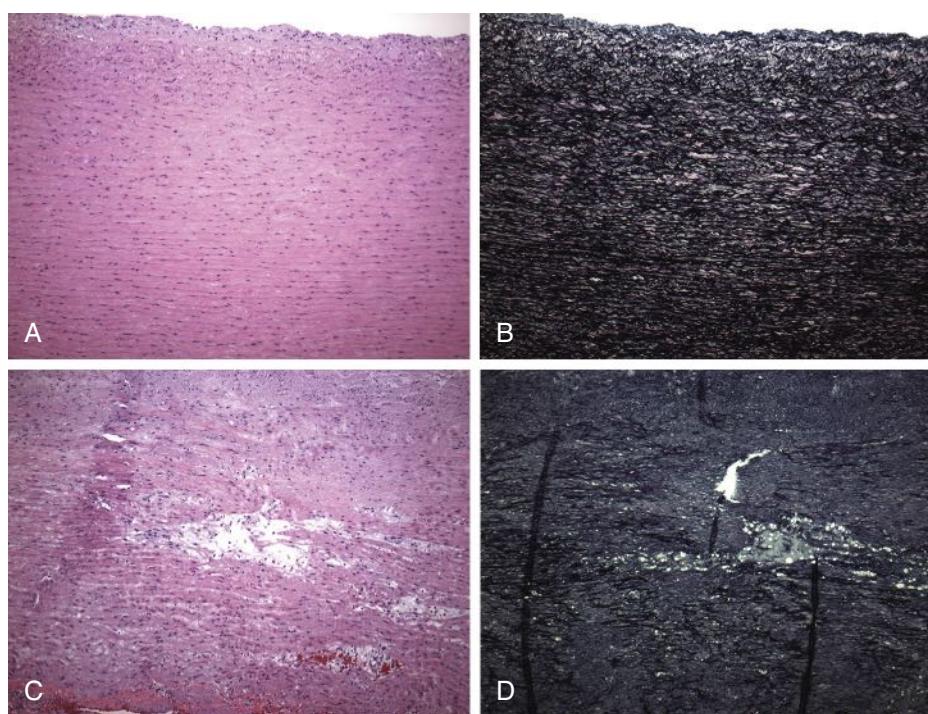


Figure 141.1 (A and B) Photomicrographs illustrating the regular and parallel nature of the elastic lamellae found within the media of the normal ascending aorta. The lamellae are composed of elastic fibers running in parallel with intervening smooth muscle, ground substance, and collagen. The Verhoeff–van Gieson (VVG) stain highlights these major elastic fibers (black) (A, hematoxylin-eosin [H&E], $\times 100$; B, VVG, $\times 100$). (C and D) Photomicrographs showing profound fragmentation of the elastic fibers, with spaces left within the media of the ascending aorta. Though often referred to as cystic medial degeneration, the spaces created by this fragmentation lack a lining and hence are not truly “cysts.” These spaces often contain increased amounts of glycoproteins. The VVG stain further highlights the severe elastic fiber (black) fragmentation. The vertical black lines are fixation artifacts from folding of the elastic sheet (C, H&E; D, VVG). (Plates courtesy Joseph Maleszewski, MD, Johns Hopkins Hospital Department of Pathology.)

Interaction with Transforming Growth Factor

The discovery of the role of microfibrils in regulating cytokines has further advanced our understanding of the pathogenesis of MFS and raised the possibility of a new treatment paradigm. FBN1 shares a high degree of homology with the latent transforming growth factor- β (TGF- β)-binding proteins. The TGF- β cytokines are secreted as large latent complexes consisting of TGF- β , a latency-associated peptide, and one of three latent TGF- β -binding proteins (Fig. 141.2).²¹ In normal trafficking, the large latent complex is sequestered and bound to microfibrils, and TGF- β cytokine signaling is prevented. As depicted in Figure 141.2, without proper microfibrils, the TGF- β complex cannot form, thereby leaving TGF- β in the milieu to incite excess signaling. This pathogenetic mechanism of dysregulated TGF- β activity seems more plausible in explaining the clinical features of MFS that are poorly reconciled with structural failure, such as long-bone overgrowth, craniofacial abnormalities, and muscle hypoplasia.^{22,23}

Clinical Manifestations and Diagnostic Evaluation

MFS is a multisystem disorder with manifestations principally within the cardiovascular, ocular, and skeletal systems. The disorder occurs worldwide, with no gender or race predilection.

However, the cardinal manifestation of aortic root aneurysm and its risk of life-threatening aortic dissection or rupture can lead to a shortened life expectancy. Consequently the leading cause of mortality has been cardiovascular in more than 90% of cases (aortic dissection, valve disease, or congestive heart failure), which decreased life expectancy to approximately two-thirds that of unaffected individuals.⁵ Improvements in the recognition of MFS and surgical advances have returned life expectancy to the nearly normal range by addressing the most threatening manifestations of MFS – aortic catastrophe in the form of dissection or rupture of the ascending aorta.

Diagnostic Criteria

Ghent criteria

Clinical diagnostic criteria for MFS were outlined at the International Nosology of Heritable Connective Tissue Disorders in 1986 during the Connective Tissue Meeting in Berlin.²⁴ Thereafter, the recognition that many individuals diagnosed by means of these original criteria did not have the *FBN1* mutation (genetic testing became possible after 1986) led to a focused revision in 1996 and another in 2010.^{25,26} Termed the *Ghent criteria*, the current nosology places emphasis on the cardinal manifestations of the syndrome, namely aortic root aneurysm, ectopia lentis, and *genetic testing*, versus the

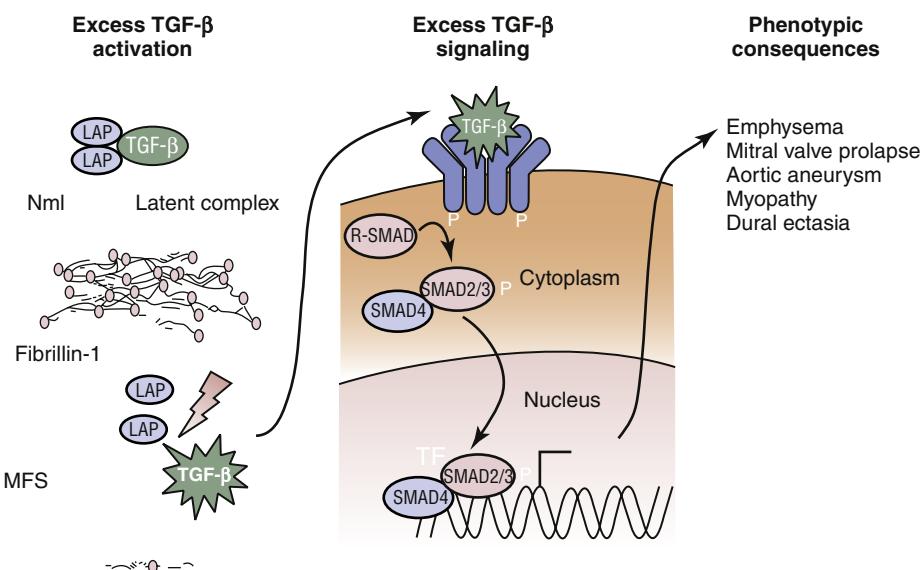


Figure 141.2 Excess activation of transforming growth factor- β (TGF- β) causes many of the features of Marfan syndrome. Normal TGF- β metabolism requires binding of the cytokine to several proteins, including microfibrils, to prevent excess signaling. In Marfan syndrome, lack of normal microfibrillar assembly allows TGF- β to remain unsequestered in the extracellular space. As a consequence, excess TGF- β signaling can occur on the cell surfaces of TGF- β receptors. Once the TGF- β binds to its receptor, downstream receptor-associated SMAD proteins translocate to the nucleus to modulate transcriptional activity, alter protein expression, and yield phenotypic change. *LAP*, latency-associated peptide; *MFS*, Marfan syndrome; *Nml*, normal; *TF*, tissue factor.

less predictive skeletal findings (Box 141.1). Previously it was estimated that 10% of MFS causing mutations were missed by conventional screening methods²⁷; however, with the advent of next generation sequencing (NGS) even small deletions, duplications and variants of unknown significance in a panel of known aortopathy genes can be detected.²⁸ The diagnosis of MFS continues to rest primarily on physical clinical assessment based on the Ghent criteria but with increasing availability of highly sensitive genetic testing, more patients are able to obtain a genotypic diagnosis as well. Once MFS is diagnosed in an individual, all first-degree relatives should be evaluated for the presence of the condition. In children, repeated evaluations may be required to avoid missing the disorder in its evolution.

Differential Diagnosis

Other conditions also associated with *FBN1* mutations may be considered in the differential diagnosis of MFS. The MASS phenotype is based on the association of mitral valve prolapse, myopia, mild aortic root dilatation, striae, and mild skeletal changes.²⁹ The skeletal features of MASS often include the mild manifestations of tall stature, mild dolichostenomelia (long-bone growth), and scoliosis. Occasionally, a major Ghent criterion from the skeletal system may be met but no other major criteria are noted. For patients with MASS, mutations in the *FBN1* gene have generally created premature termination codons, and the mutant transcript can be easily and rapidly degraded.³⁰

Shprintzen–Goldberg syndrome is characterized by craniostenosis, facial hypoplasia, anterior chest deformity, arachnodactyly (long, spider-like fingers), and aortic root

BOX 141.1	2010 Revised Ghent Criteria for the Diagnosis of Marfan Syndrome and Related Disorders
	In the absence of family history:
	1. Ao (Z > 2) AND EL = MFS
	2. Ao (Z > 2) and FBN1 = MFS
	3. Ao (Z > 2) and systemic score (>7 pts) = MFS
	4. EL and FBN1 with known Ao = MFS
	EL with or without systemic and with an FBN1 not known with Ao or no FBN1 = ELS
	Ao (Z < 2) and systemic (>5 with at least one skeletal feature) without EL + MASS
	MVP and Ao (Z > 2) and systemic (<5) without EL = MVPS
	In the presence of family history:
	1. EL and FH of MFS (as defined above) = MFS
	2. Systemic (>7) and FH of MFS (as defined above) = MFS
	3. Ao (Z > 2) above 20 years old, >3 below 20 years old + FH of MFS (as defined above) = MFS
	Caveat: without discriminating features of SGS, LDS, VEDS and TGFBR1/2, collagen biochemistry, COL 3A1 testing as indicated. Other conditions/genes will emerge over time.
	Ao, aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; FBN1, fibrillin-1 mutation (as defined in Box 141.2); FBN1 not known with Ao, FBN1 mutation that has not previously been associated with aortic root aneurysm dissection; FBN1 with known Ao, FBN1 mutation that has been identified in an individual with aortic aneurysm; MASS, myopia, mitral valve prolapsed, borderline Z-score (<2) aortic root dilatation, striae, skeletal findings; MFS, Marfan syndrome; MVP, mitral valve prolapsed syndrome; Systemic, systemic score (see Box 141.4); and Z, Z-score.

dilatation. In contrast to MFS, developmental delay is common in Shprintzen–Goldberg. Point mutations in the *SKI* gene, which codes for a component protein of the TGF- β signaling pathway, and *FBN1* have been found in some affected individuals, but phenotypic heterogeneity, specifically

BOX 141.2**Criteria for Causal *FBN1* Mutation**

- Mutation previously shown to segregate in Marfan family
- *De novo* (with proven paternity and absence of disease in parents) mutation (one of the five following categories):
 - Nonsense mutation
 - In-frame and out-of-frame deletion/insertion
 - Splice-site mutations affecting canonical splice sequence or shown to alter splicing on messenger RNA/complementary DNA level
 - Missense mutation affecting/creating cysteine residues
 - Missense mutation affecting conserved residues of epidermal growth factor consensus sequence
- Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes
- Linkage of haplotype for $n > 6$ meioses to the *FBN1* locus.

regarding development, intellectual disability, and aortic root involvement, probably indicates substantial genotypic variation.^{31,32} The aortic root enlargement in Shprintzen–Goldberg syndrome is similar to that in MFS.

Homocystinuria is caused by a deficiency of cystathione β -synthase. Patients with homocystinuria often have tall stature, long-bone overgrowth, and ectopia lentis but no aortic enlargement. Plasma homocysteine values are typically markedly elevated, easily distinguishing this disease from MFS.⁵ Congenital contractual arachnodactyly (CCA) shares many skeletal features with MFS but without the ocular and cardiovascular manifestations. The mutation in the few patients reported in the literature is located in the *FBN2* gene,³³ and physical therapy is key to maintaining joint range of motion.

The overlap of LDS and MFS is considered later in this chapter.

Surveillance

MFS is a pleiotropic disorder, and surveillance of the many systems at risk for abnormality is prudent. Regular examinations by an ophthalmologist for slit-lamp testing, a cardiologist for imaging of the aortic root, and an orthopedist for the development of scoliosis should be performed on an annual basis. In this section, focus is placed on aortic and vascular pathology. For recommendations with regard to the other body systems, the reader may find useful information at the National Marfan Foundation website (www.marfan.org). The clinical manifestations within the cardiovascular system that require preventive attention involve the atrioventricular valves, the annuloaortic valve mechanism, and the aortic root and ascending aorta.

Aortic Disease

Aortic aneurysm and dissection are the most life-threatening manifestations of MFS. The threat depends on age, with rupture and dissection rates increasing as the aortic root dilates.^{34,35} Because root dilatation at the sinuses of Valsalva can

begin *in utero*, lifelong transthoracic echocardiographic monitoring is needed. For patients in whom the aortic root and ascending aorta are poorly visualized as a result of anterior chest deformity, computed tomographic angiography or magnetic resonance angiography (to avoid radiation exposure) is a viable substitute. Absolute thresholds for replacement of the aortic root in children have not been established, given the observation that dissection is very rare in the young.⁵ However, if the aortic root is noted to grow more than 1 cm over consecutive annual assessments or if significant aortic regurgitation is present, early surgery may be necessary.²⁶ In children and teenagers, a nomogram reflects the number of standard deviations of the patient's aortic root from the mean aortic root diameter in the population and is termed a *Z-score*. If the child's *Z-score* deviates rapidly from that of the population (>2 to 3 SD) under surveillance, aortic root repair may be justified to prevent rupture. In adults, surgical repair of the aortic root and ascending aorta to prevent aortic rupture and dissection is recommended when its greatest diameter exceeds 50 mm.^{26,35} Earlier intervention may be warranted with a family history of aortic dissection at lesser diameters.

Prevention

Lifestyle modifications are routinely recommended once the diagnosis of MFS is established. On the basis of data from the United States, genetic cardiovascular diseases account for 40% of deaths in young athletes.^{36,37} A consensus document states that “burst” or Valsalva-inducing exertions such as sprinting, weightlifting, basketball, and soccer should generally be avoided. Favored are sports in which energy expenditure is stable and consistent over long periods, such as recreational jogging, biking, and lap swimming.³⁸ Importantly, litigation results suggest that physician reliance on consensus statements to determine medically reasonable levels of activity in patients with cardiovascular abnormalities is appropriate.³⁹

Medical Treatment

Medical treatment with β -adrenergic receptor blockade to delay aortic root growth or prevent aortic dissection in patients with MFS is currently considered a standard of care.^{5,26} General recommendations are a resting heart rate lower than 70 beats per minute and a heart rate less than 100 beats per minute with submaximal exercise. The rationale for this treatment paradigm is focused on decreasing proximal aortic shear stress and dP/dt . The only randomized trial assessing the effect of beta blockade treated 70 patients, 32 of whom received titrated dosages of propranolol to maintain a heart rate of ~100 beats/min during exercise and were monitored with serial echocardiograms correlated with age, height, and weight over a mean follow-up of 7 years.⁴⁰ Fewer patients in the propranolol-treated group reached the primary endpoint of aortic regurgitation, aortic dissection, surgery, heart failure, or death (5 in treatment group versus 9 in control group). Aortic growth after normalization was lower in the propranolol-treated group (0.023 cm/year) than in the control group (0.084 cm/year, $P < 0.001$).⁴⁰ For

patients with increased body weight or an end-diastolic aortic diameter greater than 40 mm, the response to beta blockade was worse, thus suggesting that beta-blockers must be given at an adequate doses and early in the course of the disorder to optimize benefit.^{26,40} Unfortunately beta blockade is poorly tolerated by some patients, with approximately 10%–20% of patients intolerant due to asthma, fatigue, or depression.

In 2006, losartan, a U.S. Food and Drug Administration-approved antihypertensive medication and selective angiotensin II receptor blocker (ARB), was demonstrated to inhibit aortic aneurysm in murine models of MFS,⁴¹ identifying a potential new medical treatment paradigm. The feedback mechanisms by which losartan inhibits TGF- β signaling in the aortic wall are likely multiple and remain incompletely understood.⁴² A multicenter trial comparing beta blockade and losartan therapy for control of aortic root growth in children and young adults with MFS was conducted, which demonstrated equivalency of losartan both in stabilizing aortic dilation rates and preventing adverse clinical events at 3 and 5 years.^{43,44} Retrospective data analysis of a large MFS cohort suggests that losartan therapy is associated with a statistically and clinically significant reduction in the risk of type B aortic dissection.⁴⁵ Currently no recommendations exist regarding the superiority of either beta blockade or ARBs in MFS; however, some patients may tolerate one better than the other. While calcium channel blockers were historically used as an alternate blood pressure control method in MFS patients unable to tolerate ARBs or beta blockade, evidence from a murine model of MFS suggest these may paradoxically accelerate aneurysm growth and we tend to avoid these in our practice.⁴⁶

Surgical Treatment

The traditional threshold for prophylactic surgical repair of the aortic root is 5 cm in patients with MFS. Operations on the arterial tree outside the ascending aorta have been reported (Fig. 141.3) and can have acceptable outcomes.⁴⁷ Indeed, as the life expectancy of individuals affected by MFS has increased with prophylactic root replacement, it is plausible that the remaining aorta or other large arteries may progress to require repair in the absence of antecedent dissection. For aortic arch and descending thoracic or thoracoabdominal aneurysms, standard criteria for repair generally follow that of atherosclerotic aneurysms – a threshold of 5.5 to 6.0 cm.²⁶

Descending Thoracic and Thoracoabdominal Aorta

The first successful replacement of the thoracoabdominal aorta in a patient with MFS was performed by Crawford⁴⁸ in the 1980s. Elective surgical repair of descending thoracic aortic aneurysm and thoracoabdominal aortic aneurysms (TAAAs) in MFS has benefited from the general refinements and the introduction of adjuncts to reduce spinal cord injury and other major complications in a manner similar to standard atherosclerotic aneurysms (see Ch. 79, Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment). Prophylactic aortic replacement is indicated when the aortic diameter reaches 5.5 to 6.0 cm or if symptoms related to the aneurysm

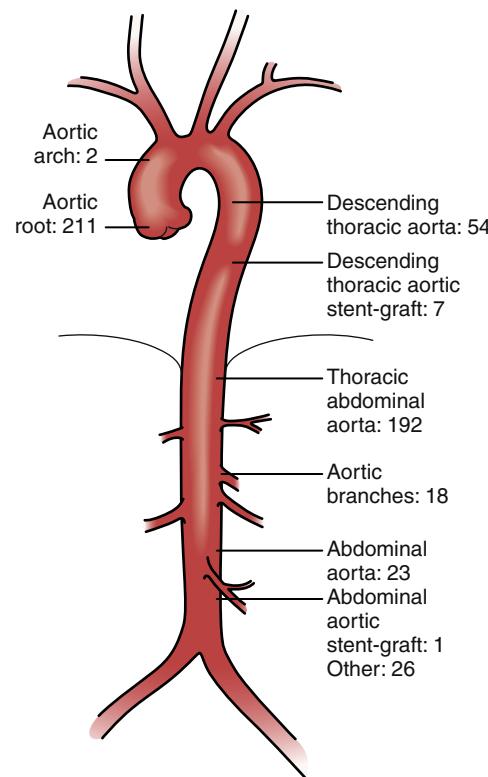


Figure 141.3 Distribution of vascular repairs in 300 patients with Marfan syndrome. (From Lemaire SA, Carter SA, Volguina IV, et al. Spectrum of aortic operations in 300 patients with confirmed or suspected Marfan syndrome. *Ann Thorac Surg*. 2006;81:2063–2078.)

occur. Because of the frequent involvement of the descending and thoracoabdominal aorta with aneurysms of chronic dissection etiology, the extent of repairs in MFS tend to be greater than that of atherosclerotic aneurysms, with 42% to 78% of all MFS TAAAs being DeBakey type II.⁴⁹ Paraparesis and paraplegia rates after TAAA repair in MFS compare favorably with those without connective tissue disease when matched for the extent of repair required.⁴⁹ Because of the very young mean age of patients with MFS undergoing TAAA repair versus the older mean age of patients with degenerative TAAA, overall long-term survival was better for those with MFS.⁴⁹

Given the preponderance of type II TAAA repairs in the available series, the rate of freedom from further aortic repair is high because little aorta remains to degenerate. However, secondary aortic procedures after TAAA repair in patients with MFS are often performed for pseudoaneurysm or for aneurysmal degeneration of the inclusion or Carrel patch (Fig. 141.4). Indeed, in the series reported by Lemaire et al.,⁴⁷ 95% of reoperations (19 of 20) after previous TAAA repair ($n = 178$) in patients with MFS were performed for visceral patch aneurysm.⁴⁷ In our series of 107 patients who underwent TAAA repair, including creation of visceral patches, 17 were known to have a connective tissue disease.⁵⁰ With a mean time to diagnosis of 6.5 years, 3 of these 17 patients (17.6%) were found to have aneurysmal degeneration of the visceral patch. By comparison, visceral patch aneurysms were noted after only 5.6% of atherosclerotic TAAA repairs.⁵⁰ All of these patients with

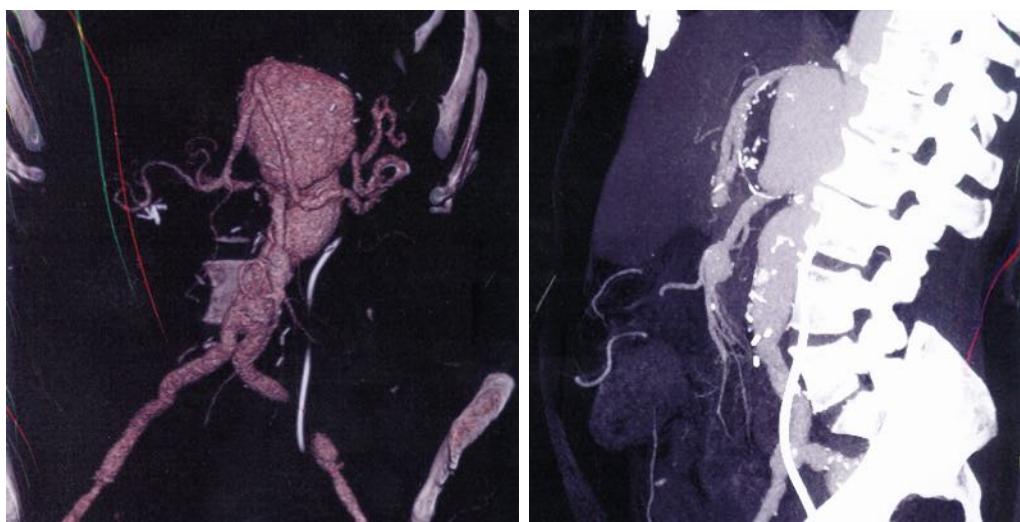


Figure 141.4 Ten-centimeter visceral patch aneurysm 7.5 years after a type II thoracoabdominal aortic aneurysm repair in a 48-year-old woman with Marfan syndrome. A hybrid open/endovascular stent-graft approach was used to repair the region. VRT reconstruction (*left*); lateral view demonstrating effacement of distance between superior mesenteric artery and celiac axis (*right*).

MFS had inclusion patches that encompassed the celiac axis, superior mesenteric artery, and both renal arteries, thus suggesting that the visceral patch should have been much smaller in all patients with connective tissue diseases to prevent late degeneration.⁵¹ I, along with many surgeons, avoid patch inclusion entirely and use a prefabricated four-branch graft to perform individual bypasses to the renal and visceral aortic branches, which we have shown to have excellent long-term patency in connective tissue patients, superior to that of the degenerative population.⁵² Intercostal inclusion patches can be limited also, but those that degenerate to aneurysm may be treated with stent-graft therapy, although paraplegia concerns are paramount. Given the morbidity associated with repair of the patch aneurysm (2 intraoperative deaths in 5 patients taken to the operating room), Dardik et al.⁵¹ recommend maintaining an indication for repair of 6.0 cm or larger.

Endovascular Treatment

In general, aortic stent grafts should not be used in the thoracic or abdominal aorta or in patients with other connective tissue diseases. The currently approved devices have never been studied in the fragile milieu of the MFS aorta (connective tissue disorder was an exclusion criteria during pivotal trials), and the question of physical damage to the aorta from the persistent radial force of the stent graft (Fig. 141.5) remains unanswered. A summary publication recommends endovascular repair only in instances of late localized pseudoaneurysm and stenting across native tissue aneurysm from “graft to graft” (see Fig. 141.5).^{53–55}

Series of patients with MFS who were treated with endovascular therapy with reasonable follow-up periods to determine clinical effectiveness are now emerging. Botta et al.⁵⁶ and Waternman et al.⁵⁷ have both published series of patients with MFS undergoing endovascular therapy, and the results are sobering, with 25%–44% of patients experiencing primary failure of the

stent grafts, many of which were converted to conventional surgical repairs. Among the primary treatment failures in one series, the mortality was 42%.⁵⁷ This topic was revisited recently in a 2018 consortium study with no improvement in outcomes. Among 31 patients with genetically mediated aortopathy, including MFS, who underwent TEVAR for type B dissection,⁵⁸ the authors found a 25% rate of retrograde dissection and a 41.9% rate of reintervention, including multiple emergent type A dissection repairs.

Indeed the issue of stent graft–induced new entry (SINE) tears seems a persistent theme in patients with MFS.⁵⁹ If stents must be used, the potential for stress-induced injury of the stent graft against the fragile MFS aortic wall should be accounted for during selection and placement of the endograft and excessive oversizing is to be avoided (Fig. 141.6); however, it is important to note that the extent of oversizing in the available series were within the instructions for use for the available devices to date. Reported experiences with stent-graft therapy in MFS universally suggest that after stent grafting, retrograde type A dissection was the most common complication among MFS patients undergoing TEVAR.⁶⁰

VASCULAR-TYPE EHLERS–DANLOS SYNDROME

EDS is a heterogeneous group of heritable disorders of connective tissue characterized by joint hypermobility, skin hyperextensibility, and tissue fragility affecting the skin, ligaments, joints, blood vessels, and internal organs. There are many subtypes of the disorder (Table 141.2 or www.ednf.org), with classic EDS (types I and II) being the most common.⁶¹ The importance of identifying the correct type cannot be overstated, because the natural history and modes of inheritance differ among the subtypes. Historically, the older

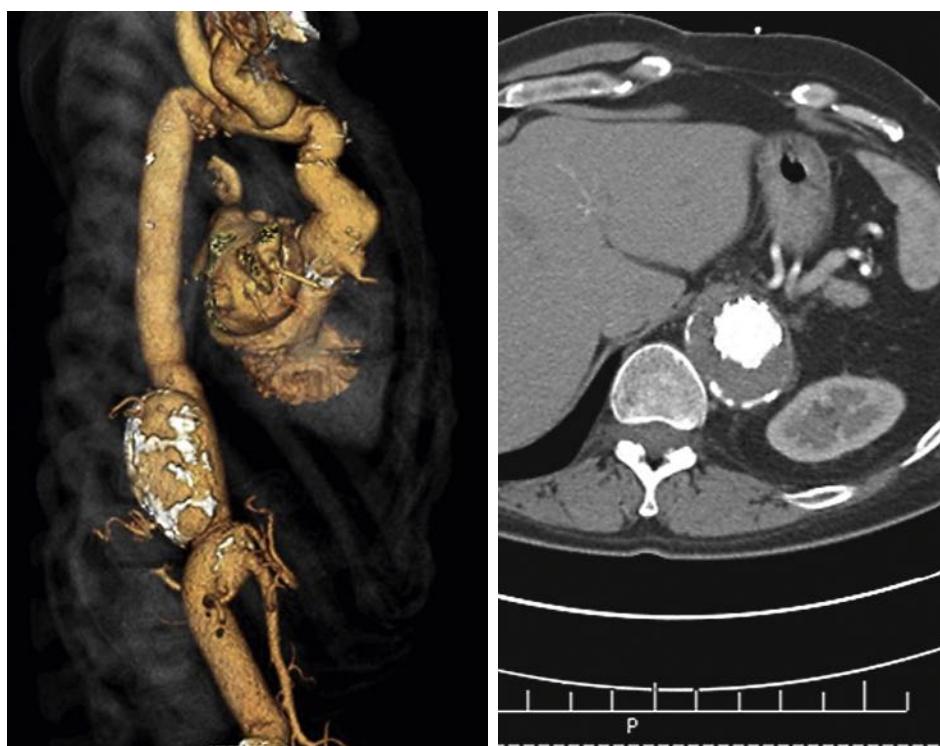


Figure 141.5 Intercostal patch aneurysm after thoracoabdominal aortic aneurysms repair. In this clinical scenario, the stent graft has “graft–graft” fixation proximally and distally (*left*) in surgical graft material. Notably, intercostal patch aneurysms that are opposite the visceral patch may contraindicate stent-graft placement. Stent graft in position with thrombosis of intercostal patch aneurysm (*right*).

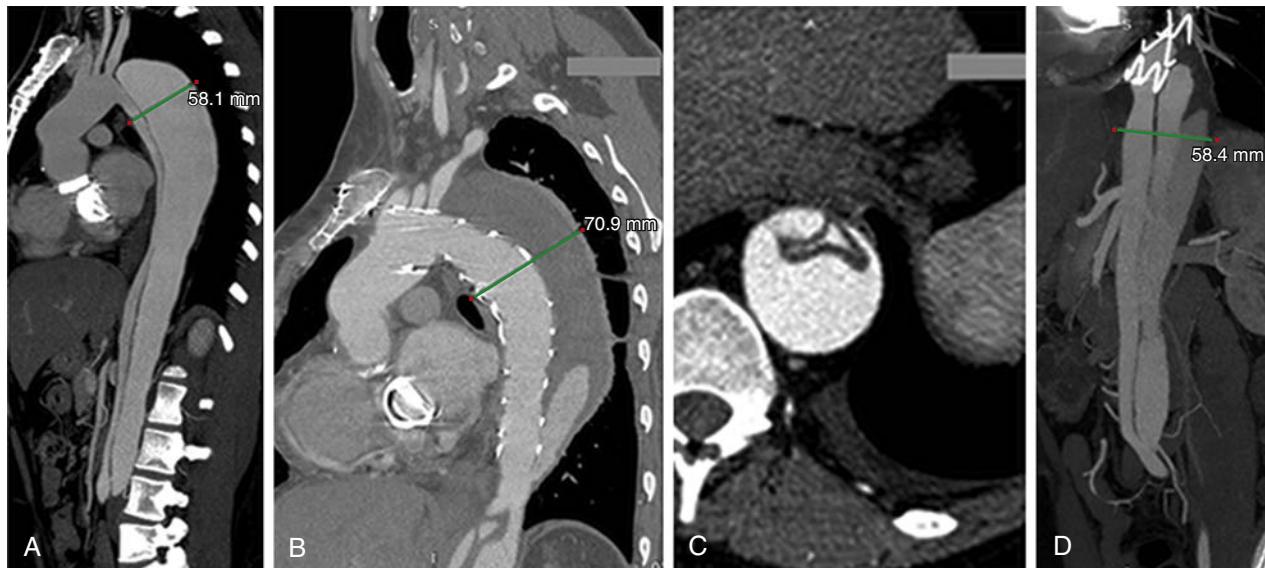


Figure 141.6 Progression of aneurysm in a patient with Marfan syndrome after thoracic endovascular aortic repair. (A) Initial stent-graft placement. (B) New distal entry tear caused by stent-graft edge seen on 1-month CT scan. (C) New presentation at 4 months with acute back pain and near-circumferential dehiscence of the intima media. The patient was treated medically until 6-month CT scan revealed (D) new progression to thoracoabdominal aortic aneurysms, which led to referral to the author for repair.

literature did not clearly differentiate among the types, and the severe complications of the vascular type of EDS were cited as being representative of the whole syndrome, thereby creating unnecessary anxiety. The current nomenclature (i.e., naming the vascular phenotype as vascular EDS) attempts to

reinforce this important separation from other subtypes. This section focuses on the vascular type (EDS IV or vEDS), its pathogenesis (defective type III procollagen encoded by the *COL3A1* gene leading to extreme vascular fragility), and its management.

TABLE 141.2 Subtypes of Ehlers–Danlos Syndrome

Nomenclature (New Terms)	Type	Skin (0 to 4+) (Elastic-Fragile)	Joint Laxity (0 to 3+)	Features	Inheritance
Classic	I, II	+++/+++	+++	Vascular complications rarely	AD
Hypermobile	III	+/-	+++	Arthritis	AR
Vascular	IV	-/-++++	+	Rupture of arteries, uterus, intestine; thin skin	AD
Kyphoscoliotic	VIA, VIB	+++/++	+++	Hypotonia, osteoporosis, kyphoscoliosis; rupture of arteries, globe of eye	AR
Arthrochalasic	VIIA, VIIB	++/+	+++	Hip subluxation, osteoporosis	AD
Dermatosparactic	VIIC	-/-++++	+	Skin doughy and lax	AR
Other	V	++/++		Skin lax	X-linked
	VIII	+/-++	++	Periodontal disease	AD
	IX	+/-	+	Lax skin, osteoporosis, bladder diverticula, intellectual disability	X-linked
	X	+/-	++	Petechiae	?

AD, autosomal dominant; AR, autosomal recessive.

Epidemiology and Natural History

The prevalence of vEDS is currently estimated to be 1 in 50,000 to 90,000, and it is inherited in an autosomal dominant manner.^{62,63} Approximately 50% of cases represent new mutations that occur sporadically and without an antecedent family history. As a rule, each patient or family carries a unique mutation in the *COL3A1* gene, which codes for type III procollagen.⁶⁴

The overall life expectancy of patients with vEDS is dramatically shortened, largely as a result of vascular rupture, with a median life span of 48 years (range, 6–73 years).⁶⁵ In a study of 220 patients with vEDS confirmed by abnormal type III procollagen molecules and 199 relatives with a clinical diagnosis of vEDS, major complications in childhood were rare, but 25% of the subjects suffered medical or surgical complications by the age of 20. By 40 years of age, major complications in the vascular or gastrointestinal systems (men and women) or reproductive system (women, e.g., uterine rupture in pregnancy) had developed in 89%.⁶⁵ Death had occurred in 131 subjects, with rupture of thoracic or abdominal vessels in 78 (60%), central nervous system hemorrhage in 9 (7%), and an unspecified bleeding source in 16 (12%). Organ rupture (heart, uterus, spleen, liver) caused death in 13 (10%) of the patients, and intestinal rupture led to death in 10 (8%).⁶⁵

Pathogenesis

Vascular EDS is due to mutations in the *COL3A1* gene, which encodes a protein for type III collagen assembly. Because most arteries and arterioles have significant amounts of type III collagen, defects in *COL3A1* lead to inherent weakness of these vessels.⁶⁵ The gene encodes a procollagen molecule, proa1(III), and basic collagen synthesis requires three polypeptide pro-collagen chains, referred to as α chains, to be folded tightly into a triple helix.⁶¹ The abnormal collagen III molecule cannot fold stably into a triple helix, is slowly degraded in the

rough endoplasmic reticulum of the fibroblast, and is never secreted extracellularly.⁶³ The central concept of heterozygous mutations leading to structural defects of collagen α chains and instability or nonsecretion of the mutant protein has proved correct in several collagen disorders and has been termed “protein suicide.”⁶⁶ A study by Pepin et al. recently demonstrated that different types of mutations may be associated with different overall survival. This genotype/phenotype correlation may have a basis in the high prevalence of glycine substitutions or deletions, as the very small molecular size of glycine is critical for proper folding of the collagen triple helix (Fig. 141.7).⁶⁷ Such glycine mutations that result in production of abnormal protein are associated with a more severe phenotype than are mutations that result in simple haploinsufficiency.⁶⁷

Clinical Evaluation

Common Manifestations

Vascular EDS has the worst prognosis among the types of EDS; for this reason, proper diagnosis is essential, because the physical findings may mimic those of other EDS subtypes or other connective tissue diseases (Box 141.3).⁶⁸ The presence of any two or more of the major criteria (easy bruising, translucent skin, facial features, and history of arterial, uterine, or intestinal rupture) is highly indicative of the diagnosis, and collagen testing is strongly recommended. The diagnosis of vEDS can be confirmed by demonstrating structurally abnormal collagen III,⁶⁹ but more recent advances in the speed and affordability of genetic sequencing have made direct analysis of the *COL3A1* gene to assess for pathogenic variants the predominant method of diagnosis.²⁸

Differential Diagnosis

The differential diagnosis of vEDS includes disorders of bruising and wound healing such as von Willebrand disease,

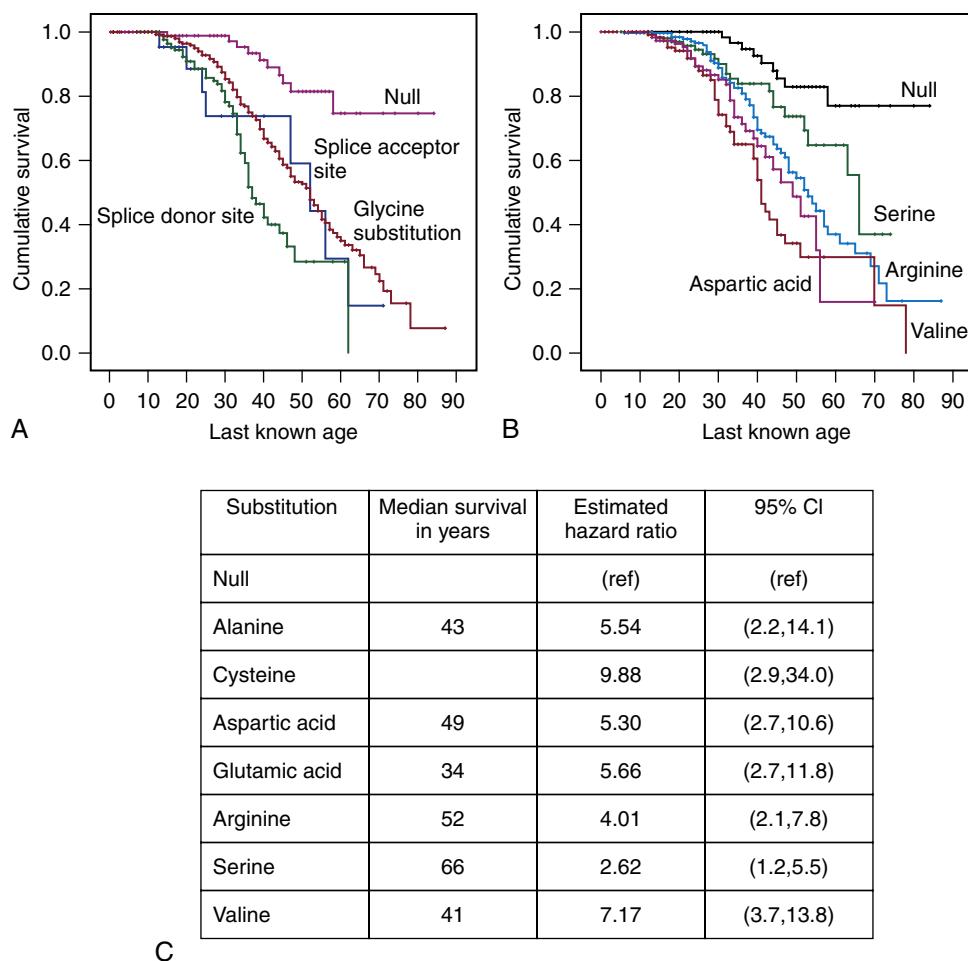


Figure 141.7 Kaplan-Meier survival curve of vascular Ehlers-Danlos syndrome study population comparing mutation type (A) to null mutations (B), and overall survival (C). (From Pepin MG, Schwarze U, Rice KM, Liu M, Leistritz D, Byers PH. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genet Med.* 2014;16(12):881–888.)

BOX 141.3

Diagnostic Criteria for Ehlers–Danlos Syndrome, Vascular Type

Major Diagnostic Criteria

- Thin, translucent skin
- Arterial/intestinal/uterine fragility or rupture
- Extensive bruising
- Characteristic facial appearance (thin delicate nose, thin lips, hollow cheeks)
- Hypermobility of small joints
- Tendon and muscle rupture
- Talipes equinovarus (clubfoot)
- Early-onset varicose veins
- Arteriovenous carotid–cavernous sinus fistula
- Pneumothorax/pneumohemothorax
- Gingival recession
- Positive family history, sudden death in one or more close relatives

Minor Diagnostic Criteria

- Acrogeria (taut, thin skin)

Data from Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers–Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers–Danlos National Foundation (USA) and Ehlers–Danlos Support Group (UK). *Am J Med Genet.* 1997;77:31–37.

platelet disorders, and scurvy. Bruisability is often elicited in children and may mimic nonaccidental trauma.⁷⁰ Indeed, excessive bruising with hematoma formation is a common first manifestation. In vEDS, rupture or dissection of arteries occurs most often in medium-sized vessels, as opposed to the predominant occurrence of rupture and dissection in the aortas of patients with MFS. The vessel tortuosity and elongation may be similar to findings in the arterial tortuosity syndrome or LDS, but vascular surgery is often much better tolerated in the latter. Multiple aneurysms through the visceral vessels may also be noted in polycystic kidney disease and hereditary forms of cerebral cavernous malformations.⁷¹ Varicose veins and venous aneurysms are commonly seen in vEDS but have little clinical or diagnostic significance versus nonsyndromic venous disease unless stripped, at which point bruising and skin injury can be extensive.

Selection of Treatment

Although no specific medical therapies exist for vEDS, knowledge of the diagnosis can influence management strategies,

assist in reproductive counseling, and direct the treatment of major complications. All patients with a confirmed diagnosis of vEDS should carry medical attention bracelets as well as papers noting information on the condition and their blood groups. General recommendations for anesthesia also exist, including cross-matching of adequate blood, avoidance of intramuscular injection, adequate peripheral access, avoidance of arterial lines and central venous catheters, and gentle intubation maneuvers.⁷² If central access is required, the use of ultrasound guidance for access is mandatory.

True Aneurysms

True aneurysms in vEDS are rare and occurred in only 14% of patients in one series.⁷³ Given the difficulty of handling the fragile tissues and vessels, management of spontaneous bleeding should be conservative as long as possible, especially in the interstitial (muscular, retroperitoneal) spaces.^{73,74} Bleeding within the peritoneal cavity usually requires immediate transfusion; if surgery is required, vessel ligation with umbilical tape appears to be the safest course, as opposed to direct repair.⁷⁵ Direct reconstructions must be tensionless, often pledgeted to reduce suture trauma, and reinforced circumferentially (Fig. 141.8). Angiography should be avoided because of severe morbidity and the risk of vessel dissection or perforation (or both) during selective catheterization or from the puncture site itself. In one study, the major complication rate from arteriography was 67% with 12% mortality,⁷⁶ although the benefit of more contemporary, lower-profile catheter and endovascular devices may have a favorable impact on this historically high percentage.

Vascular Complications

When there was bleeding from vascular rupture, the recommendation of avoiding any operation until faced with imminent risk of death remained axiomatic for many decades. This axiom further complicated the condition of patients with known aneurysms, whose vessels were allowed to dilate progressively under regular surveillance, which caused much angst for the surgeon and patient. For the individual patient, elective aneurysm repair must be considered, especially if previous operative therapies did not report excessive fragility. Patients with vEDS at highest risk of inoperable tissue fragility can be identified if seen at a very early age (<20 years) or multiple asymptomatic dissections or aneurysms apart from the index vascular lesion are noted.⁶⁸ Spontaneous abdominal bleeding without identifiable source (by CTA or angiography) is associated with an advanced stage of the disorder.⁷⁵ Factor VII transfusion may be an acceptable option, as surgical exploration should be deferred unless compartment syndrome develops.

Nonvascular Complications

Spontaneous gastrointestinal perforations account for 25% of all vEDS complications.⁶⁵ The sigmoid colon is the location of most perforations, and prompt diagnosis and immediate colostomy are favored.⁶⁵ For small bowel intestinal rupture, ostomy is also preferred, and most patients undergo restoration of

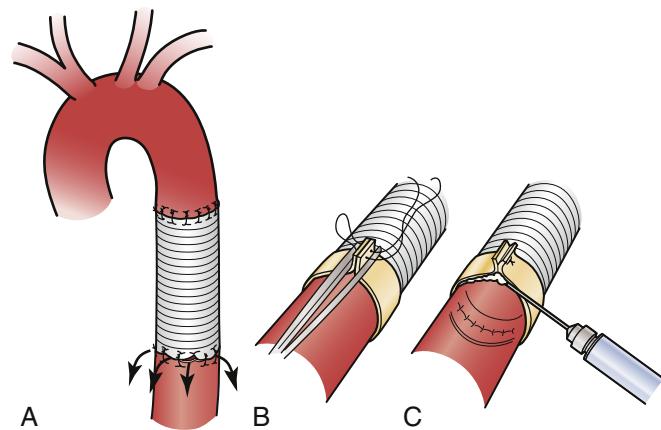


Figure 141.8 (A) Lack of adventitial and medial thickness in type IV Ehlers–Danlos syndrome promotes suture-line bleeding. Buttressing with felt (B) and the application of BioGlue (C) may reduce suture-line tension and promote hemostasis.

bowel continuity in a staged fashion without complication.⁶⁵ Recurrent bowel perforation is always a risk, occurring between 2 weeks and 26 years after the first event in 17% of patients in one study.⁶⁵ Women with vEDS who become pregnant are also at high risk for uterine rupture, as well as peripartum vascular events.⁶⁵

Medical Treatment

Celiprolol has been advanced as a treatment of choice to reduce the incidence of vascular ruptures in patients with EDS IV.⁷⁷ In a 5-year randomized study of 53 patients with suspected or proven EDS IV, celiprolol therapy reduced the incidence of vascular rupture to 20%, compared with 50% in control subjects. However, this trial has been harshly criticized for the lack of uniform genetic testing to prove that all subjects had the disorder. Recent attempts to recapitulate the success of celiprolol in a mouse model of severe vEDS demonstrated significantly increased mortality with administration of the drug⁷⁸ and it remains unapproved by the FDA for use in vEDS due to lack of clear evidence for its efficacy.

Beyond celiprolol, pharmacologic measures to control blood pressure and reduce atherosclerotic risk factors are recommended, including the implementation of beta-blockers or angiotensin receptor blockers and statins where appropriate; calcium channel blockers have been shown to be detrimental in a murine model of vEDS and are avoided in our practice.⁷⁸ Overall, prophylactic measures to control blood pressure and reduce atherosclerotic risk factors are recommended. Lifestyle modifications for EDS IV follow the general recommendations for other genetic diseases, as reviewed in the earlier discussion of MFS.³⁸

Surgical Treatment

Surgical management of vEDS is a formidable challenge, as the findings in patients with vEDS can include arterial

manifestations throughout the entire vascular tree⁷⁹ (Fig. 141.9) and the traditional risk assessment paradigm cites invasive procedures so fraught with complications that intervention should be performed only for imminent risk of death.^{73,74} A report of patients treated at Johns Hopkins Hospital from 1994 to 2009 reveals some very important distinctions regarding the triage of patients with vEDS.⁷⁶ Unlike in the Mayo Clinic series, in which the preponderance of patients were treated emergently, most of the patients in the Hopkins series were treated electively. Overall perioperative bleeding rate and mortality were greatly reduced by comparison (Table 141.3). Given the success of elective procedures, it may be worthwhile to consider elective intervention in patients with vEDS before rupture and the ensuing stress compound operative repair. Furthermore, it is also likely that some improvement in the Hopkins series rests in its more contemporary time period as a further updated 2018 consortium study of vEDS patients demonstrated the safety and durability of open aortic repair in these patients.⁸⁰

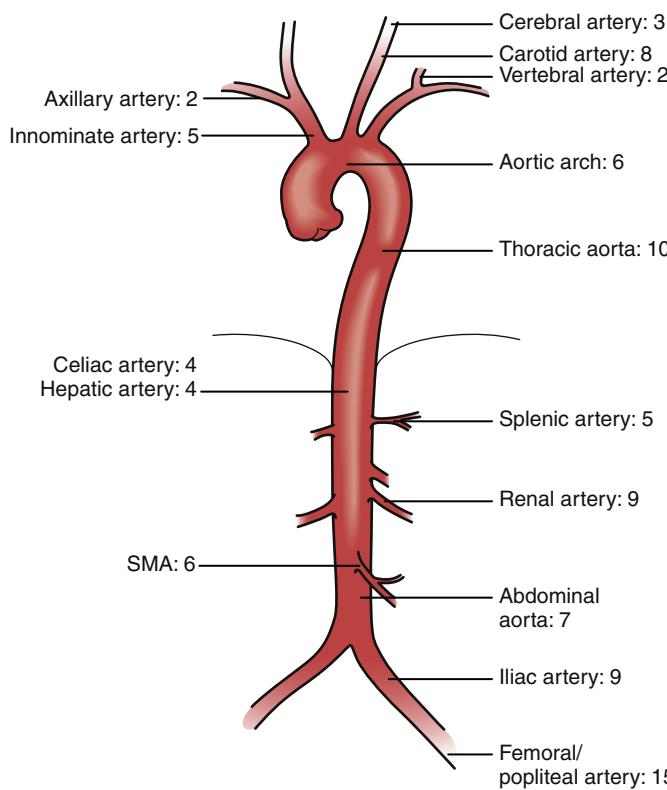


Figure 141.9 Arterial distribution of vascular complications in 24 patients with a clinical diagnosis of type IV Ehlers–Danlos syndrome. SMA, superior mesenteric artery. (From Oderich GS, Panneton JM, Bower TC, et al. The spectrum, management and clinical outcome of Ehlers–Danlos syndrome type IV: a 30 year experience. *J Vasc Surg*. 2005;42:98–106.)

Undoubtedly operative techniques have improved, and the authors offer several methods that may be helpful in successfully operating on vEDS patients⁷⁶:

1. Liberal use of adjunctive techniques to reduce operative trauma in both the endovascular and operative setting
2. Padded surgical clamps
3. Permissive hypotension (systolic blood pressure 70–80 mm Hg) during vascular clamping and suture line testing.

Patients with vEDS have been found to have unique iliac aneurysms. The configuration usually spares the aortic bifurcation, and the common iliac arteries “balloon” in a bell-bottom fashion (Fig. 141.10). In such instances, repair should be entertained in young patients electively, with emphasis on adjunctive measures to secure anastomoses as described earlier.

Ultimately, patient risk-to-benefit assessment compels any decision to proceed with a major surgical intervention. While genetic analysis of specific mutations and collagen III biochemical assay may not predict clinical course, those patients with haploinsufficient mutations have been appreciated to have a higher incidence of aortic and iliac pathology and are associated with better surgical handling.⁶⁷ As with most connective tissue disorders, clinical history can also be informative. For patients with severe phenotypic features (such as very affected skin or facial morphology), those with early-age onset, and those with prior complicated courses, complications can

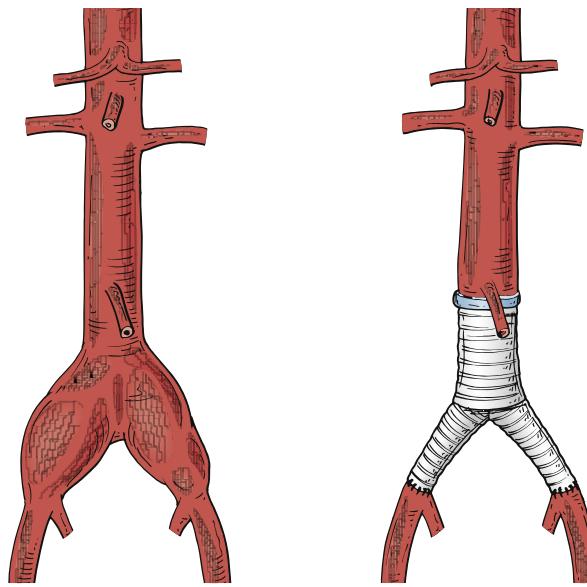


Figure 141.10 “Bell-bottom” configuration iliac aneurysms in vascular Ehlers–Danlos syndrome. In my experience, this is a typical aneurysmal configuration. The aortic bifurcation is preserved, and adjunctive felt reinforcement secures hemostasis.

TABLE 141.3 Outcomes of Endovascular and Open Procedures in Vascular Ehlers–Danlos Syndrome

Procedure	Operative Death, No. (%)	In-Hospital Death, No. (%)	Length of Stay (Days), Median (Interquartile Range)	Any Complication, No. (%)
Endovascular (<i>n</i> = 11)	0 (0)	0 (0)	3 (1–6)	0 (0)
Open (<i>n</i> = 9)	1 (11)	1 (13)	7 (6–8)	3 (38)

be expected. Furthermore, as median survival is 48 to 54 years, older patients may develop intolerance to procedural manipulations versus prior uncomplicated medical or surgical events, assuming a higher risk profile as vessel fragility worsens over a lifetime of vEDS.

Endovascular Treatment

Endovascular approaches for coil embolization of aortic branch vessels and other medium-sized arteries have been successful in vEDS patients with hemorrhage.^{73,76} Such approaches should be strongly considered for spontaneous splenic and hepatic arterial tears, many of which occur without previous trauma and may be imparted by relatively routine activities of daily living. Indeed, a report of endovascular interventions in a spectrum of patients with EDS revealed a very favorable safety profile.⁸¹ Arterial access can precipitate femoral rupture and pseudoaneurysm formation, especially when large devices are necessary. Consideration should be given to open repair of any access puncture (Fig. 141.11), particularly when a larger French size is introduced, given the rate of complications reported.⁸¹ Accordingly, stent-graft therapy for aortic aneurysms has not been reported in a

significant sample, and long-term durability and threat to the fixation zones in the setting of chronic outward radial force may increase the frequency of secondary interventions. Consequently it is generally agreed that stent-graft therapy for vEDS (as in other connective tissue diseases) should be avoided.⁵⁴ Carotid–cavernous sinus fistula is a classic complication of vEDS that is amenable to coil embolization in selected patients. It may manifest as subtle, progressive proptosis or headache, and high-quality imaging is key to determining whether the fistula can be addressed without risk of internal carotid sacrifice and resultant major stroke (Fig. 141.12).

LOEYS–DIETZ SYNDROME

LDS is a newly described aortic syndrome typified by aortic aneurysm and vascular tortuosity, the characteristic craniofacial abnormality of a bifid uvula or cleft palate, and, finally, hypertelorism (Box 141.4).⁸² The disease is caused by heterozygous mutations in the genes encoding key proteins involved in TGF- β signaling pathway.^{82,83} Since the original report, five subtypes of LDS have been delineated all with different culprit genes and slightly different clinical manifestations. LDS types I–V are caused by mutations in *TGFBR1*, *TGFBR2*, *SMAD3*,

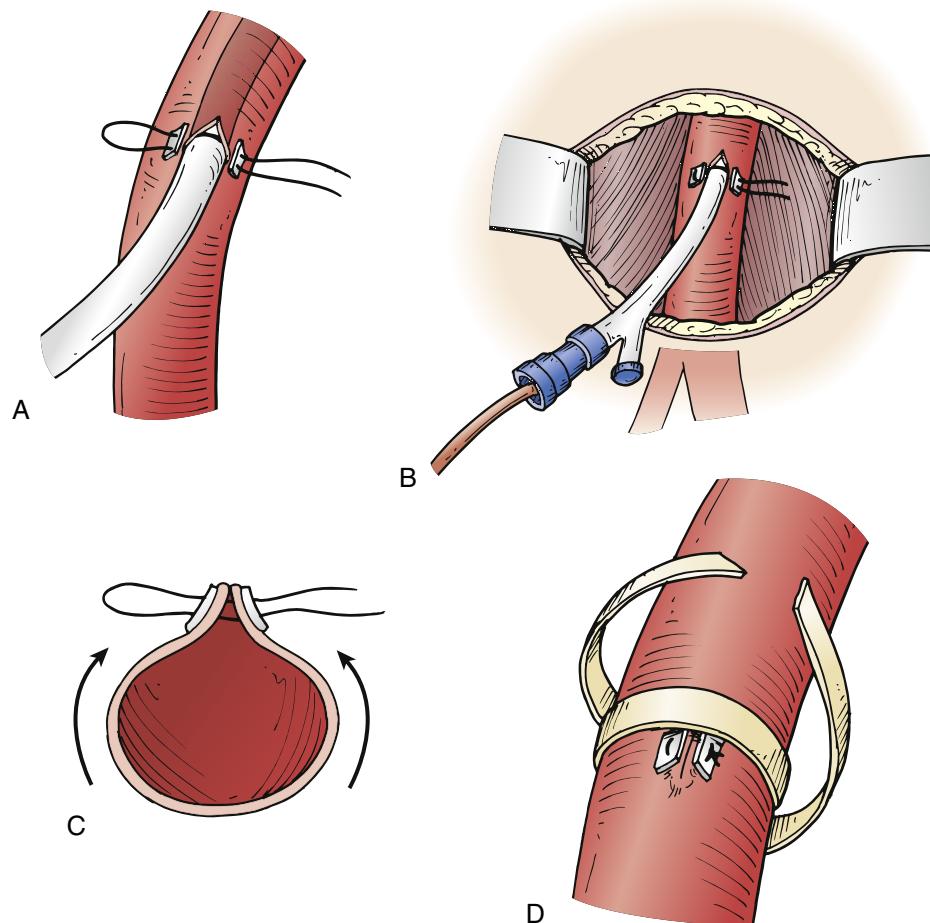


Figure 141.11 Techniques for access in severe fragility of VEDS without femoral clamp. The initial small bore sheath access through pledgetted “U” stitch (A) can be upsized to a large bore sheath (B). The initial stitch can be tied down (C) for hemostasis and the vessel circumferentially reinforced (D) to prevent a late pseudoaneurysm.

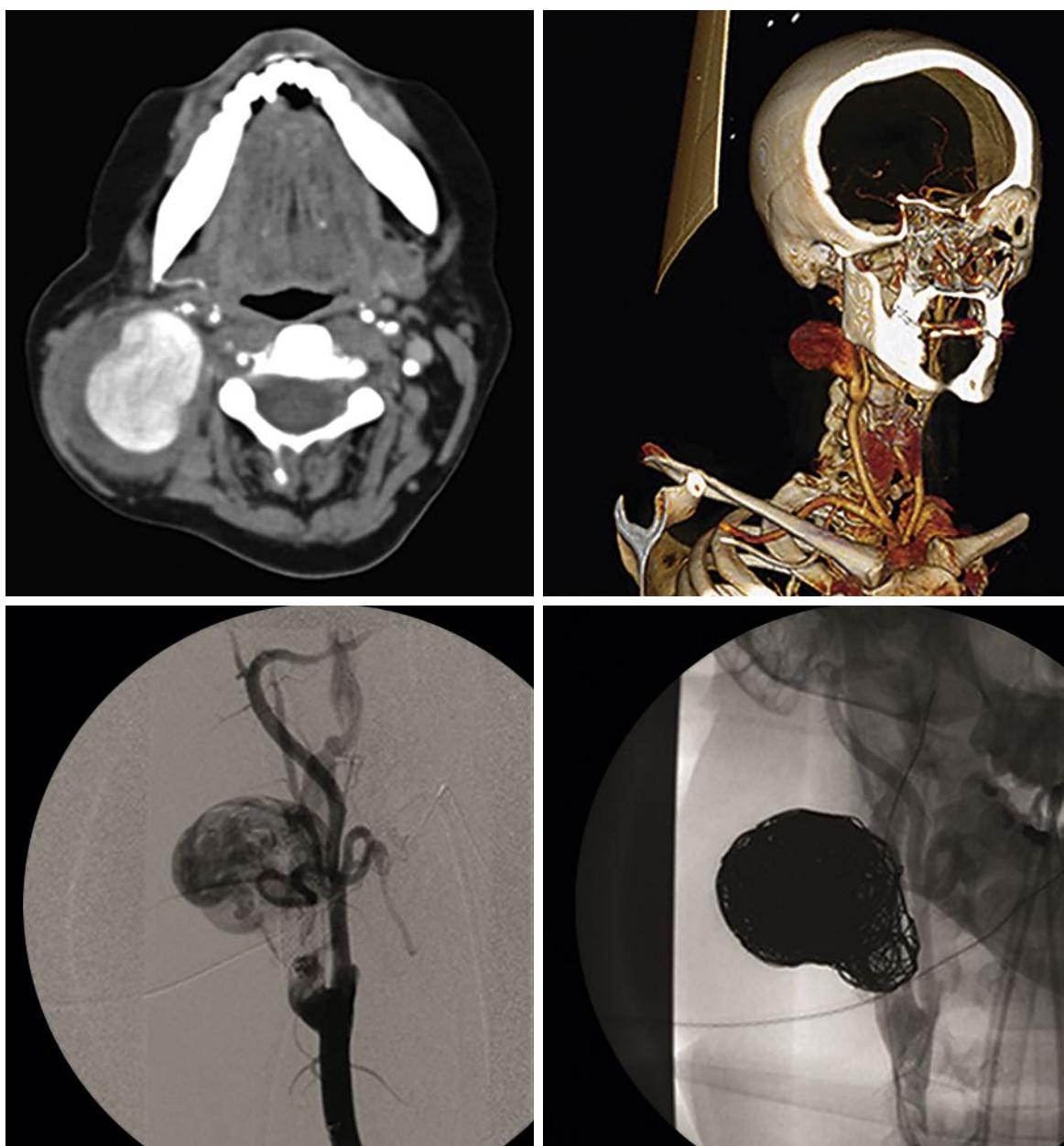


Figure 141.12 Acute development of internal carotid artery aneurysm in a woman with vascular Ehlers–Danlos syndrome 10 days postpartum, which caused significant dysphonia, dysphagia, and pain. Stent-assisted endovascular embolization was performed, and the aneurysm decreased by 50% at 3 months after the procedure.

BOX 141.4 Scoring of Systemic Features

- Wrist and thumb sign: 3 (wrist or thumb sign: 1)
- Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1)
- Hindfoot deformity: 2 (plain pes planus: 1)
- Pneumothorax: 2
- Dural ectasia: 2
- Protrusio acetabuli: 2
- Reduced upper segment/lower segment ratio and increased arm/height and no severe scoliosis: 1
- Scoliosis or thoracolumbar kyphosis: 1
- Reduce elbow extension: 1
- Facial features (3/5): 1 (dolichocephaly, enophthalmos, downsliding palpebral features, malar hypoplasia, retrognathia)
- Skin striae: 1
- Myopia >3 diopters: 1
- Mitral valve prolapse (all types): 1
- Maximum total: 20 points; score ≥7 indicates systemic involvement.

TGFB2, and *TGFB3*, respectively, with LDS I and II demonstrating particularly aggressive aortic pathology.⁸⁴ The cardinal manifestation involves the aortic root, but the aggressive nature of the root aneurysm to dissect or rupture (or both) at small diameter and in childhood separates this condition from MFS and vEDS. Identification of affected patients and testing of all first-degree relatives are of paramount importance to motivate individuals for prophylactic surgery.

Epidemiology

Comparison of survival in the two originally identified subtypes of LDS (I and II) has also been reported.⁸³ In LDS type I, the mean age at death was lower (22.6 years) than in LDS type II (31.8 years, $P = 0.06$). The mean age at the first surgery was 10 years younger in patients with LDS type I than in those with type II (16.9 years vs. 26.9 years, $P = 0.03$). Craniofacial abnormalities, when scored according to a craniofacial severity index, correlated inversely with the time of first surgery (more severe craniofacial abnormality indicated more aggressive aortic pathology).⁸³ LDS type III and LDS type IV may have a later onset of disease.⁸⁴

Clinical Evaluation

LDS is a multisystem disorder with a classic triad consisting of craniofacial abnormality (90%), hypertelorism (wide-set eyes, 90%), and arterial tortuosity/aneurysm (98%). In 40 patients with LDS who underwent anthropometric evaluation, there were findings additional to the classic triad throughout the craniofacial, skeletal, and cutaneous systems.⁸² Developmental delay was infrequent (15%) and was occasionally associated with craniosynostosis, hydrocephalus, or Arnold–Chiari malformation, thus suggesting that intellectual disability is a rare primary manifestation of LDS.⁸² A recent series had demonstrated peripheral vascular involvement is not predicted by prior aortic root repair.⁸⁵ Thus, some LDS patients may present with nonaortic root aneurysm as their index aneurysm, in which case full body imaging is required.⁸⁶

Common Manifestations

The craniofacial manifestations encountered are most commonly hypertelorism and cleft palate or bifid uvula (Fig. 141.13). Craniosynostosis was present in 48%, malar hypoplasia (flat midface) in 60%, and blue sclerae in 40% in the first study describing the syndrome. In distinction to MFS, lens dislocation (ectopia lentis) was not recorded in any patient with LDS.^{82,83} Cardiovascular involvement is a hallmark of LDS, but aneurysms are not limited to the aortic root and can occur throughout the vascular tree. Arterial tortuosity, particularly of the supra-aortic vessels, should prompt consideration of the disease, especially for LDS types III and IV.⁸⁶ Vessel elongation within tortuous segments can be difficult to diagnose without three-dimensional imaging (Fig. 141.14) and centerline measurement.



Figure 141.13 Hypertelorism is noted in 90% of patients with Loeys–Dietz syndrome. In addition, this patient demonstrates malar hypoplasia (underdeveloped and flattened midface/zygomatic arches) and retrognathia (the mandible recedes under the maxilla). (From Williams JA, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys–Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg*. 2007;83:S757–S763.)

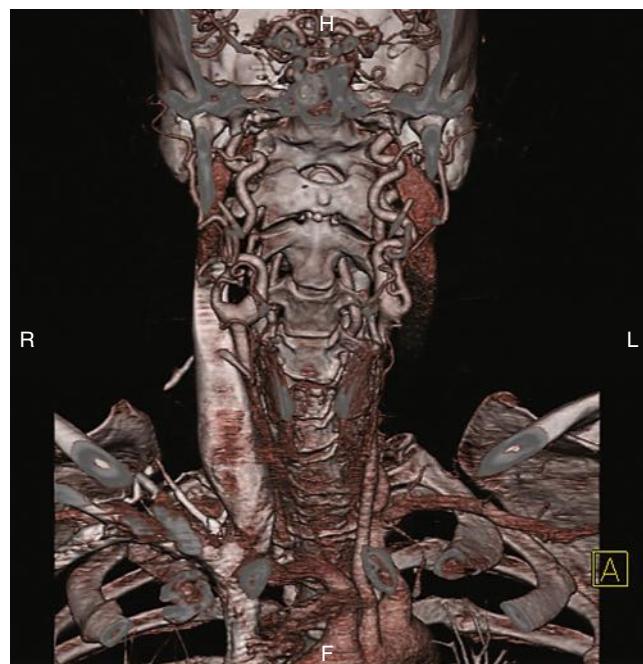


Figure 141.14 Bilateral carotid and vertebral arterial tortuosity is a common peripheral vascular finding in patients with Loeys–Dietz syndrome.

Differential Diagnosis

Because of the early age of appearance of dramatic pathology, vEDS is often considered along with LDS. It could not be more critical to differentiate the two, either by clinical examination to determine the LDS triad or by biochemical testing to confirm vEDS, because surgical management and tissue fragility are dramatically more challenging in patients with vEDS than in those with LDS.

TABLE 141.4 Surgical Thresholds for LDS 1, 2 and 3

System	Thresholds
Aortic root (children)	1. Delay surgery until aortic annulus is 2.0–2.2 cm to accommodate adult-sized graft 2. For children with slowly progressing aortic diameters and milder craniofacial features, adult threshold (4 cm) may be appropriate 3. Rapidly expanding aorta (0.5 cm/y), severe craniofacial features and family history of aggressive aortic disease should be considerations for earlier surgical intervention
Aortic root (adults)	Adults with aortic root dimensions >4.0 cm or rapid expansion (>0.5 cm/y)
Ascending aorta and arch (adults)	Aggressive monitoring of aortic dimension >4.0 cm; personalized decision-making with low threshold for surgical intervention with growth
Descending thoracic aorta ^{a,b} (adults)	Adults with descending thoracic aorta 4.5–5.0 cm or rapid expansion (>1 cm/y)
Visceral/iliac arteries (adults)	Personalized decision making; dimension exceeding 2–3 times expected arterial diameter or rapid expansion
Cerebrovascular arteries (adults and children)	Personalized decision making

Guidelines for LDS 4 and 5 have not been suggested; however, early studies suggest the risk of aortic dissection may not occur at the 4.0 cm threshold and that surgical decision-making may depend on family history and/or adult aortic dimensions in the mid 4 cm range. More information is needed on this type of LDS.

^aSurgical decisions in children with nonaortic root aneurysms should take into consideration absolute size of aorta, rate of growth, personal and family history severity and genotype severity.

^bSurgical guidelines for aneurysms are similar to aneurysmal disease with dissection.

LDS, Loeys-Dietz syndrome; y, year

From MacCarrick G, Black JH 3rd, Bowdin S, et al. Loeys-Dietz Syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.

Selection of Treatment

Risk assessment for prophylactic repair in patients with LDS must account for the aggressive nature of the aneurysms in this disorder. In adults, aneurysms of the thoracoabdominal and infrarenal aorta are repaired when they are 4.0 cm or greater (Table 141.4). A new diagnosis of LDS should prompt a head-to-toe computed tomography or magnetic resonance imaging study to determine the presence of arterial pathology outside the aortic root (Fig. 141.15).⁸⁶ Because involvement of the supra-aortic trunks and vertebral vessels is not uncommon, surgical exposure may be difficult, and embolization approaches should be considered. Given the widespread involvement of the arterial pathology in this disorder, multiple operations or interventions in a single patient are not uncommon.^{85,87}

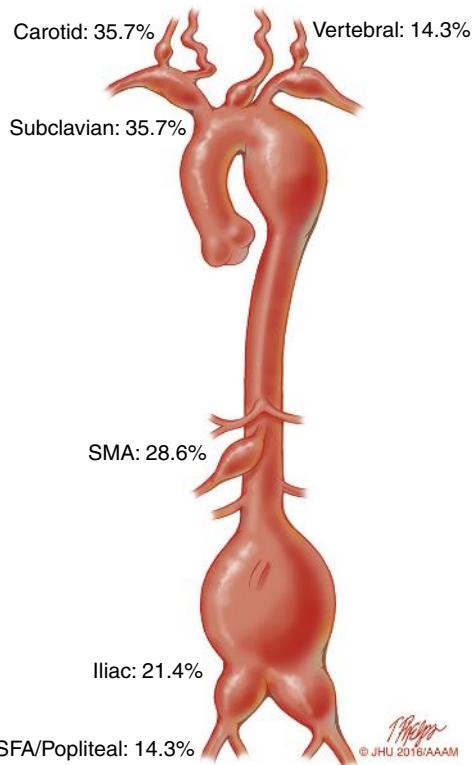


Figure 141.15 Vascular involvement of the supra-aortic branches and entire aorta is common in patients with Loeys-Dietz syndrome. SMA, superior mesenteric artery. (From Beaulieu R, Rue J, Ehrt BA, Grimm JC, Hicks CW, Black JH. Surgical management of peripheral vascular manifestations of Loeys-Dietz syndrome. *Ann Vasc Surg*. 2016;38:10–16.)

Medical Treatment

Current recommendations for medical management and surveillance in LDS are predicated on the beta blockade regimen recommended for patients with MFS, with the threshold for repair being more aggressive in LDS. Nonetheless, the pathophysiological mechanism of increased TGF- β activity in the vessel wall compels some clinicians to initiate losartan therapy for the disease on the basis of the mechanisms demonstrated in the pathophysiology of MFS. However, randomized trials for this therapy are lacking, and preliminary data for losartan therapy are not conclusive to date. Lifestyle modifications should also restrict “burst” activity, contact sports, and repeated isometric (Valsalva-inducing) exertions as in MFS.³⁸

Surgical Treatment

Early results after surgical treatment of aneurysm in LDS are now emerging because of the characterization of clinical and genetic features specific to the disease. Tissue handling and aortic anastomoses are favorable, and a small series of aortic root replacement in adults and children demonstrated no operative mortality, although 3 of 21 patients died in follow-up of thoracic aortic ($n = 2$) and abdominal aortic ($n = 1$) rupture.^{85,87} In the accumulated experience at Johns Hopkins, patients returned to surgery for descending thoracic aortic replacement

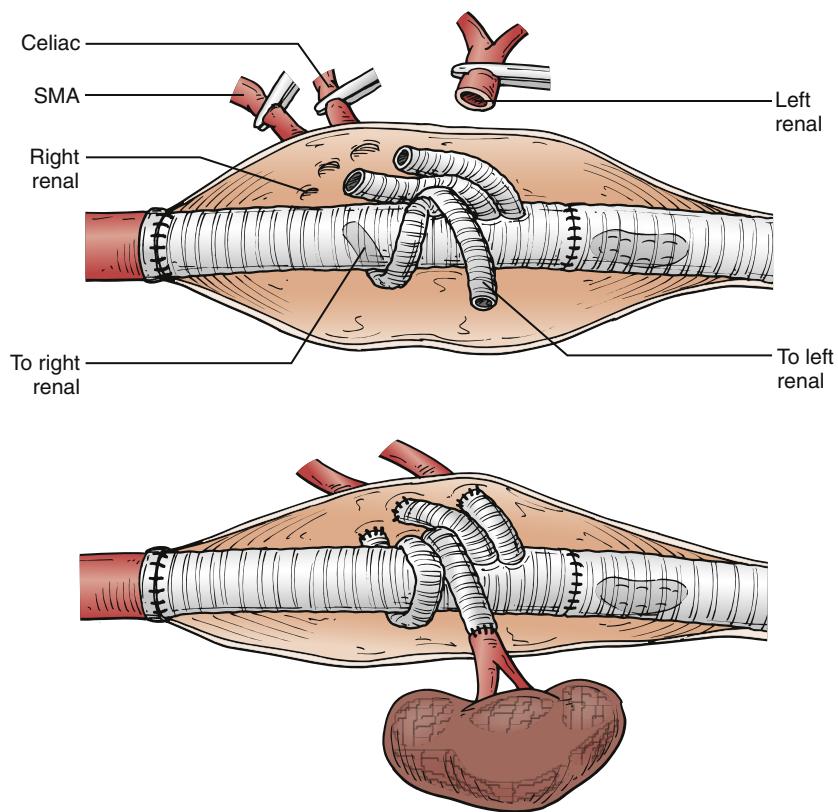


Figure 141.16 Technique for thoracoabdominal aortic reconstruction in patients with connective tissue disorder. Individual branch grafts are anastomosed in the visceral and renal origins, thus avoiding any late inclusion patch aneurysms. The 360-degree wrap helps reduce kinking of short direct branches as the retroperitoneum is closed. *SMA*, superior mesenteric artery.

after previous ascending aortic aneurysm repair or valve-sparing aortic root aneurysm repair. Three of these patients returned thereafter with patch aneurysms after previous thoracoabdominal repairs and were confirmed as having LDS on subsequent *TGFB3* testing. As in MFS, this limited experience suggests that inclusion patch size should be limited or preferably avoided by direct anastomosis to the renal and visceral origins with prefabricated, branched Dacron grafts (Fig. 141.16) to the renal and visceral vessels. On the basis of experience in the aortic root with premature rupture at small diameters, a general recommendation for repair of any aortic segment in adults would be 4 to 5 cm or growth of the aneurysm more than 0.5 cm in 1 year (Box 141.5).⁸⁷ Recommendations for repair of peripheral aneurysms in LDS may be dependent on the patient's age, body size, and history, with rate of growth factoring into the decision, thus making regular surveillance with high-quality imaging critical.⁸⁷ Vessel tortuosity may also be progressive, even though arterial dissection or degeneration in the vascular "hairpins" has not been seen.

FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION

Although it has been recognized that TAAD occurs in individuals with known genetic syndromes, a genetic basis for

patients with TAAD who do not have a defined connective tissue disease has been investigated. These patients typically exhibit minimal or no outward anthropometric evidence of MFS, vEDS, or LDS yet often relate an impressive history of aortic catastrophe in antecedents. Familial studies suggest that 11% to 19% of all nonsyndromic patients with TAAD have a first-degree relative with the disorder.^{88,89} Pedigree analysis suggests that familial TAAD is inherited as a predominantly autosomal dominant disorder with decreased penetrance and variable expression that yields considerable clinical heterogeneity.⁹⁰ Genetic mapping of loci in familial TAAD has provided new insight into the pathogenesis of aneurysms throughout the aorta.

Pathogenesis

Five loci have been mapped for familial TAAD to date, including three identified genes. Despite locus heterogeneity, the final common pathologic change in the aortic wall is medial degeneration.^{91,92} Disarray of smooth muscle cells and the accumulation of proteoglycan are also typically present. The first locus mapped for familial TAAD was the *TAAD1* locus at 5q13-14.⁹² The initial genetic screen identified the location of the defective gene by using two families with similar phenotype for mapping. Subsequent to this mapping, 15 other families with familial TAAD patterning were found to carry the same

BOX 141.5**Guidelines for Vascular Care and Surgery for Loeys–Dietz Syndrome****Vascular care**

1. Baseline head to pelvis MRA or CTA with 3D reconstruction performed at diagnosis. Repeat imaging after 1 year. Thereafter, progression rate, location, and size of aneurysm should guide frequency of head through pelvis imaging. Recommended to have visualization of each part of the vascular tree at least every 2 years. Attention should be paid to cumulative radiation from CT imaging. Imaging in severely affected individuals should begin in infancy; for infants lacking severe craniofacial or skeletal features, consider initial imaging at 2–3 years of age
2. Consultation with vascular/neurovascular specialists for surveillance and/or surgical plan with presence of aneurysms
3. Monitor type B dissections aggressively for rapid growth of aortic dimension. Standard follow-up imaging at 7–14 days, then 1, 3, 6, and 12 months post-dissection and yearly thereafter
4. Consider duplex arterial screening in presence of abnormal physical exam to identify arterial aneurysm or dissection

From MacCarrick G, Black JH 3rd, Bowdin S, et al. Loeys–Dietz Syndrome: a primer for diagnosis and management. *Genet Med.* 2014;16:576–587.

Vascular surgical considerations

1. Note vascular tortuosity, aberrant or multiple arteries that may impact surgical intervention
2. Lumbar cerebrospinal fluid drainage is not contraindicated in patients with LDS, even with dural ectasia, but dural leaks after drain removal may require epidural blood patching
3. Surgical technique for arch and thoracoabdominal reconstruction should avoid inclusion patch techniques in favor of direct branched surgical grafts directly to the great vessel, visceral and renal origins
4. Endovascular repair may be used as a lifesaving procedure with referral to institution that can perform a later open repair. May be considered between previous repairs in which both proximal and distal landing zones for the endograft are within existing Dacron grafts
5. Personalized decision making for type of visceral or cerebrovascular aneurysm repair

genetic defect, which was segregated as an autosomal dominant disease. In families with this gene, women seemed to be less affected, thus suggesting reduced penetrance of expression.⁹² Involvement of the ascending aorta is the primary finding.⁹³

Alpha-actin mutations have been discovered to cause 14% of cases of familial TAAD.⁹⁴ The actin proteins are highly conserved and are critical cytoskeletal elements. Aortic tissue demonstrates cystic medial degeneration with focal areas of marked vascular smooth muscle proliferation. The overall penetrance to express aneurysm or dissection in individuals with familial TAAD and *ACTA2* mutations was low (0.48%) and did not change with age. This fact distinguishes *ACTA2* mutations from other genes in familial TAAD, in which penetrance is clearly age-related.⁹⁴ Fundamentally, the recognition of these local proteins and the critical role of maintenance of the extracellular matrix highlights the fact that aortic disease is a very local, not global issue. All of the defective loci in TAAD are involved in maintaining aortic wall integrity and adapting to aortic wall stress; it has been postulated that mutations in structural and signaling proteins involved in these pathways can trigger defective mechanosensing and maladaptive, degenerative changes in response to stress.^{95,96}

Clinical Manifestations

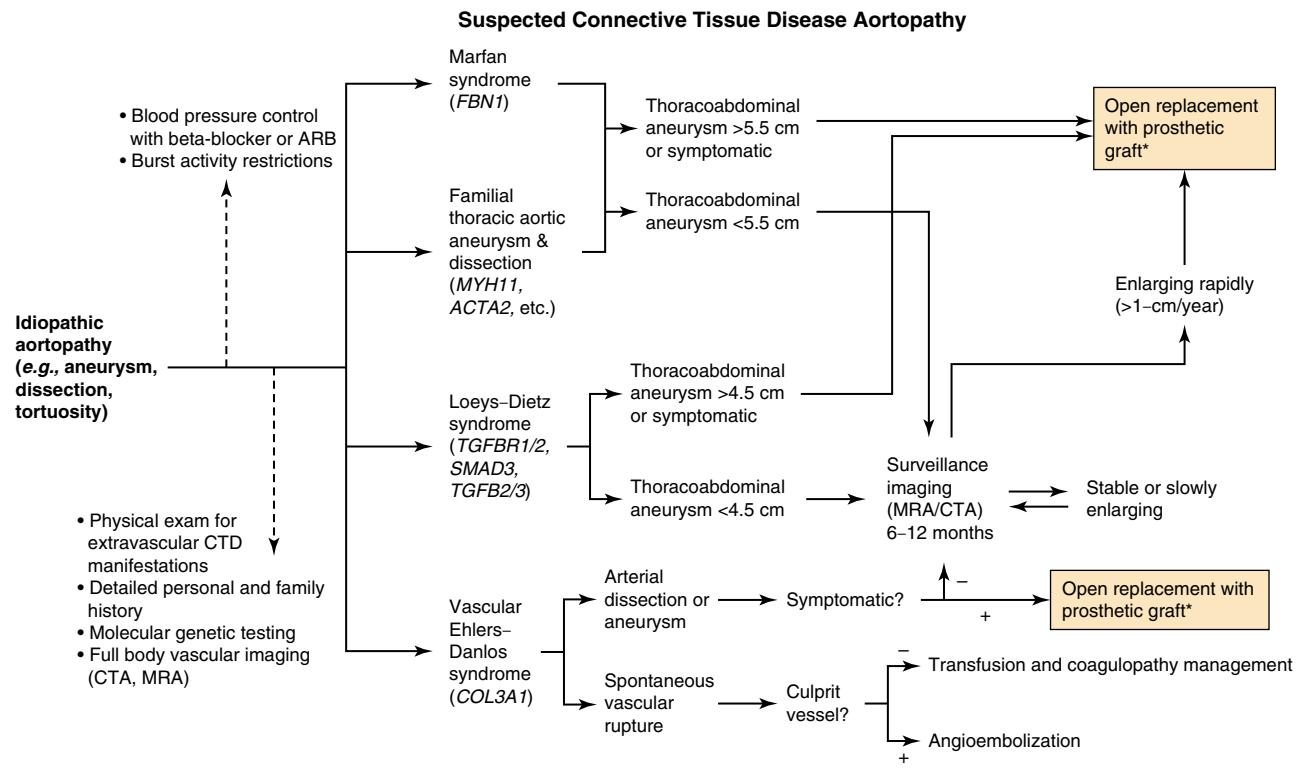
Patients with familial TAAD are seen at a younger age than those with sporadic thoracic aortic aneurysms (mean age, 58.2 vs. 65.7 years), thus suggesting a more aggressive clinical entity.⁹⁰ In familial TAAD, thoracic aneurysms are the most

common (66%), followed by AAAs (25%) and cerebral aneurysms (8% to 10%).⁹⁰ Although the ascending aorta is more commonly affected by aneurysm (82%) than by dissection (18%), an equal distribution of aortic dissections and aneurysms is observed in the descending thoracic aorta (50% each) in affected individuals.

Selection of Treatment

Selection of treatment for patients with familial TAAD is complicated by the variable penetrance and expressivity of the disorder and the lack of an established genotype–phenotype correlation. In some families, the clinical history may suggest aortic catastrophe at very minimal aortic diameter dilatation, and treatment thresholds should be considered in the context of the pedigree history. For patients with a minimal contributory family history, treatment recommendations should follow typical sporadic thresholds – of 6.0 cm for thoracic aortic aneurysms and 5.5 cm for AAAs. Thoracic aortic growth rates in familial TAAD are comparatively higher than those of sporadic aneurysms, on average 0.21 versus 0.16 cm per year, respectively.⁹⁰ Endovascular stent-grafting approaches have not been reported in familial TAAD, but as in other connective tissue diseases, concerns about the inherent weakness and fragility of the aortic wall are paramount. Consensus on stent-graft therapy for patients with familial TAAD is not available, but one should follow the previous documents advising against such approaches for connective tissue diseases.⁵⁴

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT-1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–121.

Landmark publication implicating TGF- β in Marfan syndrome and the experimental evidence for losartan therapy.

Humphrey JD, Milewicz DM, Tellides G, Schwartz MA. Dysfunctional mechanosensing in aneurysms. *Science*. 2014;344(6183):477–479.

Short review of the role of mechanosensing in the development and exacerbation of genetically mediated thoracic aortic aneurysm and dissection.

Humphrey JD, Schwartza MA, Telldies G, Milewicz DM. Role of mechano-transduction in Vascular Biology. *Circ Res*. 2015;116:1448–1461.

An excellent review of the pathophysiology of matrix interactions in genetic aortic disorders.

Loeys BL, Schwarze U, Holm T. Aneurysm syndromes caused by mutations in the TGF- β receptor. *N Engl J Med*. 2006;355:788–798.

Natural history of Loeys-Dietz syndrome and initial experience in surgical intervention.

MacCarrick G, Black 3rd JH, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.

Review of indications for arterial repairs in Loeys-Dietz syndrome.

Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos type IV, the vascular type. *N Engl J Med*. 2000;342:673–680.

Widely quoted paper on the natural history of the vascular type of Ehlers-Danlos syndrome type IV.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. McKusick V. *Heritable Disorders of Connective Tissue*. St. Louis, MO: CV Mosby; 1956.
2. Marfan A-B. Un cas de déformation congénitale des quatre membres plus prononcée aux extrémités caractérisée par l'allongement des os avec un certain degré d'amincissement. *Bull Mem Soc Med Hop Paris*. 1896;13:220–226.
3. Mery H, et al. Un cas de déformation congénitale des quatres membres: hyperchondroplasie. *Bull Mem Soc Med Hop Paris*. 1902;19:671–676.
4. Baer RW, et al. Congenital aneurysmal dilatation of the aorta associated with arachnodactyly. *Bull Johns Hopkins Hosp*. 1943;72:309–331.
5. Judge DP, et al. Marfan's syndrome. *Lancet*. 2005;366:1965–1976.
6. Gray JR, et al. Ascertainment and severity of Marfan syndrome in a Scottish population. *J Med Genet*. 1994;31:51–54.
7. Dietz HC, et al. Marfan syndrome caused by a recurrent de-novo missense mutation in the fibrillin gene. *Nature*. 1991;352:337–339.
8. Kinoshita N, et al. Aortic root dilatation among young competitive athletes: echocardiographic screening of 1929 athletes between 15 and 34 years of age. *Am Heart J*. 2000;139:723–728.
9. Murdoch JL, et al. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med*. 1972;286:804–808.
10. Silverman DJ, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol*. 1995;75:157–160.
11. McKusick VA. The cardiovascular aspects of Marfan syndrome: a heritable disorder of connective tissue. *Circulation*. 1955;11:321–342.
12. Halme T, et al. Elastin and collagen in the aortic wall: changes in the Marfan syndrome and annuloaortic ectasia. *Exp Mol Pathol*. 1985;43:1–12.
13. Tsuji T. Marfan syndrome: demonstration of abnormal elastic fibers in skin. *J Cutan Pathol*. 1986;13:144–153.
14. Fahrenbach WH, et al. Ultrastructural studies on early elastogenesis. *Anat Rec*. 1966;155:563–576.
15. Ross R, et al. The elastic fiber: the separation and partial characterization of its macromolecular components. *J Cell Biol*. 1969;40:366–381.
16. Sakai LY, et al. Fibrillin, a new 350-kD glycoprotein, is a component of extracellular microfibrils. *J Cell Biol*. 1986;103:2499–2509.
17. Kainulainen K, et al. Location of chromosome 15 of the gene defect causing Marfan syndrome. *N Engl J Med*. 1990;323:935–939.
18. Corson GM, et al. Fibrillin binds calcium and is coded by cDNAs that reveal a multidomain structure and alternatively spliced exons at the 5' end. *Genomics*. 1993;17:476–484.
19. Biery NJ, et al. Revised genomic organization of FBN1 and significance for regulated gene expression. *Genomics*. 1999;56:70–77.
20. Bunton TE, et al. Phenotypic alteration of vascular smooth muscle cells precedes elastolysis in a mouse model of Marfan syndrome. *Circ Res*. 2001;88:37–43.
21. Saharinen J, et al. Latent transforming growth factor β binding proteins (LTBPs)—structural extracellular matrix proteins for targeting TGF- β action. *Cytokine Growth Factor Rev*. 1999;10:99–107.
22. Neptune ER, et al. Dysregulation of TGF- β activation contributes to pathogenesis in Marfan syndrome. *Nat Genet*. 2003;33:407–411.
23. Ng CM, et al. TGF- β dependent pathogenesis of mitral valve prolapse in a mouse model of Marfan syndrome. *J Clin Invest*. 2004;114:1586–1592.
24. Beighton P, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. *Am J Med Genet*. 1988;29:581–594.
25. De Paepe A, et al. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet*. 1996;62:417–426.
26. Loeys BL, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet*. 2010;47:476–485.
27. Loeys B, et al. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. *Hum Mutat*. 2004;24:140–146.
28. Woorderchak-Donahue W, et al. Clinical utility of a next-generation sequencing panel assay for Marfan and Marfan-like syndromes featuring aortopathy. *Am J Med Gen A*. 2015;167(8):1747–1757.
29. Glesby MJ, et al. Association of mitral valve prolapse and systemic abnormalities of connective tissue: a phenotypic continuum. *JAMA*. 1989;262:523–528.
30. Nijbroek G, et al. Fifteen novel FBN1 mutations causing Marfan syndrome detected by heteroduplex analysis of genomic amplicons. *Am J Hum Genet*. 1995;57:8–21.
31. Sood S, et al. Mutation in fibrillin-1 and the marfanoid craniosynostosis (Schprintzen-Goldberg) syndrome. *Nat Genet*. 1996;12:209–211.
32. Greally MT. *Shprintzen-Goldberg syndrome*. *GeneReviews*; 2006; updated Apr 2020.
33. Wang M, et al. Familial occurrence of typical and lethal congenital contractual arachnodactyly caused by misplacing of exon 34 in FBN2. *Am J Hum Genet*. 1997;59:1027–1034.
34. Roman MJ, et al. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol*. 1989;59:795–797.
35. Gott VL, et al. Replacement of the aortic root in patients with Marfan syndrome. *N Engl J Med*. 1999;340:1307–1313.
36. Maron BJ, et al. Sudden death in young athletes: clinical, demographic, and pathologic profiles. *JAMA*. 1996;276:199–204.
37. Yeatman AT, et al. Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of death? *J Am Coll Cardiol*. 2003;41:329–332.
38. Maron BJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation*. 2004;109:2807–2816.
39. Maron BJ, et al. Competitive athletes with cardiovascular disease: the case of Nicholas Knapp. *N Engl J Med*. 1998;339:1632–1635.
40. Shores J, et al. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med*. 1994;330:1335–1341.
41. Habashi JP, et al. Losartan, an AT-1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–121.
42. Matt P, et al. Recent advances in Marfan syndrome: should we now treat surgical patients with losartan? *J Thorac Cardiovasc Surg*. 2008;135:389–394.
43. Lacro RV, Dietz HC, Slepper LA, et al. Atenolol versus losartan in children and young adults with Marfan's Syndrome. *N Engl J Med*. 2014;371(22):2061–2071.
44. Teixido-Tura G, et al. Losartan versus atenolol for prevention of aortic dilation in patients with Marfan syndrome. *J Am Coll Cardiol*. 2018;72(14):1613–1618.
45. Den Hartog AW, Franken R, Zwinderman AH, et al. The risk for type B aortic dissection in Marfan syndrome. *J Am Coll Cardiol*. 2015;65:246–254.
46. Doyle JJ, et al. A deleterious gene-by-environment interaction imposed by calcium channel blockers in Marfan syndrome. *Elife*. 2015;27(4). e08648.
47. Lemaire SA, et al. Spectrum of aortic operations in 300 patients with confirmed or suspected Marfan syndrome. *Ann Thorac Surg*. 2006;81:2063–2078.
48. Crawford ES. Marfan's syndrome: broad spectral surgical treatment of cardiovascular manifestations. *Ann Surg*. 1983;198:487–505.
49. Coselli JS, et al. Marfan syndrome: the variability and outcome of operative management. *J Vasc Surg*. 1995;21:432–443.
50. Dardik A, et al. Durability of thoracoabdominal aortic aneurysm repair in patients with connective tissue disorders. *J Vasc Surg*. 2002;36:696–703.
51. Dardik A, et al. Aneurysmal expansion of the visceral patch after thoracoabdominal aortic replacement: an argument for limiting patch size? *J Vasc Surg*. 2001;34:405–410.
52. Hicks CW, et al. A 10-year institutional experience with open branched graft reconstruction of aortic aneurysms in connective tissue disorders versus degenerative disease. *J Vasc Surg*. 2017;66(5):1406–1416.
53. Milewicz DM, et al. Treatment of aortic disease in patients with Marfan syndrome. *Circulation*. 2005;111:e150–e157.
54. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular grafts. *Ann Thorac Surg*. 2008;85:S1–S41.

55. Hiratzka LF, et al. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation*. 2010;121:e266–e369.
56. Botta L, et al. Stent graft repair of the descending thoracic aortic disease using endovascular grafts in patients with Marfan syndrome: an effective alternative to open operation? *J Thorac Cardiovasc Surg*. 2009;138:1108–1114.
57. Waterman AL, et al. Endovascular treatment of acute and chronic pathology in patients with Marfan syndrome. *J Vasc Surg*. 2012;55:1234–1241.
58. Shalhub S, et al. Endovascular thoracic aortic repair in confirmed or suspected genetically triggered thoracic aortic dissection. *J Vasc Surg*. 2018;68(2):364–371.
59. Dong ZH, et al. Stent-graft induced new entry tear after endovascular repair for Stanford type B aortic dissection. *J Vasc Surg*. 2010;52:1450–1458.
60. Dong ZH, et al. Retrograde type A aortic dissection after endovascular stent graft placement for treatment of type B dissection. *Circulation*. 2009;119:735–741.
61. Steinman B, et al. Ehlers-Danlos syndrome. In: Royce PM, et al., ed. *Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects*. 2nd ed. New York: Wiley-Liss; 2002:431–523.
62. Bergqvist D, Björck M, Wanhainen A. Treatment of vascular Ehlers-Danlos syndrome: a systematic review. *Ann Surg*. 2013;258:257–261.
63. Superti-Furga A, et al. Type III collagen deficiency. *Lancet*. 1989;1:903–904.
64. Pope FM, et al. Inheritance of Ehlers-Danlos type IV syndrome. *J Med Genet*. 1977;14:200–204.
65. Pepin M, et al. Clinical and genetic features of Ehlers-Danlos type IV, the vascular type. *N Engl J Med*. 2000;342:673–680.
66. Prockop DJ. Osteogenesis imperfecta: phenotypic heterogeneity, protein suicide, short and long collagen. *Am J Hum Genet*. 1984;36:499–505.
67. Pepin MG, Schwarze U, Rice KM, et al. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genet Med*. 2014;16:881–888.
68. Beighton P, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. *Am J Med Genet*. 1997;77:31–37.
69. Nuytinck L, et al. Detection and characterization of an overmodified type III collagen by analysis of non-connective tissues in a patient with Ehlers-Danlos syndrome IV. *J Med Genet*. 1992;29:375–380.
70. Roberts DL, et al. Ehlers-Danlos syndrome type IV mimicking non-accidental injury in a child. *Br J Dermatol*. 1984;111:341–345.
71. Leblanc R, et al. Type III collagen mutations and cerebral aneurysms. *Stroke*. 1989;20:1432–1433.
72. Dolan P, et al. Anesthetic considerations for Ehlers-Danlos syndrome. *Anesthesiology*. 1980;52:266–269.
73. Oderich GS, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30 year experience. *J Vasc Surg*. 2005;42:98–106.
74. Freeman RK, et al. The surgical complications of Ehlers-Danlos syndrome. *Am Surg*. 1996;62:869–873.
75. Cikrit DF, et al. Spontaneous arterial perforation: the Ehlers-Danlos specter. *J Vasc Surg*. 1987;5:248–255.
76. Brooke BS, et al. Contemporary management of vascular complications associated with Ehlers-Danlos syndromes. *J Vasc Surg*. 2010;51:131–138.
77. Ong KT, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective, randomized, open, blinded endpoints trial. *Lancet*. 2010;376(9751):1476–1484.
78. Bowen CJ, et al. Targetable cell signaling events mediate vascular pathology in vascular Ehlers-Danlos syndrome. *J Clin Invest*. 2020;130(2):686–698.
79. Shalhub S, Black 3rd JH, Cecchi AC, et al. Molecular diagnosis in vascular Ehlers-Danlos Syndrome predicts pattern of arterial involvement and outcomes. *J Vasc Surg*. 2014;28:160–169.
80. Shalhub S, et al. A multi-institutional experience in the aortic and arterial pathology in individuals with genetically-confirmed vascular Ehlers-Danlos syndrome. *J Vasc Surg*. 2019;70(5):1543–1554.
81. Lum YW, et al. Endovascular procedures in patients with Ehlers-Danlos syndrome: a review of clinical outcomes and iatrogenic complications. *Ann Vasc Surg*. 2012;26:25–33.
82. Loeys BL, et al. Aneurysm syndromes caused by mutations in the TGF- β receptor. *N Engl J Med*. 2006;355:788–798.
83. Loeys B, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive, and skeletal development caused by mutations in TGFBR1 and TGFBR2. *Nat Genet*. 2005;37:275–281.
84. Krohg-Sorensen K. Cardiovascular surgery in Loeys-Dietz syndrome type I-4. *Eur J Cardiothorac Surg*. 2017;52(6):1125–1131.
85. Beaulieu RJ, et al. Surgical management of peripheral vascular manifestations of Loeys-Dietz syndrome. *Ann Vasc Surg*. 2017;38:10–16.
86. MacCarrick G, Black 3rd JH, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.
87. Williams JA, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg*. 2007;83:s757–s763.
88. Albornoz G, et al. Familial thoracic aortic aneurysms and dissections—incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg*. 2006;82:1400–1406.
89. Biddinger AM, et al. Familial thoracic aortic dilatations and dissections: a case control study. *J Vasc Surg*. 1997;25:506–511.
90. Pannu H, et al. Genetic basis of thoracic aortic aneurysms and dissections: potential relevance to abdominal aortic aneurysms. *Ann NY Acad Sci*. 2006;1085:242–255.
91. Pannu H, et al. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin 2. *Hum Mol Genet*. 2007;16:2453–2462.
92. Guo D, et al. Familial thoracic aortic aneurysms and dissections: genetic heterogeneity with major locus mapping to 5q13-14. *Circulation*. 2001;103:2461–2468.
93. Tran-Fadulu V, et al. Familial thoracic aortic aneurysms and dissections: three families with early-onset ascending and descending aortic dissections in women. *Am J Med Genet*. 2006;140A:1196–1202.
94. Guo DC, et al. Mutations in smooth muscle α -actin (ACTA-2) lead to thoracic aortic aneurysms and dissections. *Nat Genet*. 2007;39:1488–1493.
95. Humphrey JD, et al. Role of mechanotransduction in vascular biology. *Circ Res*. 2015;116:1148–1461.
96. Humphrey JD, et al. Dysfunctional mechanosensing in aneurysms. *Science*. 2014;344:477–488.

Raynaud Phenomenon

GREGORY J. LANDRY and TANA L. REPELLA

EPIDEMIOLOGY AND NATURAL HISTORY 1878

NORMAL ARTERIAL FLOW TO THE HAND 1878

REGULATION OF BLOOD FLOW IN THE DIGITS 1878

PATHOGENESIS 1879

Vascular 1879

Impaired Vasodilatation 1879

Increased Vasoconstriction 1879

Neural Factors 1879

Humoral Factors 1880

Risk Factors 1880

Associated Diseases 1880

CLINICAL FINDINGS 1881

DIAGNOSIS 1881

Physical Examination 1882

Vascular Laboratory Evaluation 1882

Segmental Pressure Measurements and Duplex

Ultrasonography 1883

Finger Systolic Blood Pressure 1883

Cold Challenge Testing 1883

Nail-Fold Capillary Microscopy 1884

Serologic Evaluation 1884

TREATMENT 1884

Preventive Measures 1884

Behavioral Therapies and Maneuvers 1884

Pharmacologic Therapy 1884

Calcium-Channel Blockers 1885

Alpha Adrenergic Blockers 1886

Prostaglandins and Analogues 1886

Phosphodiesterase Inhibitors 1886

Endothelin Inhibitors 1886

Nitrates 1886

Other Medications 1886

Surgical Therapy 1887

Sympathectomy 1887

Botulinum Toxin 1887

Nerve Stimulation 1887

Alternative Therapies 1888

CHAPTER ALGORITHM 1889

Raynaud phenomenon (RP) was first described by Maurice Raynaud (1834–1881) in 1862 when he reported 25 patients with intermittent digital ischemia and recognized the relationship of local cold and emotional stress in the causation of the episodes.¹ RP is an exaggeration of the normal physiologic response and is defined as episodic pallor or cyanosis of the fingers caused by vasoconstriction of small digital arteries or arterioles occurring in response to cold or emotional stress. Although this term typically applies to the fingers, the toes can also be affected. The hallmark of RP is the change in skin temperature and color brought on by exposure to cold. A typical vasospastic attack is characterized by the sudden onset of pallor of part or all of one or more digits. Cyanosis follows as static blood in the capillaries becomes desaturated. The attack subsides with the return of arterial inflow, and postischemic vasodilatation results in hyperemia and rubor of the skin (Figs. 142.1 and 142.2).

Raynaud's through the years has been described as both a disease and phenomenon. Early literature referred to Raynaud's

as "Raynaud's disease" almost exclusively until the 1940s. The nomenclature "Raynaud phenomenon" started appearing in the literature soon thereafter. People have differentiated Raynaud disease, which is primary Raynaud's, versus Raynaud phenomenon, which is secondary or associated with other diseases. This nomenclature can be confusing, as many patients who start out with primary Raynaud's will develop associated connective tissue disorders over time. We have preferred to refer to all people with this condition as having Raynaud syndrome (RS).

RP consists of two sub-types: primary and secondary RP. Primary RP is the most common and is the idiopathic form. Secondary RP is associated with an underlying disease process, such as systemic sclerosis, rheumatoid arthritis, or other connective tissue disease (CTD). Primary RP is considered to be a benign process and is not associated with structural vascular change. In contrast, patients with secondary RP have some degree of fixed vascular obstruction to blood flow, which decreases the threshold for cold-induced vasospasm. This can progress to digital ulceration, scarring, or gangrene.



Figure 142.1 Palmer view of the hands of a patient with a typical example of Raynaud phenomenon. (Note that attacks of digital vasospasm cause well-demarcated pallor affecting one or more fingers brought on by exposure to cold or emotional stress.)



Figure 142.2 Palmer view of the hands of a patient with Raynaud phenomenon demonstrating both pallor and cyanosis in multiple fingers.

EPIDEMIOLOGY AND NATURAL HISTORY

The prevalence of RP in the general population varies greatly with climate and ethnic origin. Several epidemiologic studies investigating disease prevalence have been performed, primarily in populations in colder climates. Overall estimates of disease prevalence in the general population range from 3.3% to 22%. Women are also more commonly affected than men, with a prevalence of 0.5% to 8.3% in men and 2.5% to 21% in women.^{2–6} Two longitudinal population-based studies have been performed to determine the incidence of primary RP. In a 14-year study in a community in southern France, the annual incidence of primary RP was 0.25%.² In addition, similar findings were noted in the epidemiologic analysis of the Framingham off spring study cohort. Over a 7-year period, the incidence of RP was 2.2% in women and 1.5% in men.⁶ Patients with primary RP typically follow a benign clinical course, with up to 33% experiencing a resolution of symptoms over time.



Figure 142.3 Normal hand arterial anatomy. 1, radial artery; 2, ulnar artery; 3, deep palmer arch; 4, common digital (metacarpal) artery; 5, proper digital artery.

In contrast, secondary RP is more frequently associated with digital ulcers and amputations. Furthermore, secondary RP is a marker for early mortality compared to age and sex-matched controls, particularly in the presence of abnormal nail-fold capillaroscopy or decreased hemoglobin levels.⁷

NORMAL ARTERIAL FLOW TO THE HAND

Circulation in the hand is complex with frequent anatomic variants. The deep and superficial arches supply the metacarpal arteries and in turn the proper digital arteries (Fig. 142.3). In most patients, branches of both the deep and superficial arches provide blood flow to all five fingers, and the two palmar arches provide important collateral flow between the radial and ulnar systems.⁸ The superficial arch is incomplete in 21.5% of people.^{9,10} Severe digital ischemia can occur with occlusion of the radial or ulnar artery and an incomplete superficial arch.

The metacarpal arteries in the palm originate from the superficial arch and provide blood flow to the digits. At the web space, the common digital (metacarpal) arteries branch to supply the proper digital arteries that run the length of each finger. In at least 86% of extremities, all five digits are supplied by arteries from both the deep and superficial arches.⁸ Each finger has two digital arteries, which is important in preventing critical ischemia if one digital artery becomes occluded. The end of the finger is highly vascular with a dense network of blood vessels in the pulp of the fingers.

REGULATION OF BLOOD FLOW IN THE DIGITS

Blood flow in the digits is highly variable and can range from less than 1 mL/min per 100 mL of tissue to 180 mL/min.¹¹ Blood flow to the skin of the digits has two functions, nutritional and thermoregulatory. Approximately 80% to 90% of blood flow through the digits is controlled by thermoregulatory mechanisms and serves an important role in controlling body temperature.¹² Blood vessels that are superficially located

in the skin dilate to radiate excess heat to the environment, and this reduces body core temperature. In response to cold, these arteries constrict to decrease blood flow and conserve body heat.

Maximum vasoconstriction in response to cold occurs at 10°C to 20°C. At lower temperatures, cold-induced vasodilatation results in slight reopening of arteries to allow a trickle of blood into the digits.¹³ With cold exposure, there is a regular rhythmic fluctuation in finger flow caused by periods of vasoconstriction and vasodilatation in the fingers every 30 seconds to 2 minutes.¹⁴ Other investigators have found similar rhythmic fluctuations in finger flow with a frequency of 5 to 10 per minute.¹⁵ These alternating periods of vasoconstriction and dilatation have been called the hunting response.¹⁶ This cold-induced vasodilatation, which protects the fingers from freezing in a cold environment, is impaired in those with secondary RP because of the presence of occlusive arterial disease.

PATHOGENESIS

The exact pathogenesis of RP is unknown. Originally, Raynaud proposed that hyperactivity of the sympathetic nervous system was the cause. Lewis in 1929, disproved this theory by demonstrating that blockade of digital nerve conduction did not prevent vasospasm. Lewis, in turn, theorized that “local vascular fault” in the digital arteries causing increased sensitivity of the blood vessel to cold led to RP.¹⁷ It is most likely a multifactorial problem involving a combination of vascular, neural, and humoral factors (Fig. 142.4).¹⁸

Vascular

Impaired Vasodilatation

Vascular endothelial cells synthesize several vasodilating and vasoconstricting substances.^{19–22} Endothelial-derived relaxing factors include nitric oxide (NO), prostacyclin, adenosine triphosphate (ATP), and bradykinin. NO is a potent vasodilator synthesized from amino acid L-arginine by the activity of the enzyme NO synthase. NO diffuses from the endothelium into smooth muscle, where it activates guanylate cyclase to increase intracellular guanosine monophosphate (cGMP), which leads to vascular relaxation. Decreased NO formation can be found in patients with both systemic sclerosis and RP.^{23–26} S-nitrosothiols are bioactive forms of NO that are involved in cell signaling and have been shown to be decreased in patients with systemic sclerosis and RP.²⁷ Additionally, decreased levels of asymmetric dimethyl-arginine, an inhibitor of endothelial NO synthase, have also been demonstrated in patients with secondary RP. A deficiency of one or more of these factors could potentially increase responsiveness of digital arteries to vasoconstrictive influences and increase the likelihood of vasospasm.

Endothelial dysfunction has been shown to be an important cause of RP in numerous studies. In one study, patients underwent a series of sequential infusions with acetylcholine, prostacyclin, glyceryl trinitrate, and L-arginine. Patients with a history of RP had a greater digital artery vasodilator response to intra-arterial glyceryl trinitrate (an endothelium-independent

PRIMARY RAYNAUD DISEASE: POTENTIAL MECHANISMS

- Increased sensitivity of α_2 receptors to norepinephrine
- Insufficient nitric oxide
- Increased endothelin-1
- Decreased distending pressure
- Platelets release increased 5-HT and TXA2

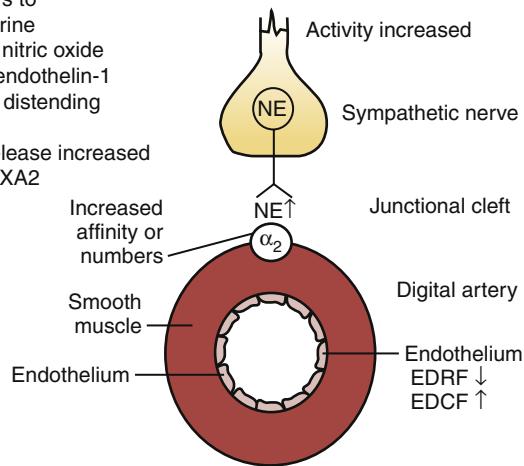


Figure 142.4 There are many potential causes of vasospastic attacks in primary Raynaud phenomenon. Norepinephrine (NE) released from the sympathetic nerve ending acts on the post junctional α_2 receptor located on vascular smooth muscle. Local cooling enhances the response of the α_2 receptor, thereby causing increased arterial contraction. Endothelial dysfunction may lead to insufficient nitric oxide or increased endothelin-1, which changes the balance toward arterial constriction. Activated platelets release thromboxane A2 (TXA2) and serotonin (5-hydroxytryptamine [5-HT]), which may aggravate arterial vasospasm. A decrease in intraluminal distending pressure may decrease the “critical dosing pressure” threshold and result in a vasospastic attack. EDCF, endothelium-derived contracting factor; EDRF, endothelium-derived relaxing factor.

vasodilator), whereas in control patients, the difference in response was less pronounced.²⁸

Increased Vasoconstriction

The endothelial cell also produces factors that cause vessel contraction, such as endothelin-1 (ET-1), which is a potent vasoconstrictor, as well as a promoter of fibroblast and smooth muscle proliferation. Plasma ET-1 levels become elevated in response to cold, which may suggest an association between the rise in ET-1 levels and cold-induced vasoconstriction.²⁹ A threefold rise in ET-1 concentration has been reported in subjects with primary RP. However, more recent literature has challenged the relationship of ET-1 and RP. Smyth and colleagues found that increases in ET-1 levels in patient with both primary RP and scleroderma were similar to control subjects with cooling-induced vasospasm.³⁰

Angiotensin is another endogenous peptide with vasoconstrictive effects that has been implicated in the mechanism of vasospasm. The exact mechanism of involvement of angiotensin in RP remains unclear. Increased levels of angiotensin II have been shown in patients with scleroderma.³¹ However, activation of the renin–angiotensin system has not been demonstrated in primary RP.³²

Neural Factors

The current focus of RP pathophysiology has been on alterations in peripheral adrenoceptor activity. Early laboratory

studies showed a marked reduction in cold-induced digital arterial vasospasm after the intra-arterial administration of reserpine.³³ This suggested that patients with RP may possess abnormal adrenergic receptors that become increasingly sensitive to stimulation after exposure to cold.

Characterization of α_1 and α_2 adrenoceptors has led to an improved understanding of the mechanisms of RP. Sympathetic nerves can respond to cold and emotional stress by releasing neurotransmitters such as norepinephrine, which act on the postsynaptic α_2 receptor and cause vascular smooth muscle contraction. Cold also causes increased affinity of the α_2 receptor for norepinephrine, which results in enhanced smooth muscle contraction in the cold.^{34–38} The initiation of the α_2 adrenoceptor to cold is due to the activation of Rho-protein kinase signaling.^{37–40}

Freedman and colleagues studied the effects of brachial artery infusions of an alpha-1, an alpha-2 antagonist, or both while vasospastic attacks were induced by cooling in 23 patients with idiopathic RP.⁴¹ They found that in patients who were infused with yohimbine (α_2 antagonist), there were significantly fewer attacks compared to the non-infused hand and compared to the group receiving prazosin (α_1 antagonist) alone, demonstrating the importance of α_2 adrenoceptors. However, in another randomized, controlled trial to evaluate the efficacy of a high potency α_{2c} adrenoceptor antagonist (ORM-12741) in patients with systemic sclerosis, subjects randomized to ORM-12741 had a longer time to temperature recovery time.⁴² These mixed results show continued investigations regarding the effect of α adrenoceptors in the pathophysiology of RP and the therapeutic potential of adrenoceptor antagonists are needed.

Humoral Factors

Many circulating humoral factors have been implicated in the pathogenesis of RP. These include hormonal, genetic, platelet activation, and fibrinolysis. RP is more frequent in women than men and tends to be more frequent and severe between menarche and menopause. Investigators have demonstrated elevated sympathetic tone and decreased basal cutaneous circulation in women in comparison to men.⁴³ The role of estrogen is less clear. In human cell culture and in mouse models, estrogen has been demonstrated to increase expression of α_2 adrenoceptors.⁴⁴ Approximately one-quarter of patients with primary RP have a family history of RP in a first-degree relative.⁴⁵ However, it has been difficult to differentiate genetic factors from shared environmental causes. Although a number of chromosomal regions have been evaluated in genomic studies, no significant differences in allelic frequency have been directed between patients with RP and normal controls.

Activation of platelets and increased levels of serotonin in the plasma have been detected in patients with RP.⁴⁶ Elevated circulating levels of activated platelet products, such as thromboxane and B-thromboglobulin, have been induced by cooling of subjects with RP. The relationship between serotonin elevations in the pathogenesis of RP is less clear and remains to be defined.

Abnormalities of fibrinolysis have been primarily implicated in patients with secondary RP, and elevated levels of tissue plasminogen activator inhibitor have been shown in patients with scleroderma.⁴⁷ Impairment in thrombolysis is also thought to predispose to fibrin deposition and vascular obstruction.²³

Risk Factors

Many factors have been found to be associated with RP. These include genetic factors, such as gender; occupational; and drug exposure. RP predominantly affects young women, and has a male:female ratio close to 1:1.6.⁴⁸ The usual age of onset ranges from 11 to 45, while older patients with RP are more likely to have a contributing underlying arterial disease. The relationship between smoking and RP is less clear. In a study of the Framingham heart study offspring cohort, no association was found between smoking and RP in women; however, there was a significant association in men, particularly in those with other cardiovascular risk factors, with an odds ratio of 2.6.⁴⁹ Similar to smoking, the relationship between alcohol and RP remains to be clarified. A recent systematic review and meta-analysis of observational studies reported smoking as a major risk factor with an odds ratio of 1.27, while alcohol had an odds ratio of 0.33.⁴ An association between cannabis use and RP has also been reported.⁵⁰

Vibration-induced RP was first recognized in 1918 by Hamilton,⁵¹ and it has been estimated that as many as 1.5 million American workers involved in a variety of occupations using vibrating tools are now at risk.⁵² Chronic vibration appears to cause structural damage to the arterial wall with hypertrophy of the intima and media. Vibration is believed to cause sympathetic overactivity, endothelial damage, and smooth muscle hypertrophy, leading to vibration-induced vasospasm.^{53–55} The prognosis may be poor because of the development of digital artery obstruction after prolonged exposure to vibration.

Several drugs have been implicated in the development of RP. For example, the incidence of RP in hypertensive patients taking beta blockers was 40% in a Scandinavian study in which patients responded to a questionnaire.⁵⁶ Vasospasm occurs with both selective and nonselective beta-blockers. Despite this, many patients with RP tolerate beta blockers, and many studies show no adverse effects on digital blood flow. Therefore, beta-blockers are not contraindicated in patients with RP. Other drugs associated with RP include chemotherapeutic agents such as cisplatin, vinblastine and bleomycin,⁵⁷ bromocriptine, amphetamine, cocaine, and ergot preparations used for migraine headaches, which are a well-known cause of severe extremity vasospasm and ischemia.⁵⁸ More recently the tyrosine kinase inhibitors (e.g., imatinib, nilotinib, erlotinib) have been associated with the development of RP although the mechanism is unknown.⁵⁸

Associated Diseases

Secondary causes of RP are typically associated with some degree of fixed digital arterial obstruction. When the artery is narrowed because of preexisting large- or small-vessel disease,

there is a lower “critical closing pressure,” and a relatively normal vasoconstrictor response to cold or other stimuli will result in temporary closure of the vessel. RP is common in CTDs such as scleroderma, where intimal hyperplasia, thrombosis, and fibrosis result in luminal narrowing of the digital arteries, but this process may also involve the more proximal arteries of the hand and forearm.

The list of secondary causes of RP is extensive (Box 142.1). In a large series of 1039 patients with RP referred to the Oregon Health and Science University from 1970 to 1995, more than half had primary vasospasm with no identifiable disease.⁵⁹ In those with associated abnormalities, the most common underlying disorder was CTD, which accounted for 27% of cases of RP. Scleroderma was the most likely CTD, followed by undifferentiated and mixed CTD. Atherosclerosis was less common, followed by “hypersensitivity angiitis,” Buerger disease, cancer, and vibration-induced white finger. A wide range of cancers have been associated with secondary RP. The most common associated malignancies are adenocarcinomas and hematologic malignancies, and possible mechanisms of arterial disease caused by malignancy include coagulopathy, cryoglobulinemia, or small-vessel vasculitis (Fig. 142.5).

CLINICAL FINDINGS

The diagnosis of RP is made mainly by clinical findings. The typical patient describes attacks of pallor involving part or all of one or many fingers brought on by cold exposure with full and rapid recovery on rewarming of the digits. The episodes are self-limited and may last from less than a minute to generally not more than 10 to 20 minutes. Pallor may involve part of the digit or the entire finger. Vasospastic attacks most commonly involve the fingers but can affect both the fingers and toes in up to a third of patients. For reasons that have never been clarified, the thumbs are frequently spared. Thumb involvement generally portends secondary RP.

Attacks may occur several times a day to several times a week. Episodes of vasospasm are more common in the cooler winter months, and some patients have few or no attacks during the summer. Pain is not usually a feature during the pallor or cyanotic phase of PRP. The absence of pain and lack of tissue damage during arterial vasospasm may be due to concomitant cold-induced intermittent vasodilation allowing just enough blood flow to protect the fingers from severe ischemia or freezing. Other vascular beds prone to vasospasm include coronary and cerebral vessels. Patients with Prinzmetal angina and migraine are more likely to have RP, suggesting a common factor causing generalized vasospasm.⁶⁰

In contrast, patients with underlying occlusive disease have little or no reserve and cannot increase digital blood flow, with the result that ischemic damage can occur during exposure to cold. Patients with secondary RP are more likely to complain of digital pain on rewarming of cold fingers, because the blood flow cannot increase to match the increased metabolic activity of the finger.

BOX 142.1

Conditions Associated with Secondary Raynaud Phenomenon

Connective Tissue Diseases

- Progressive systemic sclerosis (scleroderma)
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome
- Mixed connective tissue disease
- Overlap connective tissue disease
- Dermatomyositis and polymyositis
- Vasculitis (small, medium-sized vessels)

Drug-Induced Vasospasm

- β -Adrenergic blocking drugs
- Vasopressors
- Ergot
- Cocaine
- Amphetamines
- Vinblastine/bleomycin

Myeloproliferative and Hematologic Disease

- Polycythemia rubra vera
- Thrombocythosis
- Cold agglutinins
- Cryoglobulinemia
- Paraproteinemia

Malignancy

- Multiple myeloma
- Leukemia
- Adenocarcinoma
- Astrocytoma

Infection

- Hepatitis B and C antigenemia
- Parvovirus
- Purpura fulminans

Occupational Arterial Disease

- Hypotenar hammer syndrome
- Vibration induced



Figure 142.5 Paraneoplastic vasculitis with gangrene of several digits in a patient in whom small cell lung cancer was recently diagnosed. The digital ischemia improved with chemotherapy.

DIAGNOSIS

Although many tests have been used for the diagnosis of RP, no consensus exists on the optimal battery of clinical and diagnostic tests. A suggested list of criteria for the diagnosis of primary RP and differentiation of primary from secondary RP is as follows: (1) vasospastic attacks precipitated by cold or emotional stress, (2) attacks involving both hands, asynchronous and/or asymmetric, (3) absence of tissue necrosis or gangrene, (4) no



Figure 142.6 Raynaud phenomenon secondary to limited systemic sclerosis in a young male patient. Cyanotic discoloration is apparent on the left second and third fingers, and the diagnosis of scleroderma can be made by physical examination. There is resorption with healed ulcerations of several fingernails.

history or physical findings suggestive of a secondary cause, (5) normal nail-fold capillaries, and (6) negative serologic findings, particularly a negative test or low titer antinuclear antibodies (ANA).^{61–64} The Chapter Algorithm, below, outlines an algorithm for workup and diagnosis of RP.

Physical Examination

The diagnosis of RP is primarily made by history and physical examination. The physical examination in patients with suspected RP is often normal. Nonetheless, determination of primary or secondary disease is aided by a focused physical examination. The vascular examination should determine the presence of large-, medium-, or small-vessel occlusive disease and should detect signs of a CTD.

The hand and fingers should be examined for evidence of skin thinning, tightening, sclerodactyly, or telangiectasias, all of which may suggest associated autoimmune disease (Fig. 142.6). The skin of the hand and fingers should be inspected for ulceration or hyperkeratotic areas on the fingertips suggestive of healed ulceration (Fig. 142.7). Splinter hemorrhages under the nails may be an indicator of distal atheroemboli, although this finding may be a normal finding in manual workers (Fig. 142.8).

Pulse examination should include palpation of the subclavian, brachial, radial, and ulnar arteries. However, a palpable radial or ulnar pulse at the wrist does not mean that arteries are patent into the hand. The most common site of blockage of the ulnar artery is at the hypothenar eminence where it crosses



Figure 142.7 Advanced scleroderma with flexion contracture of the fingers and ulceration of multiple fingertips. Even with the best wound care, these ulcers can be difficult to heal.



Figure 142.8 Splinter hemorrhages under the nails may be a normal finding with local trauma but can also be an important indicator of distal atheroembolism, as seen in this patient. Note the splinter hemorrhages under the nail and subtle skin mottling consistent with microembolization.

the hook of hamate. The Allen test should be performed in every patient with suspected RP to detect the presence of radial or ulnar artery occlusion and to test for completeness of the palmar arch.

Vascular Laboratory Evaluation

The noninvasive vascular laboratory is an important adjunct to the office-based clinical assessment of patients with RP.⁶⁵ Vascular laboratory testing can assist in differentiating between fixed arterial obstruction and pure vasospasm and can provide assessment of the location and severity of the circulatory impairment. However, the diagnosis of RP should not be made based on any laboratory test, and the vascular laboratory should not take the place of a good history and physical examination.⁷

The most useful noninvasive laboratory tests for RS include room-temperature evaluation of arm, hand, and digital arterial perfusion, supplemented by measurement of digital temperature, systolic blood pressure, and laser Doppler flow of the fingers before and after local digital cooling.

Segmental Pressure Measurements and Duplex Ultrasonography

To evaluate for large-vessel occlusive arterial disease, segmental blood pressure measurements in the upper extremity can be obtained. Pneumatic cuffs are placed on the brachial, upper elbow, and wrist levels, and systolic blood pressure is measured. A pressure differential exceeding 10 mm Hg between levels may be significant and indicative of proximal occlusive disease.

Duplex scanning is useful for evaluation of proximal upper extremity arterial obstruction and aneurysmal disease. Traditionally, its role in the diagnosis of RP has been limited; however, power Doppler has emerged as a means of evaluating the digital arteries for the diagnosis of RP. Lee and colleagues compared power Doppler with a 10-MHz scan head focused at 5 mm with nail-fold capillaroscopy for the diagnosis of primary and secondary RP.⁶⁶ The investigators could correctly diagnose RP in all cases and were able to correctly classify patients as having primary or secondary RP in 89% of cases.

Finger Systolic Blood Pressure

Finger systolic pressure is measured by applying small digital cuffs to the proximal part of the finger. The cuff is inflated above systolic blood pressure to occlude the digital artery. As the cuff is slowly deflated, the pulse returns to the distal part of the finger, and systolic blood pressure can be assessed by pulse-volume recording, strain-gauge plethysmography, or photoplethysmography.^{67,68} Decreased systolic pressure usually indicates fixed arterial occlusive disease in that finger; however, the range of normal digital pressure is variable and is influenced by temperature. A difference of more than 15 mm Hg between fingers or an absolute finger systolic blood pressure of less than 70 mm Hg may indicate occlusive disease.⁶⁹

Evaluation of digital plethysmographic waveforms is also useful, particularly identifying obstructive RP. For example, patients with obstructive RP have blunted waveforms, whereas patients with vasospastic RP have either normal waveforms or a “peaked pulse.” The peaked pulse pattern, first described by Sumner and Strandness, appears to reflect increased vasospastic arterial resistance.⁷⁰

Cold Challenge Testing

The first vascular laboratory test used widely for the objective diagnosis of RP was the measurement of recovery in fingertip temperature after digital exposure to ice water.⁷¹ There are many variations of the cold immersion test with various immersion times and temperatures. Baseline digital temperatures are recorded with a temperature probe at the end of the finger pulp. The hands are then immersed in cold water at 4°C for 20 seconds (Fig. 142.9). The hands are dried, and digital skin temperature is recorded for each finger as the hands and fingers gradually warm to ambient room temperature. The length of time that it takes for the hands to rewarm to baseline is noted by recording finger temperatures or laser Doppler flux at 5-minute intervals until recovery of pre-immersion temperatures. A

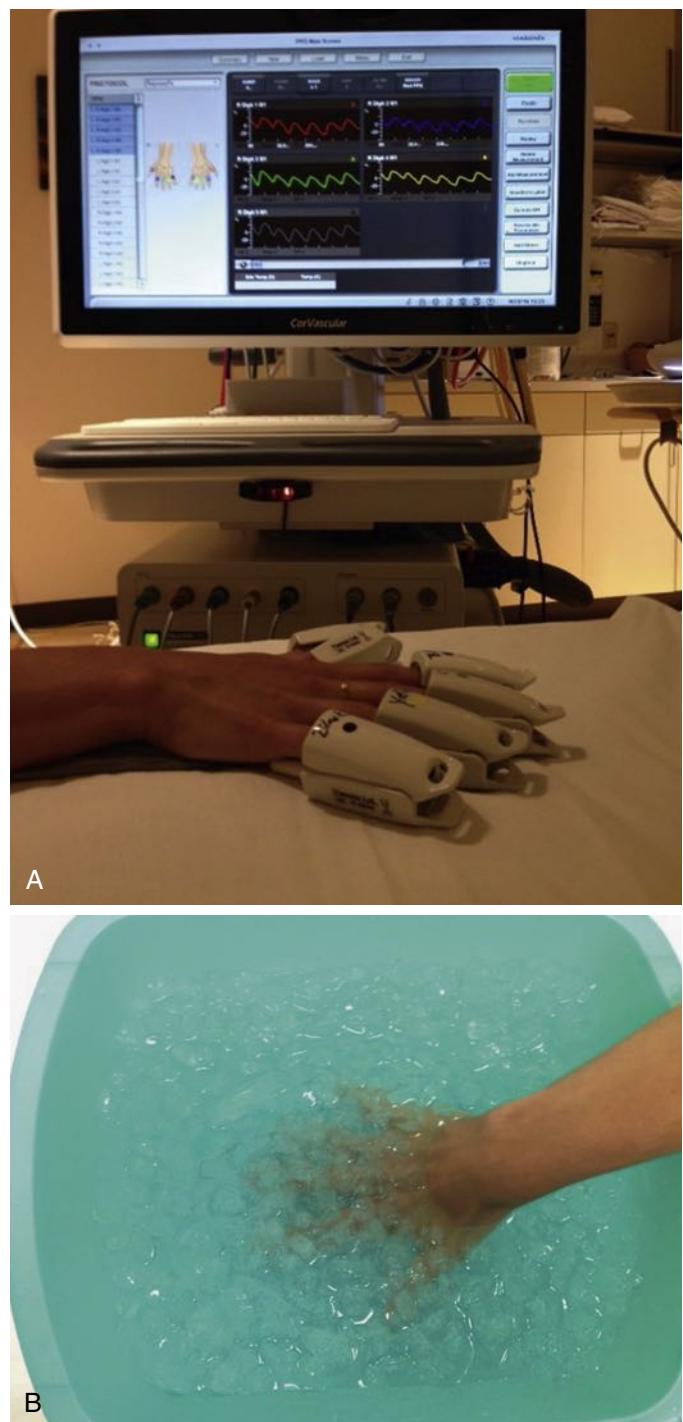


Figure 142.9 (A,B) Photoplethysmogram (PPG) may be completed as part of the work-up for Raynaud phenomenon. PPGs may be combined with a cold challenge. When completed together, a room temperature PPG is done, followed by submersion of the hands in ice cold water for 1 minute or as long as tolerated, then PPGs are done and recorded every minute thereafter until recovery is complete.

delay in rewarming suggests a tendency for vasospasm. Patients with RP typically take more than 10 minutes and sometimes 30 minutes or longer. However, although the ice water immersion test is 100% sensitive, it is only 50% specific and therefore is neither sufficiently accurate nor reproducible for routine clinical use.^{72,73}

Nail-Fold Capillary Microscopy

The superficial capillaries in the nail fold can be visualized with a low-powered microscope or an ophthalmoscope at 40 diopters by applying a drop of immersion oil over the cuticle of the finger to make it translucent. Normal capillaries are seen as regularly spaced hairpin loops with a venous limb and an arterial limb. The arterial limb has a narrower diameter with more rapid flow, and the venous limb has a larger diameter with slower capillary flow.⁷

Abnormal capillaries are seen in scleroderma and mixed CTDs as enlarged, tortuous, and deformed or as loop drop-out causing avascular areas.^{74–76} The presence of abnormal nail folds in patients without CTD is a strong predictor of the subsequent development of CTD. With a mean follow-up of 6.5 years, Meli and colleagues demonstrated that 80% of patients with abnormal nail-fold findings at the time of initial diagnosis of RS eventually developed CTD, primarily scleroderma, CREST, and mixed CTD. Thus, there may be significant prognostic utility in the use of nail-fold capillaroscopy in the early phases of RS.⁷⁷

Serologic Evaluation

Serologic studies may help confirm the diagnosis of CTD and are useful in screening for occult underlying CTD. Several screening tests can be done, and the most useful include ANA and rheumatoid factor (RF). ANA is present in 90%–95% of patients with systemic sclerosis,⁷⁸ but they are not specific for scleroderma and can be present in several other CTDs. A positive ANA raises the suspicion for CTD but does not make the diagnosis. RF is a commonly used diagnostic marker for rheumatoid arthritis.⁷⁹

TREATMENT

Treatment for RP varies greatly, and the natural history differs greatly between primary vasospastic and secondary obstructive causes. The approach to therapy must be individualized according to the patient's symptoms, the frequency of vasospastic attacks, the underlying disease, and the risk for development of ischemic ulceration, gangrene, or digital loss. For most patients with primary RP, there is no cure; however, several simple measures can be effective in reducing the frequency and duration of attacks.

Preventive measures consisting of education, reassurance, and avoidance of exposure to cold constitute the basis for most patients. Management principles can generally be considered in three groups: nonpharmacologic behavioral therapy, pharmacologic treatment, and interventional-surgical procedures. Connective tissue disorders associated with secondary RP are frequently managed with immunosuppression or immunomodulation.

Preventive Measures

Most patients with primary RP have only mild symptoms that do not require the use of vasodilatory medications. Primary RP

is a benign disease, with few patients progressing to digital ulcers or tissue loss. In a longitudinal study from Oregon, digital ulcers occurred in 5% of patients in whom vasospastic RP was initially diagnosed when observed for more than 10 years.⁵⁹ These patients are best managed with a conservative program involving preventive measures, and education and reassurance is the mainstay of therapy.

Simple measures to maintain warmth and avoid cold are effective (Fig. 142.10). Ceramic-impregnated gloves that absorb ambient infrared light to generate heat resulted in significantly improved hand function and visual analog pain scores when compared with a placebo group wearing cotton gloves.⁸⁰ Situations likely to cause vasospasm should be avoided or minimized. Finally, avoiding agents that cause vasoconstriction, such as nicotine and vasoconstricting medications, is also an important aspect of therapy.^{81,82}

Behavioral Therapies and Maneuvers

Temperature biofeedback is a type of mind/body therapy whereby patients are taught methods of self-regulation of skin temperature.⁸³ The primary goal is to teach methods of avoiding RP attacks; however, with training, individuals can learn to reverse the existing vasospasm. Temperature biofeedback has been studied in randomized trials with variable results. Two recent meta-analyses and systematic reviews suggest that biofeedback is not superior to placebo.^{84,85} However, they also concluded that the literature is inconclusive, and more robust trials are needed to further evaluate complementary and alternative therapies.

Pharmacologic Therapy

Pharmacologic therapy is indicated in patients who have failed conservative therapy. Some patients will require medications only during the colder winter months. The goal of



Figure 142.10 A vascular mitten protects and maintains warmth of the hands. Patients with critical hand and finger ischemia can have further compromise in distal perfusion because of cool ambient room temperature causing vasoconstriction. A vascular mitten keeps the hands at body temperature and maximizes distal finger blood flow by avoiding cold-induced vasoconstriction.

pharmacologic therapy is to decrease the frequency and severity of attacks rather than cure the underlying disease, and medications may be useful for both primary and secondary RP. However, patients with secondary RP often have fixed obstructive arterial disease, and vasodilators are less effective or at times have no benefit at all.

A number of medications have been used for RP (Table 142.1).⁸⁶ Choosing the best medication is difficult given the lack of large prospective, randomized, double-blind studies comparing the efficacy of different medications. There is also

a significant placebo effect in published clinical trials ranging from 20% to 40%,⁸⁷ which needs to be considered when interpreting the results of uncontrolled trials. Additionally, most clinical trials rely on the patient's self-assessment of the frequency and severity of RP.

Calcium-Channel Blockers

Calcium-channel blockers are the most extensively researched medications and remain first-line therapy for RP. Nifedipine is considered by many to be the drug of first

TABLE 142.1 Medical Therapy for Raynaud Phenomenon

Drug Class	Drug Names	Dosage	Results	Most Frequent Side Effects
Calcium channel blockers (dihydropyridine)	Nifedipine	10–30 mg PO qd–tid	33%–66% reduction in frequency and severity of attacks; most extensively studied medication	Hypotension, flushing, edema, palpitations, dizziness (similar for entire class of drugs)
	Nicardipine	20–50 mg PO bid	Mixed results compared with placebo	
	Amlodipine	10 mg PO qd	27% reduction in frequency of attacks	
	Felodipine	5–20 mg PO qd	Similar to nifedipine	
Alpha 1 receptor antagonists	Prazosin	1mg PO tid	1–2 fewer attacks per day, decreased duration; modest benefit in secondary RP	
	Terazosin	1mg PO qhs	Not systematically studied	Orthostatic hypotension; palpitations
Renin–angiotensin system mediators (ACE inhibitors)	Captopril	12.5–25 mg PO bid–tid	Improved finger blood flow; symptom relief mixed	Dry cough, headaches, fatigue, dizziness (similar for entire drug class)
	Enalapril	20 mg PO qd	Mixed results in clinical trials	
	Quinapril	80 mg PO qd	No clinical benefit	
Renin–angiotensin system mediators (angiotensin II receptor blockers)	Losartan	12.5–50 mg PO qd	Up to 50% reduction in severity and frequency of attacks	Dizziness
Serotonin reuptake inhibitors	Fluoxetine	20–40 mg PO qd	Significant decrease in severity and frequency of attacks vs. nifedipine	Headaches, nausea, palpitations, lethargy
Phosphodiesterase V inhibitors	Sildenafil	50 mg PO qd–bid Extended release 100–200 mg qd	Decreased duration and frequency of attacks; improvement of capillary blood flow; benefit primarily in secondary RP	Headache, flushing, nausea, muscle pain, dyspepsia, dizziness (similar for all drugs in this class)
	Tadalafil	20 mg every other day	Decreased frequency and duration of attacks and improved ulcer healing as add-on therapy; less beneficial as monotherapy	
	Vardenafil	10 mg PO bid	Improved digital blood flow and symptoms in secondary RP	
Nitrates	Topical nitroglycerin (MQX-503)	0.5 g of gel up to four times a day	Improved Raynaud Condition Score, no change in duration or frequency of attacks	Headache, upper respiratory tract infection; dizziness
Prostaglandins	Epoprostenol	1–2 ng/kg/min IV	Decreased severity of symptoms in patients with scleroderma and pulmonary hypertension	Flushing, headache, nausea, vomiting, hypotension
	Iloprost	0.5–2 ng/kg/min IV or 50 µm PO bid	IV form effective in ulcer healing and reducing symptoms; PO form not more effective than placebo	Headache, nausea, vomiting
Endothelin receptor antagonist	Bosentan	62.5 mg PO bid	Decreased new ulcer formation in patients with scleroderma. No effect on healing of existing ulcers	Elevated hepatic transaminases, peripheral edema

ACE, angiotensin-converting enzyme; *bid*, twice a day; *IV*, intravenous; *PO*, orally; *qd*, once a day; *qhs*, every evening; *tid*, three times a day.

From Landry G. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg*. 2013;57:1710–1716.

choice for RP. One multicenter, randomized controlled trial of 313 patients with primary RP treated with sustained-release nifedipine compared with placebo showed a 66% reduction in frequency of attacks.⁸⁸ In addition, a meta-analysis of 12 randomized, controlled trials demonstrated an overall reduction in severity of attacks graded on visual analog scale of 33%, with an average of 2.8 to 5.0 fever attacks per week in patients treated with nifedipine.⁸⁹ However, a recent Cochrane review found only moderate quality evidence showing that oral calcium-channel blockers are minimally effective in the treatment of primary RP as measured by frequency of attacks. Participants experienced 1.72 fewer attacks per week on calcium-channel blockers compared to placebo.⁹⁰ Other calcium-channel blockers may be used. Drugs in the dihydropyridine class are more potent vasodilators than the nondihydropyridine class, but they are more frequently associated with side effects.^{91–93}

Alpha Adrenergic Blockers

Sympathetic nerve stimulation results in norepinephrine release, which acts on the α_1 receptor located on vascular smooth muscle, causing vasoconstriction. This action is inhibited by α_1 -selective blockers. Prazosin is a selective α_1 -adrenergic antagonist that significantly reduces the number of attacks in both primary and secondary RP.⁹⁴ In a double-blind, placebo-controlled, crossover study of 24 patients, prazosin was reported superior to placebo in the treatment of RP.⁹⁵ Terazosin is a long-acting form of prazosin, which allows once-daily dosing, and has been shown to be effective therapy for treatment for RS by decreasing the number, intensity, and duration of attacks.⁹⁶

In contrast, the results for α_2 antagonist have been mixed. OPC-28326, a selective α_2 antagonist, improved skin temperature recovery in patients with scleroderma compared to placebo.⁹⁷ However, more recently, ORM-12741, an α_2c adrenoceptor antagonist, was found to increase skin temperature recovery time.⁴²

Prostaglandins and Analogues

Prostacyclins are vasodilators that have been used to treat critical digital ischemia secondary to fixed occlusive disease. Epoprostenol is a naturally occurring prostaglandin given as an intravenous infusion. In one randomized controlled trial significant benefit was achieved in skin temperature and laser Doppler flow, but benefit was not sustained.⁹⁸ Iloprost is a prostacyclin analog reported to reduce the severity, frequency, and duration of RP attacks and promote healing of ischemic ulcers. Intravenous iloprost was directly compared with oral nifedipine in two randomized controlled trials. Forty-six patients with systemic sclerosis were randomized in one, and 12 patients with systemic sclerosis in the other. Although medication regimen differed, both showed reduced mean number, duration, severity of RP attacks, improved ulcer healing, and increased hand temperature and blood flow.^{99,100} Unfortunately, oral formulations of iloprost have not shown similar benefit.^{101,102}

Phosphodiesterase Inhibitors

The phosphodiesterase type 5 (PDE5) inhibitors are selective inhibitors of cGMP-specific PDE5, which increase cGMP, and result in enhanced cGMP-dependent micro- and macro-vascular dilatation. In a placebo-controlled, double blind crossover trial comparing 4 weeks of therapy with sildenafil, 50 mg twice daily, versus placebo in 16 patients, the frequency of RP attacks was reduced by 33%, and the duration of attacks was reduced by 44% in the sildenafil group.¹⁰³ Similar benefits were also reported in a randomized, controlled trial comparing long-acting sildenafil with placebo.¹⁰⁴ However, a single dose prior to anticipated cold exposure has not been shown to be effective.¹⁰⁵ Tadalafil and vardenafil have longer half-lives than sildenafil and have been less well studied in RP but have shown benefit in limited trials.^{106–108} Topical sildenafil has also been evaluated in RP with increased hand blood flow noted on ultrasound and no adverse effects.¹⁰⁹

Endothelin Inhibitors

Endothelin is a potent endogenous vasoconstrictor. Bosentan is an endothelin receptor antagonist currently used to treat pulmonary hypertension. In the RAPIDS-2 trial, bosentan was shown to significantly decrease the incidence of new digital ulcers in patients with scleroderma, although there was no change in rates of ulcer healing, in pain, or in disability.¹¹⁰

Nitrates

Nitrates have been used in the treatment of RP as oral, topical, or intravenous preparations, but, in general, they are not first-line therapy due to potential side effects, particularly headaches and hypotension. Topical nitrates in the form of 2% nitroglycerine ointment or as a transdermal patch can be applied locally to an ischemic finger, and have been shown to be effective in the treatment of RS in randomized controlled trials.^{111,112} A recent meta-analysis of 7 placebo-controlled trials of topical nitrates did demonstrate significant efficacy in the treatment of both primary and secondary RP.¹¹³

Other Medications

ACE inhibitors, angiotensin II receptor blockers, and serotonin reuptake inhibitors have been used to treat RP. Captopril has been the most extensively used ACE inhibitor. In a randomized controlled crossover trial of 15 subjects with primary RP, captopril caused a significant increase in cutaneous blood flow, but there was no change in frequency or severity of RP attacks.¹¹⁴ Losartan, an angiotensin II receptor blocker, was found to be more effective than nifedipine in reducing the frequency and severity of vasospastic episodes in a randomized controlled trial in patients with primary RP and those with secondary RP due to systemic sclerosis following 12 weeks of therapy.¹¹⁵ Fluoxetine, a serotonin reuptake inhibitor, was shown to reduce the frequency and severity of attacks in both primary and secondary RP in a randomized crossover trial with nifedipine (Fig. 142.11).¹¹⁶



Figure 142.11 This patient was evaluated for acute ischemia of the fingertip. She was found to have positive antinuclear antibody and anticentromere antibody. An angiogram showed severe digital artery occlusive disease consistent with a connective tissue disease. Topical nitroglycerin ointment often fails to improve blood flow in the setting of critical ischemia because of severe underlying fixed small-vessel disease. The patient was treated with multiple agents, including oral, topical, and intravenous vasodilators; antiplatelet therapy; doxazosin; and nifedipine.

Surgical Therapy

Surgical intervention tends to be reserved for patients who have failed conservative and pharmacologic therapy. Surgical therapies include botulinum toxin injection, sympathetic block, thoracoscopic sympathectomy, digital sympathectomy, and spinal cord stimulator (Table 142.2). Local debridement of dead tissue or removal of the fingernail is sometimes necessary. Partial or complete phalangeectomy may be necessary in 10% to 20% of patients with digital ulcers or gangrene.⁵⁹

Sympathectomy

Sympathectomy is rarely if ever indicated in patients with primary RP, in which recurrence rates are high, but it may be effective in some patients who have critical ischemia of the digits. The evidence regarding thoracic sympathectomy was summarized by Coveliers and associates,¹¹⁷ who found thoracic sympathectomy may maximize tissue preservation or prevent amputation. Currently, thoracoscopic sympathectomy has supplanted open cervicothoracic sympathectomy as a technique of choice. Coveliers more recently showed moderate long-term efficacy of thoracoscopic sympathectomy in 35 patients with both PRP and secondary systemic disorders.¹¹⁸

More favorable results have been seen in lumbar sympathectomy, with long-term symptomatic relief noted in more than 90% of patients undergoing this procedure.¹¹⁹ Lumbar sympathectomy remains a viable option in the rare patient with severely symptomatic lower extremity vasospasm.

Adventitial stripping of hand and digital arteries has been successful in healing ulcers and improving ischemic pain.^{120,121} Results are anecdotal with no controlled trials comparing digital arterial sympathectomy with other less invasive treatment modalities, and in general, arterial sympathectomy should be reserved for refractory cases with risk for tissue loss.

TABLE 142.2 Surgical and Other Invasive Therapy for Raynaud Phenomenon

Invasive Therapy	Results
Botulinum toxin	Improved pain and ulcer healing in small case series
Sympathetic block	Improved ulcer healing in small case series
Thoracoscopic sympathectomy	High recurrence rate in primary RP; improved ulcer healing and pain control in selected patients with secondary RP
Digital sympathectomy	Anecdotal reports of improved pain and ulcer healing
Spinal cord stimulators	Reduced pain and improved ulcer healing in small case series

RP, Raynaud phenomenon.

From Landry G. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg*. 2013;57:1710–1716.

Botulinum Toxin

Botulinum toxin is a commonly used medication that primarily inhibits muscle contraction. Botulinum toxin-A (BoNT-A) is injected into the interstitial space around the digital neurovascular bundles causing a chemical sympathectomy. Recently, increased use of botulinum toxin in the treatment of RP has been reported. Case series using BoNT-A injections demonstrated reduced pain, improved ulcer healing and increased blood flow in both primary and secondary RP.^{122,123} A randomized, double-blind, placebo-controlled trial randomized patients with Raynaud phenomenon secondary to scleroderma to receive either 50 units BoNT-A or sterile saline. Patients were followed with laser Doppler imaging, patient-reported clinical outcomes, and physical exam. While there was a reduction in average blood flow in those treated with BoNT-A as compared to placebo at one month, this difference was not significant at four months. Clinical outcomes such as Raynaud's Condition Score, McCabe Cold Sensitivity Score, and pain on a visual analog scale improved slightly in the BoNT-A-treated group.¹²⁴

In a randomized controlled trial studying botulinum toxin-B (BoNT-B) for treatment of Raynaud phenomenon, 45 patients with systemic sclerosis and Raynaud phenomenon were randomized into 4 groups (control or 250, 1000, or 2000 international units (U) BoNT-B). At 4 weeks post-injection pain/numbness visual analog scores, Raynaud's score, and the numbers of digital ulcers in the 1000 and 2000 U BoNT-B groups were significantly lower than control. Skin temperature recovery in the group treated with 2000 U BoNT-B was significantly improved.¹²⁵

Nerve Stimulation

Transcutaneous nerve stimulation has been used in some patients to induce vasodilatation with varying results.¹²⁶ In addition, spinal cord stimulators are occasionally indicated for the treatment of various intractable pain syndromes of the upper

extremities. A spinal cord stimulator may reduce pain and promote ulcer healing in severe cases of secondary RP with trophic lesions.

Alternative Therapies

Acupuncture may be of benefit in some patients. In a small, randomized trial, acupuncture was found to be effective in reducing the frequency and severity of attacks in patients with PRP. The mechanism of action is believed to be stimulation of sensory nerves, causing release of vasodilators such as substance P and calcitonin gene-related peptide.¹²⁷

Seredine, a high-potency extract of ginkgo biloba, has had mixed results in the treatment of PRP. A randomized placebo-controlled trial in patients with PRP showed a 56% drop in event rates in the group treated with ginkgo compared to placebo.¹²⁸ However, more recently, a placebo-controlled, double-blind, pilot study of 41 patients randomized to either ginkgo biloba special extract EGb 761 versus placebo for 10 weeks found no statistically significant reduction in clinically relevant symptoms.¹²⁹

Fish oil and arginine have also been investigated. Fish oil failed to demonstrate any benefit in patients with SRP in a small controlled trial.¹³⁰ Arginine, which is a substrate for NO synthesis and has a theoretical benefit of improving endothelial dysfunction, has failed to show benefit in patients with both primary and secondary RP.^{131,132}

Laser therapy has been investigated as a potential treatment for a variety of vascular and rheumatologic disorders including RP. A randomized controlled trial evaluated low-level laser therapy with 685-nm wavelength diode laser versus sham in 48 patients with PRP.¹³³ They found the frequency and intensity of RP attacks were significantly reduced in the laser-treated group. More recently, a group in Poland studied the effects of multiwave locked system (MLS) laser therapy on clinical features, microvascular changes in nail-fold videocapillaroscopy (NVC), and circulating modulators, such as vascular endothelial growth factor (VEGF), and angiopoietin 2 (Ang-2) in

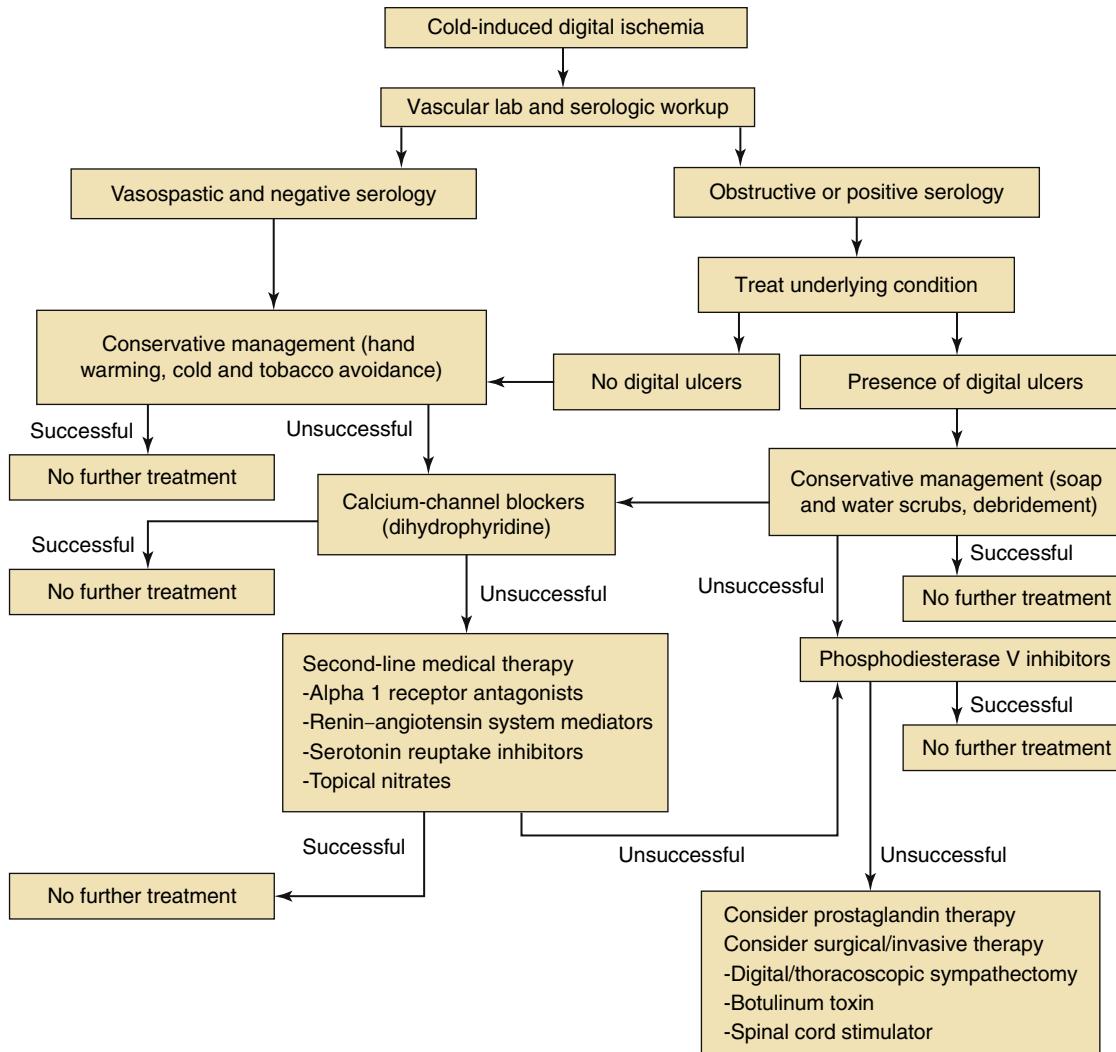
patients with primary and secondary RP.¹³⁴ All patients with RP received MLS laser irradiation for 3 weeks. After 3 weeks, patients with RP reported a decrease in the number, mean duration, and pain intensity of attacks. In addition, 65% of patients with primary and 35% of patient with secondary RP were noted to have an increase in the loop number and/or a reduction in avascular areas in NVC. Patients with RP had higher levels of both VEGF, and Ang-2 compared to matched controls prior to laser therapy; however, post-therapy Ang-2 levels were found to be reduced in patients with RP. The authors concluded that Ang-2 may be a useful marker of microvascular abnormalities in RP patients treated with laser therapy.

In a study looking at ozone therapy, 50 female patients with systemic sclerosis from recurrent Raynaud phenomenon with digital ulcers were randomized to receive either noninvasive oxygen–ozone treatments plus calcium-channel blockers or calcium-channel blockers only. The group treated with ozone therapy had a significantly higher effective healing rate (96% vs. 44% in control) and a significantly greater wound size reduction. The ozone therapy group was found to have significantly higher levels of vascular endothelial growth factor (VEGF) and lower levels of endothelin-1 type A receptor (ETAR) leading the authors to postulate that ozone treatments work at the molecular level by induction of VEGF and downregulation of ETAR.¹³⁵

High-intensity interval training (HIIT) has also been studied as a therapy and was shown to increase peak oxygen uptake, improve life satisfaction, and decrease discomfort and pain due to Raynaud phenomenon. Specific types of exercise such as arm-cranking was shown to have the greatest effect on endothelial-dependent vasodilation.¹³⁶

Another study investigated the use of extracorporeal shock wave lithotripsy (ESWT), a minimally invasive therapy, in the treatment of patients with systemic sclerosis and Raynaud phenomenon and found that ulcer size and number decreased and average scores for clinical indicators (Health Assessment questionnaire, EuroQOL 5 dimensions, and PainVision system) improved with ESWT.¹³⁷

CHAPTER ALGORITHM



SELECTED KEY REFERENCES

- Carpentier PH, Satger B, Poensin D, et al. Incidence and natural history of Raynaud phenomenon: a long-term follow-up (14 years) of a random sample from the general population. *J Vasc Surg.* 2006;44(5):1023–1028.
- Coveliers H, Hoexum F, Rauwerda JA, et al. Endoscopic thoracic sympathectomy for upper limb ischemia. A 16 year follow-up in a single center. *Surgeon.* 2016;14(5):265–269.
- Ennis H, Hughes M, Anderson ME, et al. Calcium channel blockers for primary Raynaud's phenomenon. *Cochrane Database Syst Rev.* 2016;(2): CD002069.
- Garner R, Kumari R, Lanyon P, et al. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. *BMJ Open.* 2015;5(3):e006389.
- Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. *Nat Rev Rheumatol.* 2012;8(8):469–479.
- Kuryliszyn-Moskal A, Kita J, Dakowicz A, et al. The influence of Multiwave Locked System (MLS) laser therapy on clinical features, microcirculatory abnormalities and selected modulators of angiogenesis in patients with Raynaud's phenomenon. *Clin Rheumatol.* 2015;34(3):489–496.
- Landry G. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg.* 2013;57:1710–1716.
- Landry GJ, Edwards JM, McLafferty RB, et al. Long-term outcome of Raynaud's syndrome in a prospectively analyzed patient cohort. *J Vasc Surg.* 1996;23(1):76–85; discussion 85–76.
- Scorza R, Caronni M, Mascagni B, et al. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomized, controlled study. *Clin Exp Rheumatol.* 2001;19(5):503–508.
- Suter LG, Murabito JM, Felson DT, et al. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *Am J Med.* 2007;120(3):264–271.
- Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med.* 2016;375:556–565.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Raynaud M. On local asphyxia and symmetrical gengrene of the extremities. *Arch Neurol.* 1969;20(6):669–672.
2. Carpentier PH, Satger B, Poensin D, et al. Incidence and natural history of Raynaud phenomenon: A long-term follow-up (14 years) of a random sample from the general population. *J Vasc Surg.* 2006;44(5):1023–1028.
3. Valter I, Maricq HR. Prevalence of Raynaud phenomenon in Tartu and Tartumaa, southern Estonia. *Scand J Rheumatol.* 1997;26(2):117–124.
4. Garner R, Kumari R, Lanyon P, et al. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. *BMJ Open.* 2015;5(3):e006389.
5. Silman A, Holligan S, Brennan P, et al. Prevalence of symptoms of Raynaud's phenomenon in general practice. *BMJ.* 1990;301(6752):590–592.
6. Suter LG, Murabito JM, Felson DT, et al. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum.* 2005;52(4):1259–1263.
7. Mueller M, Gschwandtner ME, Gamper J, et al. Chronic inflammation predicts long-term mortality in patients with Raynaud's phenomenon. *J Intern Med.* 2018;283:293–302.
8. Koman LA, Smith BP, Smith TL. Stress testing in the evaluation of upper-extremity perfusion. *Hand Clin.* 1993;9(1):59–83.
9. Coleman SS, Anson BJ. Arterial patterns in the hand based upon a study of 650 specimens. *Surg Gynecol Obstet.* 1961;113:409–424.
10. Maslarski I. The artery blood supply variant of the upper limb. *Clujul Med.* 2015;88(4):545–549.
11. Greenfield AD, Shepherd JT. A quantitative study of the response to cold of the circulation through the fingers of normal subjects. *Clin Sci.* 1950;9(3):323–347.
12. Coffman JD. Total and nutritional blood flow in the finger. *Clin Sci.* 1972;42(3):243–250.
13. Lewis T. Observations upon reactions of vessels of human skin to cold. *Heart.* 1930;15:177.
14. Burton ATR. A study of the adjustment of peripheral vascular tone to the requirements of the regulation of body temperature. *Am J Physiol.* 1940;129:565.
15. Engelhart M, Kristensen JK. Raynaud's phenomenon: blood supply to fingers during indirect cooling, evaluated by laser Doppler flowmetry. *Clin Physiol.* 1986;6(6):481–488.
16. Marshall RJ, Shepherd JT, Thompson ID. Vascular responses in patients with high serum titres of cold agglutinins. *Clin Sci.* 1953;12(3):255–264.
17. Lewis T. Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers, a variety of Raynaud's disease. *Heart.* 1929;15:7.
18. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. *Nat Rev Rheumatol.* 2012;8(8):469–479.
19. Furchtgott RF, Vanhoutte PM. Endothelium-derived relaxing and contracting factors. *FASEB J.* 1989;3(9):2007–2018.
20. Luscher TTV. *Modulator of Cardiovascular Function. The Endothelium.* Boca Raton: CRC Press; 1990.
21. Shepherd JT, Vanhoutte PM. Endothelium-derived relaxing (EDRF) and contracting factors (EDCF) in the control of cardiovascular homeostasis: The pioneering observations. In: Rubanyi GM, ed. *Cardiovascular Significance of Endothelium-Derived Vasoactive Factors.* Mount Kisco, NY; 1991.
22. Cooke JP, Marshall JM. Mechanisms of Raynaud's disease. *Vasc Med.* 2005;10(4):293–307.
23. Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology.* 2005;44(5):587–596.
24. Smith PJW, Ferro CJ, McQueen DS, et al. Impaired cholinergic dilator response of resistance arteries isolated from patients with Raynaud's disease. *Br J Clin Pharmacol.* 2001;47(5):507–513.
25. Khan F, Litchfield SJ, McLaren M, et al. Oral L-arginine supplementation and cutaneous vascular responses in patients with primary Raynaud's phenomenon. *Arthritis Rheum.* 1997;40(2):352–357.
26. Allanore Y, Borderie D, Hilliquin P, et al. Low levels of nitric oxide (NO) in systemic sclerosis: inducible NO synthase production is decreased in cultured peripheral blood monocyte/macrophage cells. *Rheumatology (Oxford).* 2001;40(10):1089–1096.
27. Kundu D, Abraham D, Black CM, et al. Reduced levels of S-nitrosothiols in plasma of patients with systemic sclerosis and Raynaud's phenomenon. *Vasc Pharmacol.* 2014;63(3):178–181.
28. Singh S, De Trafford JC, Baskerville PA, et al. Response of digital arteries to endothelium dependent and independent vasodilators in patients with Raynaud's phenomenon. *Eur J Clin Invest.* 1995;25(3):182–185.
29. Fyhrquist F, Saajanmaa O, Metsarinne K, et al. Raised plasma endothelin-I concentration following cold pressor test. *Biochem Biophys Res Commun.* 1990;169(1):217–221.
30. Smyth AE, Bell AL, Bruce IN, et al. Digital vascular responses and serum endothelin-1 concentrations in primary and secondary Raynaud's phenomenon. *Ann Rheum Dis.* 2000;59(11):870–874.
31. Kawaguchi Y, Takagi K, Hara M, et al. Angiotensin II in the lesional skin of systemic sclerosis patients contributes to tissue fibrosis via angiotensin II type 1 receptors. *Arthritis Rheum.* 2004;50(1):216–226.
32. Coppo M, Boddi M, Poggesi L, et al. Exaggerated local hand sympathetic but not renin-angiotensin system activation in patients with primary Raynaud's phenomenon. *Microvasc Res.* 2006;71(2):128–134.
33. Rosch J, Porter JM, Gralino BJ. Cryodynamic hand angiography in the diagnosis and management of Raynaud's syndrome. *Circulation.* 1977;55(5):807–814.
34. Flavahan NA. Regulation of vascular reactivity in scleroderma: new insights into Raynaud's phenomenon. *Rheum Dis Clin North Am.* 2008;34(1):81–87.
35. Flavahan NA, Lindblad LE, Verbeuren TJ, et al. Cooling and alpha 1- and alpha 2-adrenergic responses in cutaneous veins: role of receptor reserve. *Am J Physiol.* 1985;249(5 Pt 2):H950–H955.
36. Flavahan NA, Cooke JP, Shepherd JT, et al. Human postjunctional alpha-1 and alpha-2 adrenoceptors: differential distribution in arteries of the limbs. *J Pharmacol Exp Ther.* 1987;241(2):361–365.
37. Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. *Nat Rev Rheumatol.* 2015;11(3):146–158.
38. Bailey SR. Rho kinase mediates cold-induced constriction of cutaneous arteries: role of 2C-adrenoceptor translocation. *Circ Res.* 2004;94(10):1367–1374.
39. Chotani MA, Flavahan NA. Intracellular alpha(2C)-adrenoceptors: storage depot, stunted development or signaling domain? *Biochim Biophys Acta.* 2011;1813(8):1495–1503.
40. Flavahan NA, Flavahan S, Mitra S, et al. The vasculopathy of Raynaud's phenomenon and scleroderma. *Rheum Dis Clin North Am.* 2003;29(2):275–291. vi.
41. Freedman RR, Baer RP, Mayes MD. Blockade of vasospastic attacks by alpha 2-adrenergic but not alpha 1-adrenergic antagonists in idiopathic Raynaud's disease. *Circulation.* 1995;92(6):1448–1451.
42. Herrick AL, Murray AK, Ruck A, et al. A double-blind, randomized, placebo-controlled crossover trial of the α_{2C} -adrenoceptor antagonist ORM-12741 for prevention of cold-induced vasospasm in patients with systemic sclerosis. *Rheumatology.* 2014;53:948–952.
43. Cooke JP, Creager MA, Osmundson PJ, et al. Sex differences in control of cutaneous blood flow. *Circulation.* 1990;82(5):1607–1615.
44. Eid AH, Maiti K, Mitra S, et al. Estrogen increases smooth muscle expression of alpha2C-adrenoceptors and cold-induced constriction of cutaneous arteries. *Am J Physiol Heart Circ Physiol.* 2007;293(3):H1955–H1961.
45. Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. *Arthritis Rheum.* 1996;39(7):1189–1191.
46. Biondi ML, Marasini B, Bianchi E, et al. Plasma free and intraplatelet serotonin in patients with Raynaud's phenomenon. *Int J Cardiol.* 1988;19(3):335–339.
47. Ames PR, Lupoli S, Alves J, et al. The coagulation/fibrinolysis balance in systemic sclerosis: evidence for a haematological stress syndrome. *Rheumatology.* 1997;36(10):1045–1050.
48. Maricq HR, Weinrich MC, Keil JE, et al. Prevalence of Raynaud phenomenon in the general population. A preliminary study by questionnaire. *J Chronic Dis.* 1986;39(6):423–427.

49. Suter LG, Murabito JM, Felson DT, et al. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *Am J Med.* 2007;120(3):264–271.
50. Shimol JB, Sheinberg O. Development of Raynaud phenomenon following use of medical cannabis. *J Clin Rheumatol.* 2021;27(8S):S430–S431.
51. Taylor W, Wasserman D, Behrens V, et al. Effect of the air hammer on the hands of stonemasons. The limestone quarries of Bedford, Indiana, revisited. *Br J Ind Med.* 1984;41(3):289–295.
52. McLafferty RB, Edwards JM, Ferris BL, et al. Raynaud's syndrome in workers who use vibrating pneumatic air knives. *J Vasc Surg.* 1999;30:1–7.
53. Stoyneva Z, Lyapina M, Tzvetkov D, Vodenicharov E. Current pathophysiological views on vibration-induced Raynaud's phenomenon. *Cardiovasc Res.* 2003;57(3):615–624.
54. Sonza A, Robinson CC, Achaval M, Zaro MA. Whole body vibration at different exposure frequencies: infrared thermography and physiological effects. *Scientific World Journal.* 2015;2015:452657.
55. Nilsson T, Burstrom L, Hagberg M. Risk assessment of vibration exposure and white fingers among plasters. *Int Arch Occup Environ Health.* 1989;61(7):473–481.
56. Feleke E, Lyngstam O, Rastam L, et al. Complaints of cold extremities among patients on antihypertensive treatment. *Acta Med Scand.* 1983;213(5):381–385.
57. Steiner JA, Cooper R, Gear JS, et al. Vascular symptoms in patients with primary Raynaud's phenomenon are not exacerbated by propranolol or labetalol. *Br J Clin Pharmacol.* 1979;7(4):401–403.
58. Khouri C, Blaise S, Carpenter P, et al. Drug-induced Raynaud's phenomenon: beyond β-adrenoceptor blockers. *Br J Clin Pharm.* 2016;82:6–16.
59. Landry GJ, Edwards JM, McLafferty RB, et al. Long-term outcome of Raynaud's syndrome in a prospectively analyzed patient cohort. *J Vasc Surg.* 1996;23(1):76–85; discussion 85–86.
60. Miller D, Waters DD, Warnica W, et al. Is variant angina the coronary manifestation of a generalized vasospastic disorder? *N Engl J Med.* 1981;304(13):763–766.
61. LeRoy EC, Medsger Jr TA. Raynaud's phenomenon: a proposal for classification. *Clin Exp Rheumatol.* 1992;10(5):485–488.
62. Wigley FM. Clinical practice. Raynaud's Phenomenon. *N Engl J Med.* 2002;347(13):1001–1008.
63. Ratchford EV, Evans NS. Raynaud's phenomenon. *Vasc Med.* 2015;20(3):269–271.
64. Maverakis E, Patel F, Kronenberg DG, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. *J Autoimmun.* 2014;48–49:60–65.
65. Ouriel K. Noninvasive diagnosis of upper extremity vascular disease. *Semin Vasc Surg.* 1998;11(2):54–59.
66. Lee SI, Lee SY, Yoo WH. The usefulness of power Doppler ultrasonography in differentiating primary and secondary Raynaud's phenomenon. *Clin Rheumatol.* 2006;25(6):814–818.
67. Hirai M, Nielsen SL, Lassen NA. Blood pressure measurement of all five fingers by strain gauge plethysmography. *Scand J Clin Lab Invest.* 1976;36(7):627–632.
68. Krahenbuhl B, Nielsen SL, Lassen NA. Closure of digital arteries in high vascular tone states as demonstrated by measurement of systolic blood pressure in the fingers. *Scand J Clin Lab Invest.* 1977;37(1):71–76.
69. Greenfield LJ, Rajagopalan S, Olin JW. Upper extremity arterial disease. *Cardiol Clin.* 2002;20(4):623–631.
70. Sumner DS, Strandness DE Jr. An abnormal finger pulse associated with cold sensitivity. *Ann Surg.* 1972;175(2):294–298.
71. Porter JM, Snider RL, Bardana EJ, et al. The diagnosis and treatment of Raynaud's phenomenon. *Surgery.* 1975;77(1):11–23.
72. Bartelink ML, Wollersheim H, Jansen RW, et al. Reproducibility of the finger cooling test. *Microvasc Res.* 1993;45(1):65–73.
73. Bartelink ML, Wollersheim H, Leesmans E, et al. A standardized finger cooling test for Raynaud's phenomenon: diagnostic value and sex differences. *Eur Heart J.* 1993;14(5):614–622.
74. Maricq HR. Capillary abnormalities, Raynaud's phenomenon, and systemic sclerosis in patients with localized scleroderma. *Arch Dermatol.* 1992;128(5):630–632.
75. Dolezalova P, Young SP, Bacon PA, et al. Nailfold capillary microscopy in healthy children and in childhood rheumatic diseases: a prospective single blind observational study. *Ann Rheum Dis.* 2003;62(5):444–449.
76. Smith V, Herrick AL, Ingegnoli F, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev.* 2020;19(3):102458.
77. Meli M, Gitzelmann G, Koppensteiner R, et al. Predictive value of nailfold capillaroscopy in patients with Raynaud's phenomenon. *Clin Rheumatol.* 2006;25(2):153–158.
78. Stochmal A, Czuwara J, Trojanowska M, et al. Antinuclear antibodies in systemic sclerosis: an update. *Clin Rev Allerg Immun.* 2020;58:40–51.
79. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007;146(11):797–808.
80. Ko GD, Berbrayer D. Effect of ceramic-impregnated "thermoflow" gloves on patients with Raynaud's syndrome: randomized, placebo-controlled study. *Altern Med Rev.* 2002;7(4):328–335.
81. Dreyfuss D, Calif E, Stahl S. The adverse effects of smoking on the hands. *Harefuah.* 2015;154(5):327–329, 338.
82. Goodfield MJ, Hume A, Rowell NR. The acute effects of cigarette smoking on cutaneous blood flow in smoking and non-smoking subjects with and without Raynaud's phenomenon. *Br J Rheumatol.* 1990;29(2):89–91.
83. Karavidas MK, Tsai PS, Yucha C, McGrady A, et al. Thermal biofeedback for primary Raynaud's phenomenon: a review of the literature. *Appl Psychophysiol Biofeedback.* 2006;31(3):203–216.
84. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology (Oxford).* 2009;48(7):791–795.
85. Daniels J, Pauling JD, Eccleston C. Behaviour change interventions for the management of Raynaud's phenomenon: a systematic literature review. *BMJ Open.* 2018;8(12):e024528.
86. Landry GJ. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg.* 2013;57:1710–1716.
87. Hummers LK, Wigley FM. Management of Raynaud's phenomenon and digital ischemic lesions in scleroderma. *Rheum Dis Clin North Am.* 2003;29(2):293–313.
88. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med.* 2000;160(8):1101–1108.
89. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford).* 2005;44(2):145–150.
90. Ennis H, Hughes M, Anderson ME, et al. Calcium channel blockers for primary Raynaud's phenomenon. *Cochrane Database Syst Rev.* 2016;(2):CD002069.
91. La Civita L, Pitaro N, Rossi M, et al. Amlodipine in the treatment of Raynaud's phenomenon. *Br J Rheumatol.* 1993;32:524–525.
92. Wollersheim H, Thien T. Double-blind placebo-controlled crossover study of nicardipine in the treatment of Raynaud's phenomenon. *J Cardiovasc Pharmacol.* 1991;18:813–818.
93. Schmidt JF, Valentin N, Nielsen SL. The clinical effect of felodipine and nifedipine in Raynaud's phenomenon. *Eur J Clin Pharmacol.* 1989;37:191–192.
94. Harding SE, Tingey PC, Pope J, et al. *Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database of Systematic Reviews.* Wiley-Blackwell; 1998.
95. Wollersheim H, Thien T, Fennis J, et al. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther.* 1986;40:219–225.
96. Paterna S, Pinto A, Arrosturo A, et al. Raynaud's phenomenon: effects of terazosin. *Minerva Cardioangiolog.* 1997;45:215–221.

97. Wise RA, Wigley FM, White B, et al. Efficacy and tolerability of a selective alpha(2C)-adrenergic receptor blocker in recovery from cold-induced vasospasm in scleroderma patients: a single-center, double-blind, placebo-controlled, randomized crossover study. *Arthritis Rheum.* 2004;50(12):3994–4001.
98. Kingma K, Wollersheim H, Thien T. Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. *J Cardiovasc Pharmacol.* 1995;26:388–393.
99. Rademaker M, Cooke ED, Almond NE, et al. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ.* 1989;298(6673):561–564.
100. Scorz R, Caronni M, Mascagni B, et al. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: A randomized, controlled study. *Clin Exp Rheumatol.* 2001;19(5):503–508.
101. Wigley FM, Korn JH, Csuka ME, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum.* 1998;41:670–677.
102. Black CM, Halkier-Sorensen L, Belch JJ, et al. Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multi-centre, placebo-controlled, dose-comparison study. *Br J Rheumatol.* 1998;37:952–960.
103. Fries R, Shariat K, von Wilmowsky H, et al. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation.* 2005;112:2980–2985.
104. Herrick AL, van den Hoogen F, Gabrielli A, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. *Arth Rheum.* 2011;63:775–782.
105. Roustit M, Gaij J, Gaget O, et al. On-demand sildenafil as a treatment for Raynaud phenomenon. *Ann Intern Med.* 2018;169:694–703.
106. Schiopu E, Hsu VM, Impens AJ, et al. Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. *J Rheumatol.* 2009;36(10):2264–2268.
107. Shenoy PD, Kumar S, Jha LK, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheum.* 2010;49:2420–2428.
108. Caglayan E, Axmann S, Hellmich M, et al. Vardenafil for the treatment of Raynaud phenomenon: a randomized, double-blind, placebo-controlled crossover study. *Arch Int Med.* 2012;172:1182–1184.
109. Wortsman X, Del Barrio-Díaz P, Meza-Romero R, et al. Nifedipine cream versus sildenafil cream for patients with secondary Raynaud phenomenon: A randomized, double-blind, controlled pilot study. *J Am Acad Dermatol.* 2018;78(1):189–190.
110. Matucci-Cerinic M, Denton CP, Furst DE, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomized, doubleblind placebo-controlled trial. *Ann Rheum Dis.* 2011;70:32–38.
111. Hummers LK, Dugowson CE, Dechow FJ, et al. A multi-centre, blinded, randomized, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. *Ann Rheum Dis.* 2013;72:1962–1967.
112. Chung L, Shapiro L, Fiorentino D, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: A randomized, controlled trial. *Arthritis Rheum.* 2009;60(3):870–877.
113. Curtiss P, Schwager Z, Cobos G, et al. A systematic review and meta-analysis of the effects of topical nitrates in the treatment of primary and secondary Raynaud's phenomenon. *J Am Acad Dermatol.* 2018;78:1110–1118.
114. Rustin MH, Almond NE, Beacham JA, et al. The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. *Br J Dermatol.* 1987;117(6):751–758.
115. Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum.* 1999;42(12):2646–2655.
116. Coleiro B. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology.* 2001;40(9):1038–1043.
117. Coveliers HM, Hoexum F, Nederhoed JH, et al. Thoracic sympathectomy for digital ischemia: a summary of evidence. *J Vasc Surg.* 2011;54(1):273–277.
118. Coveliers H, Hoexum F, Rauwerda JA, et al. Endoscopic thoracic sympathectomy for upper limb ischemia. A 16 year follow-up in a single center. *Surgeon.* 2016;14(5):265–269.
119. Janoff KA, Phinney ES, Porter JM. Lumbar sympathectomy for lower extremity vasospasm. *Am J Surg.* 1985;150(1):147–152.
120. Balogh B, Mayer W, Vesely M, et al. Adventitial stripping of the radial and ulnar arteries in Raynaud's disease. *J Hand Surg Am.* 2002;27(6):1073–1080.
121. Ortensi A, Salsano F, Trinch S, et al. Microsurgical distal sympathectomy in chronic vasospastic syndromes of the hand. *Int Surg.* 2005;90(2):88–92.
122. Neumeister MW. The role of botulinum toxin in vasospastic disorders of the hand. *Hand Clin.* 2015;31(1):23–37.
123. Neumeister MW. Botulinum toxin type A in the treatment of Raynaud's phenomenon. *J Hand Surg Am.* 2010;35(12):2085–2092.
124. Bello RJ, Cooney CM, Melamed E, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol.* 2017;69(8):1661–1669.
125. Motegi SI, Uehara A, Yamada K, et al. Efficacy of botulinum toxin b injection for Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis. *Acta Derm Venereol.* 2017;97(7):843–850.
126. Kaada B. Vasodilation induced by transcutaneous nerve stimulation in peripheral ischemia (Raynaud's phenomenon and diabetic polyneuropathy). *Eur Heart J.* 1982;3(4):303–314.
127. Appiah R, Hiller S, Caspary L, et al. Treatment of primary Raynaud's syndrome with traditional Chinese acupuncture. *J Intern Med.* 1997;241(2):119–124.
128. Muir AH, Robb R, McLaren M, et al. The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial. *Vasc Med.* 2002;7(4):265–267.
129. Bredie SJ, Jong MC. No significant effect of ginkgo biloba special extract EGb 761 in the treatment of primary Raynaud phenomenon: a randomized controlled trial. *J Cardiovasc Pharmacol.* 2012;59(3):215–221.
130. DiGiacomo RA, Kremer JM, Shah DM. Fish-oil dietary supplementation in patients with Raynaud's phenomenon: a double-blind, controlled, prospective study. *Am J Med.* 1989;86(2):158–164.
131. Khan F, Litchfield SJ, McLaren M, et al. Arginine supplementation and cutaneous vascular responses in patients with primary Raynaud's phenomenon. *Arthritis Rheum.* 1997;40(2):352–357.
132. Khan F, Belch JJ. Skin blood flow in patients with systemic sclerosis and Raynaud's phenomenon: effects of oral L-arginine supplementation. *J Rheumatol.* 1999;26(11):2389–2394.
133. Hirsch M, Katzenschlager R, Francesconi C, et al. Low level laser therapy in primary Raynaud's phenomenon—results of a placebo controlled, double blind intervention study. *J Rheumatol.* 2004;31(12):2408–2412.
134. Kuryliszyn-Moskal A, Kita J, Dakowicz A, et al. The influence of Multiwave Locked System (MLS) laser therapy on clinical features, microcirculatory abnormalities and selected modulators of angiogenesis in patients with Raynaud's phenomenon. *Clin Rheumatol.* 2015;34(3):489–496.
135. Hassaniem M, Rashad S, Mohamed N, et al. Non-invasive Oxygen-Ozone therapy in treating digital ulcers of patients with systemic sclerosis. Non-invasive Oxygen-Ozone therapy in treating digital ulcers of patients with systemic sclerosis. *Acta Reumatol Port.* 2018;43(3):210–216.
136. Mitropoulos A, Gumber A, Crank H, et al. The effects of upper and lower limb exercise on the microvascular reactivity in limited cutaneous systemic sclerosis patients. *Arthritis Res Ther.* 2018;20(1):112.
137. Saito S, Ishii T, Kamogawa Y, et al. Extracorporeal Shock Wave Therapy for Digital Ulcers of Systemic Sclerosis: A Phase 2 Pilot Study. *Toboku J Exp Med.* 2016;238(1):39–47.

Fibromuscular Dysplasia

EFTHYMIOS D. AVGERINOS, PETER A. SCHNEIDER, and RABIH A. CHAER

INTRODUCTION	1890	Results of Open Surgery	1899
PATHOGENESIS OF FIBROMUSCULAR DYSPLASIA	1891	Complications of Open Surgery	1900
Etiology	1891	FIBROMUSCULAR DYSPLASIA AND ANEURYSM	1901
Differential Diagnosis	1892	PEDIATRIC RENAL ARTERY STENOSIS AND ARTERIAL DYSPLASIA	1901
Classification	1892	Endovascular Treatment in Children	1901
RENAL ARTERY FIBROMUSCULAR DYSPLASIA	1893	Open Surgery for Pediatric Renovascular Hypertension	1902
Epidemiology	1893	EXTRACRANIAL CEREBROVASCULAR FIBROMUSCULAR DYSPLASIA	1902
Pathophysiology	1893	Epidemiology	1902
NATURAL HISTORY	1895	Pathophysiology	1903
CLINICAL PRESENTATION	1895	Natural History	1904
History and Physical Examination	1895	Clinical Presentation	1904
Screening for Secondary Hypertension	1895	Diagnostic Evaluation	1905
DIAGNOSTIC EVALUATION	1895	Treatment Selection	1905
TREATMENT SELECTION	1895	<i>Therapeutic Challenges</i>	1905
MEDICAL TREATMENT	1896	<i>Clinical Considerations</i>	1906
ENDOVASCULAR TREATMENT IN ADULTS	1896	<i>Anatomic Considerations</i>	1906
Technical Considerations	1896	CEREBRAL PROTECTION	1906
Stenting	1897	<i>Stents</i>	1906
Procedure-Related Complications	1897	<i>Medical Management</i>	1906
Early and Late Outcomes	1897	<i>Mechanical Repair</i>	1906
SURGICAL MANAGEMENT	1898	OPEN SURGICAL DILATION	1906
Patient Selection	1898	<i>BALLOON ANGIOPLASTY</i>	1908
Techniques	1898	FIBROMUSCULAR DYSPLASIA IN OTHER ARTERIAL BEDS	1910
<i>Aortorenal Bypass</i>	1898		
<i>Autotransplantation</i>	1899		

INTRODUCTION

Fibromuscular dysplasia (FMD) is an idiopathic, nonatheromatous, noninflammatory, proliferative disease of the musculature of arterial walls, first described in 1938 as a rare cause of renovascular hypertension with a “string-of-beads” appearance. The pathogenesis is still unknown, but up to 10% of cases are familial. Its principal pathologic form involves primarily the media; it affects long, unbranched segments of medium-sized conduit arteries such as the renal artery and the internal carotid

artery but has been observed in almost every artery in the body (Table 143.1).^{1–3}

FMD occurs most frequently (>90%) in women between 20 and 60 years of age but may also be seen in men, older persons, or pediatric individuals. Although many clinicians believe that FMD is a rare disease, its prevalence in the general population is not known. There is evidence to suggest that FMD may be more common than previously thought.⁴

Although FMD is a systemic process, it is usually described in terms of the artery in which it occurs; its principal clinical

TABLE 143.1

Arterial Involvement in Fibromuscular Dysplasia Based on the U.S. Registry for Fibromuscular Dysplasia

Arteries Involved	Number of Investigated Arteries in the U.S. Registry ^a	Frequency of Involvement (%) ^b
Total number in U.S. Registry	447	
Renal arteries	369	80 (75–89)
Bilateral renal arteries		(23–65)
Unilateral Renal Artery – Localization		
Right renal artery		(66–81)
Left renal artery		(19–34)
Other Arteries		
Carotid artery	338	74 (3–74)
Vertebral artery	224	37
Aorta	145	0
Lower extremity arteries	70	60
Mesenteric arteries	198	26
Coronary arteries	447	7
Upper extremity arteries	63	16
Intracranial carotid arteries	206	17
Multiple vascular involvement		35 (8–35)

^aData from Olin JW, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. *Circulation*. 2012;125:3182–3190.

^bData shown in parentheses are based on results in various published studies.

manifestations involve the spectrum of arterial obstruction and/or aneurysmal degeneration and depend on the arterial bed involved: the renal arteries are often associated with hypertension and the extracranial carotid or vertebral arteries with headache (migraine-type), pulsatile tinnitus, transient ischemic attack (TIA), or stroke.^{4–7}

PATHOGENESIS OF FIBROMUSCULAR DYSPLASIA

Etiology

Several theories have been proposed as to the etiology of FMD, including environmental and genetic factors, each with partial supporting evidence.

The fact that FMD is more common among women suggests that hormonal factors may be important, but the exact association remains unclear. Of the 57 women in one study, 9, or 16%, had a previous diagnosis of hypertension during pregnancy, compared with 4% to 5% of pregnancies affected by hypertension in the general population.⁸ The number of pregnancies and the frequency of oral contraceptive use or hormonal therapy did not differ between patients with FMD and the general population, however.⁸

Vessel wall ischemia, mechanically induced, may also be important for the development of FMD. The vasa vasorum of muscular arteries, which supply oxygen and nutrients to the arterial wall, originate from branch points of the parent arteries. Occlusion of the vasa vasorum induces the formation of dysplastic lesions in animal studies.⁹ The vessels most commonly affected by FMD – such as the renal, internal carotid, and vertebral arteries – have long segments that lack branches and thus have fewer vasa vasorum. These arteries are subjected to repeated stretching during motion and respiration, which may injure the sparse vasa vasorum, causing arterial wall ischemia and subsequent development of FMD. This hypothesis is supported by the observation that FMD is more common in the right renal artery,¹⁰ which is longer than the left. Its greater length makes the right kidney more susceptible to renal ptosis, which is also common among patients with renal FMD.¹¹ Vasospasm in the vessel wall might also induce ischemia in the vasa vasorum, and cases of FMD combined with Raynaud disease have been reported.¹² *In vitro* studies have also demonstrated increased production of collagen, hyaluronan, and chondroitin sulfate in arteries exposed to cyclic stretching.¹³ Mural ischemia due to functional defects in the vasa vasorum, possibly in association with developmental renal malposition, has also been postulated as a cause of FMD.¹⁴ However, these theories do not explain the gender difference.

FMD is associated with cigarette smoking. The prevalence of smoking is higher among patients with FMD than in matched controls, and patients with FMD who smoke have more severe arterial disease than nonsmokers.¹⁵ In the U.S. Registry for Fibromuscular Dysplasia, 37% of patients were current or former smokers compared with 18% reported for US women.¹⁶ The mechanisms by which smoking contributes to FMD have not been elucidated.

The occurrence of renal FMD in siblings and identical twins suggests possible inheritance of the disease.¹⁷ Rushton suggested that FMD is transmitted in an autosomal dominant manner, with incomplete penetrance and variable clinical symptoms.¹⁸ A French study of renal FMD showed that 11% of patients had at least one sibling with renal FMD.¹⁹ The U.S. Registry study reported a 7% incidence in relatives; however, it also reported that stroke (54%), aneurysm (24%), and sudden death (20%) were common in first- or second-degree relatives.¹⁶ The presence of FMD can be easily overlooked in relatives because it may be associated with only mild hypertension or may be asymptomatic. Subclinical dysplasia of the carotid artery also occurs in patients with renal FMD, in accordance with a possible autosomal dominant transmission.^{20,21}

Along with the high prevalence of asymptomatic FMD (~3%–6%) and the influence of environmental factors, a complex genetic basis is suspected. Associations with polymorphisms in the angiotensin-converting enzyme (ACE) insertion allele ACE-I have been reported, and an autoimmune origin of FMD has been suggested by genetic associations with HLA-Drw6. Currently several groups are trying to delineate further gene patterns predisposing individuals for the development of FMD.^{3,22}

TABLE 143.2 Classification of Dysplasias

Classification	Gender/Age	Cases (%)	Pathologic Features	Angiographic Appearance
Intimal fibroplasia	Often young; no gender difference	5–10	Collagen deposition within the intima internal elastic lamina may be disrupted	Unifocal – ring-like focal stenosis or a long, irregular tubular stenosis
Medial Dysplasias				
Medial fibroplasia	Adolescents and females 20–70 years of age; female-to-male ratio 5–9:1	80	Areas of thinned media alternating with thickened fibromuscular ridges containing collagen Advanced medial dysplasia, especially in children, also shows secondary intimal hyperplasia (see Figs. 143.1 and 143.2)	Multifocal – “string of beads” appearance, with the “bead” larger than the proximal vessel Normally involves distal two-thirds of main renal artery but can also extend into branches (25%) (see Fig. 143.3)
Perimedial fibroplasia	Young girls and women up to 50 years of age	1–5	Patchy collagen deposition between media and adventitia External elastic lamina intact	Multifocal or unifocal – can also result in “string of beads” appearance, but diameter of “beads” does not exceed diameter of proximal artery (see Fig. 143.4)
Adventitial fibroplasia	No gender difference	<1	Dense collagen replaces normally loose connective tissue of adventitia and may extend into surrounding tissue	Unifocal – long stenosis

FMD might coexist with other diseases of the vessel wall and endocrine system. Ehlers–Danlos syndrome type IV has been associated with medial fibroplasias and should be suspected in patients with multiple aneurysms and FMD.²³ FMD has also been reported in association with pheochromocytoma, Marfan syndrome, Alport syndrome, and Takayasu arteritis.^{22–26}

Differential Diagnosis

FMD is primarily a stenotic disease but aneurysm, dissection, and arterial tortuosity frequently occur in affected patients. It is important, however, to recognize that the presence of aneurysms, dissections, or tortuosity in the absence of a focal or multifocal FMD stenotic lesion does not suffice to establish a diagnosis.

Important differential diagnoses for FMD are type 1 neurofibromatosis, vascular Ehlers–Danlos syndrome, Williams syndrome, and vasculitis.^{24,27} The diagnoses of these conditions rely on associated phenotypic traits: characteristic skin lesions in type 1 neurofibromatosis²⁸; acrogeric dysmorphism, skin elasticity, and distal joint laxity in vascular Ehlers–Danlos syndrome²⁹; and facial dysmorphism, supra-aortic stenosis, and particular behavior in Williams syndrome.³⁰ Genetic tests can also be used to rule out these conditions as alternative diagnoses.

Because FMD is a noninflammatory process, it is not associated with anemia, thrombocytopenia, or the increased acute-phase reactants that often occur in patients with vasculitis. Large-vessel vasculitis sometimes occurs in the absence of changes in acute-phase reactants. It might therefore be difficult to distinguish FMD from inflammatory vessel disease in the

absence of tissue samples and without laboratory markers confirming inflammation.

Classification

Traditionally a histopathologic scheme was used to classify FMD, but in the current era fewer patients are undergoing surgical procedures to obtain specimens. The classification now uses an angiographic system, the most common of which is the American Heart Association system adopted in 2014 that distinguishes between multifocal, characterized by the string-of-beads appearance, and focal (or unifocal) FMD, with a single area of stenosis.⁷ There is international consensus on this classification. Unifocal FMD has less female predominance, is diagnosed in younger individuals, and is treated with better short- and long-term results than multifocal FMD.³¹ This classification has not been applied to FMD in children.

The histopathologic scheme classified FMD into three categories related to the pathologic layer of the arterial wall affected – fibroplasia of the intima, media, or adventitia (periarterial fibroplasia) (Table 143.2; Figs. 143.1–143.4). FMD affecting the media is by far the most common type and is further subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Although this classification was initially proposed for the renal arteries, it is also applicable to other arterial beds and has been angiographically correlated with FMD elsewhere. Complications of arterial dysplasia – such as aneurysm formation (in 17% of patients with FMD, one-third in the renal artery) and dissection (in 20% of patients with FMD, more common in carotid and vertebral arteries, one-fifth in the renal artery)¹⁶ – should be classified as secondary events and differentiated from primary dysplastic lesions.

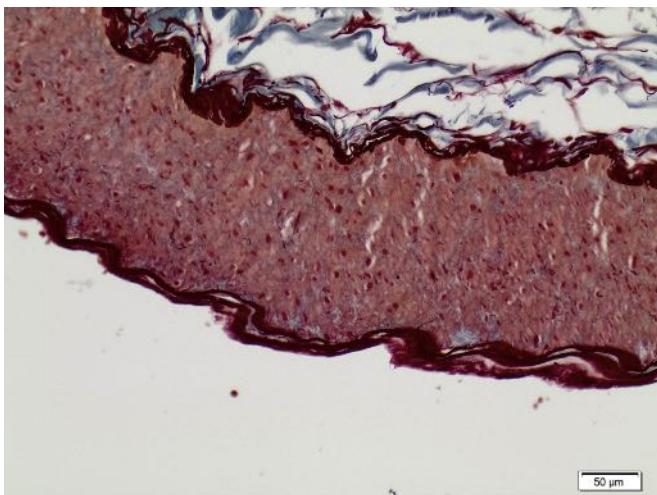


Figure 143.1 Normal renal artery with distinct wall layers. (Courtesy J Malina, Department of Pathology, Malmö, Sweden.)

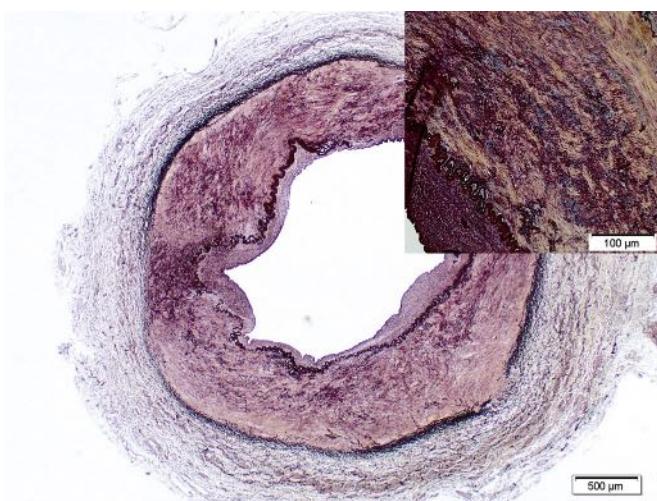


Figure 143.2 Medial fibrodysplasia with dense fibrous connective tissue in the outer media and disordered inner medial smooth muscle. (Courtesy J Malina, Department of Pathology, Malmö, Sweden.)

RENAL ARTERY FIBROMUSCULAR DYSPLASIA

FMD is the second most frequent cause of renal artery stenosis (RAS), after atherosclerosis, and the most common cause of renal hypertension in young individuals, predominantly Caucasian women in their 20s to 40s with normal kidney function.

Epidemiology

Symptomatic fibrodysplastic RAS occurs in 0.4% of the population,⁴ but the prevalence of asymptomatic FMD in potential renal donors is around 4%.^{20,21,32–34} The true prevalence is difficult to ascertain because there are no easily applicable screening tests. FMD is usually diagnosed in patients 15 to 70 years of age but it has been reported from infancy to age 89.^{1,16,35,36} Lesions may be bilateral, but in unilateral disease the right renal artery is affected more often than the left.

FMD is more likely to manifest in patients with treatment-resistant or malignant hypertension than in the general hypertensive population and accounts for up to 10% of all cases of renovascular hypertension^{37–40}; most of the remaining cases of renovascular hypertension are caused by atherosclerosis. Compared with patients with atherosclerotic RAS, patients with FMD are younger and have both fewer risk factors for atherosclerosis and a lower occurrence of atherosclerosis in other vessels.

FMD is diagnosed most often in whites and is reported less frequently in Hispanic and Asian populations. In the U.S. Registry, which contains data for 447 patients, 95% are white, 2% are African American, and 1% are Hispanic and Asian.¹⁶ Diagnostic criteria vary and prevalence data are often derived from selected cohorts or autopsy studies, so the prevalence of FMD might be overestimated.

Multiple arterial involvements have been reported in 8 of 34 and 9 of 102 renovascular patients with FMD in earlier series; in the U.S. Registry report, two vascular beds were affected in 35% of patients and three in 22%.^{10,16,41,42} In the ARCADIA-POL study (Assessment of Renal and Cervical Artery Dysplasia – Poland), all FMD patients underwent a detailed clinical evaluation including whole body CTA. Newly diagnosed FMD lesions were found in 34.1% of the patients, and previously undetected vascular complications were found in 25% of the patients. This new information reinforces the need for a good clinical examination and imaging of all vessels from brain to pelvis, at least once and usually with CTA or MRA, to identify other areas of FMD, as well as to screen for occult aneurysms and dissections.³

In childhood, renovascular hypertension is a more important cause of hypertension. It is found in 8% to 10% of all hypertensive children and in up to 25% of those with secondary hypertension. The causes of pediatric RAS differ in different populations.^{35,43} FMD is the most common cause of pediatric renovascular hypertension in North America and western Europe, whereas Takayasu arteritis dominates in Asia and Africa.⁴⁴

Pathophysiology

Multiple septa in the renal arteries may together induce a significant reduction in renal perfusion in patients with FMD, resulting in renovascular hypertension, but the degree of RAS is often difficult to evaluate from imaging.

Subsequent reduction of arterial perfusion pressure leads to activation of the renin–angiotensin–aldosterone (RAA) system, resulting in volume expansion and hypertension. Several mechanisms – including increased endothelin-1 (ET-1) production, local RAA activation, arterial wall remodeling, and oxidative stress – help to sustain the hypertension, which now depends not only on the RAA system but also on local vasoconstrictive proliferative effects in the arterial wall, gradually leading to resistance to therapy.⁴⁵ Inflammatory mediators such as high-sensitivity C-reactive protein, tumor necrosis factor- α , interleukin-6, and neopterin and vasoconstrictive mediators such as ET-1 are increased in patients with renovascular hypertension. A separate analysis of patients with FMD, however, showed that neopterin and ET-1 were lower in patients with

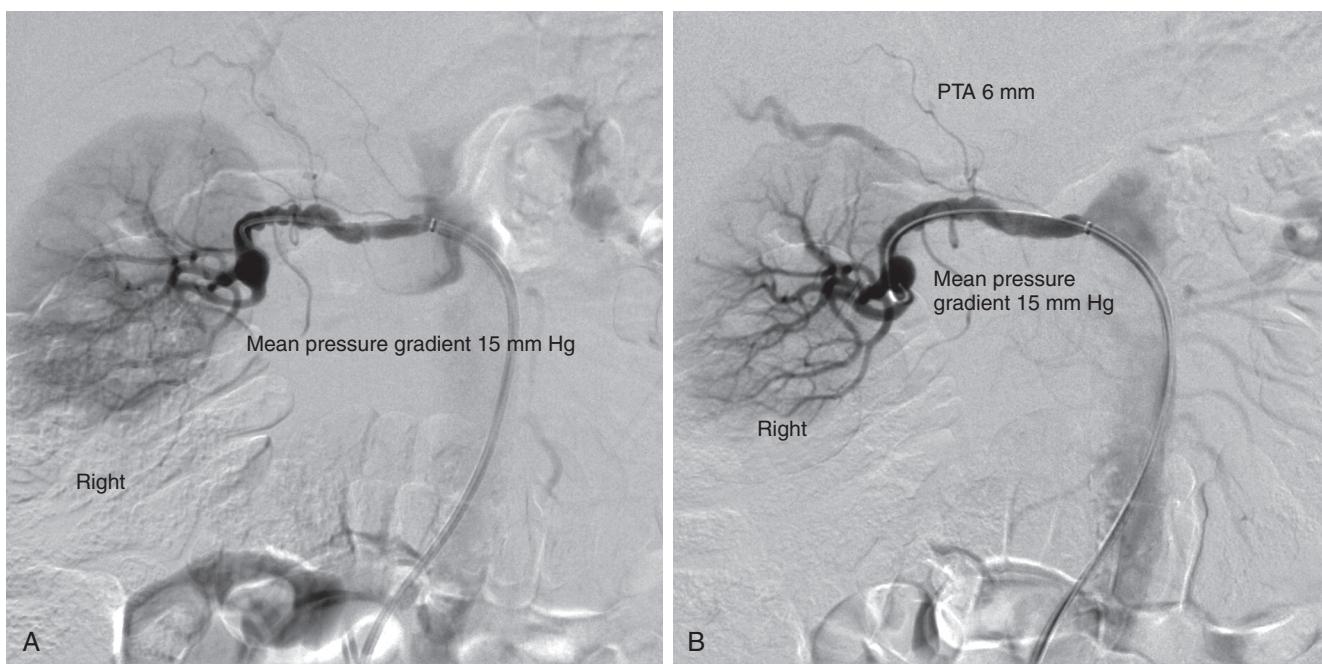


Figure 143.3 Typical selective angiographic multifocal appearance of medial fibrodyplasia with the “string of beads” in the distal main artery before (A) and after (B) balloon angioplasty.

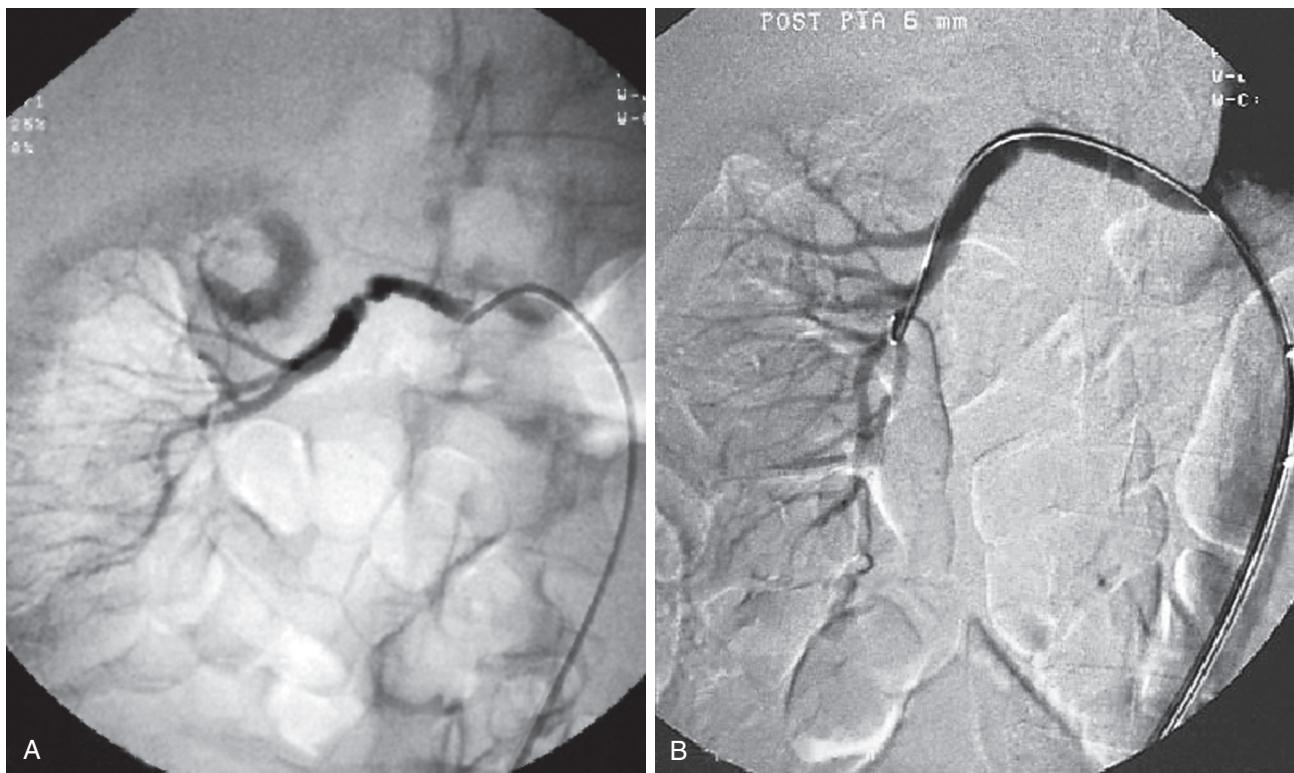


Figure 143.4 Short unifocal stenosis of the distal main artery, perhaps of the perimedial dysplastic type, before (A) and after (B) balloon dilation.

renovascular hypertension due to FMD than in those with RAS of atherosclerotic origin.^{8,46} This finding suggests that inflammatory activation might be less important for the pathophysiology of renovascular hypertension caused by FMD than for that caused by atherosclerosis.

Luminal narrowing leads to renal parenchymal damage and ischemic nephropathy in patients with FMD.⁴⁷ However, this seems to be less important in patients with FMD than in those with atherosclerotic RAS; the latter show more pronounced reductions of total kidney and cortical perfusion. In addition,

renal perfusion correlates inversely with the degree of stenosis in FMD but not in atherosclerotic RAS, further emphasizing that FMD hypertension is more truly renin-dependent than hypertension due to atherosclerosis.⁴⁸

The contralateral kidney may be damaged by exposure to hypertension in FMD.⁴⁷ Deterioration of renal function in a patient with FMD affecting one renal artery suggests the development of bilateral stenosis, parenchymal disease, or both.

NATURAL HISTORY

Data with regard to stenosis progression and risk of deteriorating renal function in patients with FMD do exist, but they are not as robust as in patients with atherosclerotic RAS. Progression is generally slower in FMD than in atherosclerotic stenosis.²⁰ About one-fourth of subjects with asymptomatic FMD demonstrate hypertension within 4 years of diagnosis,^{32,33} and serial angiograms confirm FMD progression in up to 40% of cases.⁴⁹ Because angiography is not routinely performed in patients with FMD who have favorable clinical outcomes, these progression rates may be overestimated. FMD might also result in decreasing renal size and deterioration of renal function, although less often than in patients with atherosclerotic RAS. Aneurysms and dissection are fairly frequent, but complete vessel occlusion, renal infarction, and severe renal insufficiency as well as regression of stenosis have been reported only infrequently in patients with FMD.^{6,16,50–52}

CLINICAL PRESENTATION

History and Physical Examination

Arterial hypertension of acute onset or that is increasingly difficult to treat suggests the presence of secondary hypertension – that is, a specific cause of blood pressure elevation, which can be identified in about 5% of adult hypertensive patients.³⁷ Renovascular hypertension caused by one or more stenoses of the extrarenal arteries is the second most common cause of secondary hypertension (after renal parenchymal disease) and occurs in approximately 2% of adult patients with blood pressure elevation assessed in specialized centers.⁵³ A physical sign suggesting RAS is abdominal bruit with lateralization. In patients with either high-grade stenosis of a single kidney or bilateral disease, often with one renal artery occluded and the other stenosed, acute pulmonary edema may occur, with or without renal failure. Typically, these patients present with severe and rapid-onset “flash” pulmonary edema, which can also occur in FMD and may be confused with coronary syndromes.¹⁶ Among patients with RAS, the absence of general atherosclerosis suggests that the stenosis is caused by FMD, whereas signs of atherosclerotic disease in other vessels indicate a greater possibility of an atherosclerotic cause.

Screening for Secondary Hypertension

The patient’s history can reveal acute-onset hypertension, concomitant flushing, or other paroxysmal symptoms. Physical

BOX 143.1

Indications for the Evaluation of Secondary Hypertension

Secondary hypertension should be considered in hypertensive patients with the following characteristics:

- Requirement of more than three antihypertensive drugs to control hypertension
- Sudden acceleration of serum creatinine and hypertension
- Young age (<50 years)
- Worsening of previously well-controlled hypertension
- Spontaneous hypokalemia
- Bruit
- Unexplained (flash) pulmonary edema

examination may reveal abdominal bruits, and routine laboratory investigations may show signs of renal disease, hypokalemia, or hyperthyroidism. Secondary hypertension is also suggested by a severe blood pressure elevation, a sudden onset or worsening of hypertension, and blood pressure that responds poorly to appropriate doses of at least three drugs, including a diuretic. In these cases, specific diagnostic procedures for the evaluation of potential secondary hypertension should be considered, as outlined in Box 143.1.

DIAGNOSTIC EVALUATION

In patients with suspected renovascular hypertension due to FMD, the same diagnostic tools as for arteriosclerotic RAS are used. A limitation of renal artery duplex ultrasonography (DUS), magnetic resonance angiography (MRA), and computed tomographic angiography (CTA) is their unreliability to exclude FMD, because 20% to 25% of patients with FMD have branch lesions. MRA and CTA can identify vessels as small as 2 mm but have limited resolution for distal and intrarenal arteries. These techniques can be used to screen for possible FMD but not to exclude FMD. In terms of specificity and sensitivity, gadolinium-enhanced MRA and CTA are better than ultrasound for the detection of RAS, but intra-arterial digital subtraction angiography is most accurate for confirmation or exclusion of an FMD diagnosis.^{31,54} This is still the “gold standard” for the detection of renal artery FMD (Fig. 143.5), and is especially useful in the evaluation of branch vessel disease. Angiography is generally indicated only when its findings are expected to impact patient management. Intra-arterial measurement of the pressure gradient across the stenosis may be performed before treatment of RAS. Different methods have been used for such assessments, and there is no consensus regarding what level of mean or systolic pressure gradient indicates a hemodynamically significant RAS.^{1,31,54} A renal-to-aortic pressure ratio less than 0.90 has been correlated with increased renin levels in the renal vein, suggesting a physiologically relevant stenosis.⁵⁵ A mean pressure gradient across the stenosis of more than 10 mm Hg predicts a favorable response to dilation.

TREATMENT SELECTION

The treatment options in renal artery FMD are medical, endovascular, and surgical. Treatment of patients with all forms

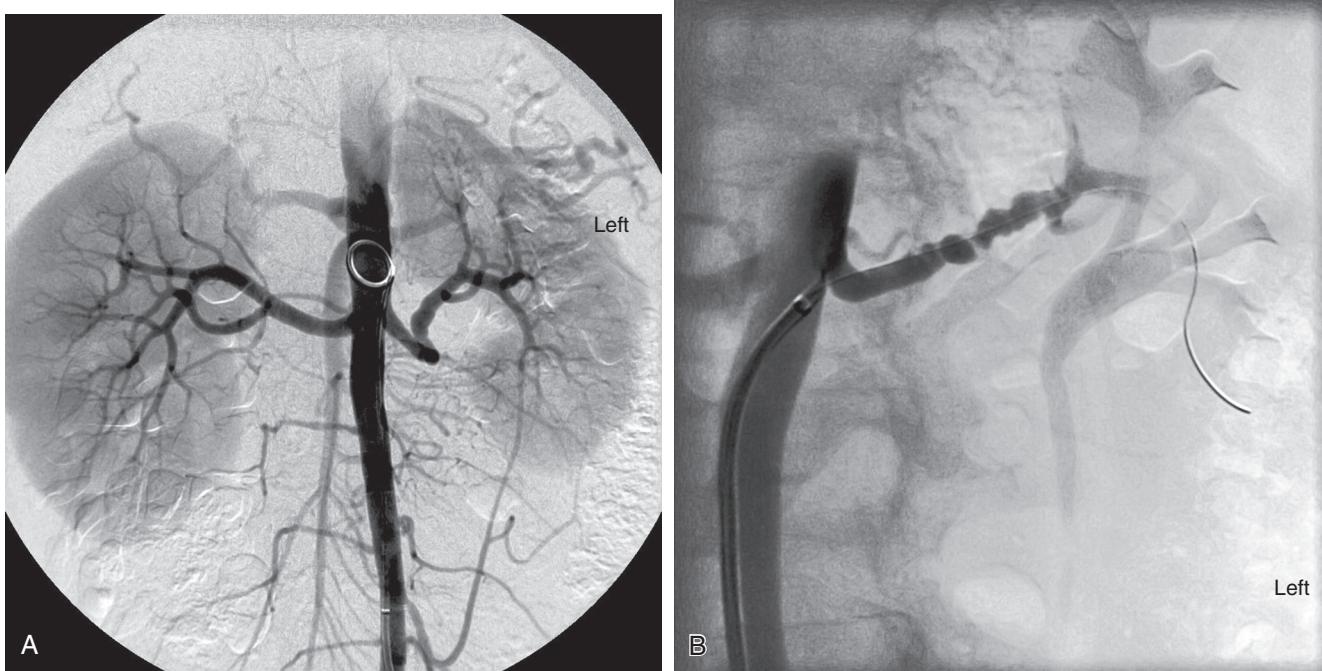


Figure 143.5 (A) Aortogram in a hypertensive young man reveals only minor findings in the left renal artery. (B) Selective angiogram from another angle shows the multifocal fibromuscular dysplastic lesion, across which a pressure gradient of 60 mm Hg was noted. The patient's hypertension was cured by percutaneous transluminal renal angioplasty.

of renovascular hypertension is controversial owing to the limited number of randomized long-term outcome trials comparing different therapeutic approaches as well as to the difficulty of predicting the blood pressure response to renal revascularization procedures in individual patients.⁴ In patients with FMD, endovascular or surgical treatment should be considered in those whose hypertension cannot be controlled with antihypertensive drugs, who are intolerant of, or noncompliant, with medication, and those with impaired renal function or ischemic nephropathy.¹ To identify progressive disease in patients undergoing medical therapy only, blood pressure and renal function should be monitored regularly. Some authors have also recommended that renal size be monitored by regular ultrasound examinations and that revascularization be recommended if the kidney length decreases by 1 cm or more.²⁰

MEDICAL TREATMENT

Many controlled trials have convincingly shown that lowering blood pressure reduces cardiovascular morbidity and mortality. All patients with renovascular hypertension caused by FMD are therefore candidates for antihypertensive treatment in accordance with current guidelines.^{37,56,57} Blood pressure should be reduced to 130 to 139 mm Hg systolic and 90 mm Hg diastolic (130 to 139/80) in hypertensive patients and further to less than 130/80 mm Hg in patients with diabetes. These guidelines specify five different groups of first-line antihypertensive treatment: ACE inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, and

diuretics. Single or combined, all of these drugs can be used in the treatment of renovascular hypertension due to FMD.

As patients with FMD may present with thrombotic and thromboembolic events, even in the absence of dissection or aneurysm, antiplatelet agents are reasonable for both symptomatic and asymptomatic FMD.⁵⁸ Statins or discontinuation of oral contraceptives haven't been shown to confer any benefit.

ENDOVASCULAR TREATMENT IN ADULTS

Percutaneous transluminal renal angioplasty (PTRA) is the treatment of choice for renovascular hypertension due to FMD. Unlike the case in patients with atherosclerotic renovascular hypertension, progressive loss of renal function is uncommon in patients with FMD. The main reason for treating FMD is uncontrolled hypertension, and treatment often leads to cure or substantial improvement.

Technical Considerations

The technique for PTRA in FMD is similar to that used to treat atherosclerotic renal artery lesions (see Ch. 129, Renovascular Disease: Endovascular Treatment). Most operators are using platforms based on 0.014- or 0.018-in guidewires to reduce vasospasm and to cross the lesion with low profile devices. In patients with FMD, the right renal artery often takes off from the aorta proximally. The diversity of available guiding catheters usually allows catheterization from a femoral

puncture. A radial or brachial approach is seldom needed to get a better angle and/or “pushability” for renal catheterization. Cannulation of the artery is often made simpler by the fact that the lesion is usually in the mid-portion of the artery and that the renal artery origin is usually free of disease.

Heparinization is the same as for other endovascular procedures. However, patients with FMD are often younger and have more pronounced vasoreactivity than those with atherosclerotic RAS. Many patients with FMD are already receiving antihypertensive treatment with calcium channel blockers; if not, premedication with a short-acting dihydropyridine such as nifedipine can be used to reduce the risk of vasospasm. Even so, vasospasm in the kidney vasculature is so frequent in patients with FMD that some operators infuse 0.15 mg nitroglycerin into the renal artery just after catheterization in hemodynamically stable patients. If required, this dose can be repeated during the procedure. A diagnostic aortogram and selective renal angiograms at different angles are obtained (see Fig. 143.5). In addition, many centers routinely measure pressure gradients. Pressure measurements can be obtained using a pressure wire or a 4-Fr catheter.

In patients with FMD, the stenotic lesion is most often located in the middle part of the main renal artery. If the distal parts of the renal artery or its branches are affected, the use of multiple guide wires may be necessary. A kissing balloon technique can be used in branches. However, multiple guidewires or kissing balloons are normally not required; inserting a balloon into the main artery first, followed by the branches, often achieves good results. The initial balloon diameter should be based upon the diameter of the normal renal artery based on CT angiography, vascular angiography quantitative software, IVUS, or OCT. The balloon diameter size should be incrementally increased by 0.5 mm until the trans-lesion gradient. Angioplasty should be aborted if the patient experiences pain during balloon inflation or if a complication occurs.³

The use of cutting balloons is not a first choice in patients with FMD, because ruptures have been reported with their use.^{59,60} CTA, MRA, or intravascular ultrasound (IVUS) may yield information about whether the lesion is dysplastic or hypoplastic. A hypoplastic lesion is a narrowing of the entire vessel with thin walls, which implies a higher risk of rupture. IVUS may add information on wall thickness. If cutting balloons are required, it is wise to start with an undersized balloon. Good results have been reported with the use of cutting balloons in complex lesions.⁵⁹

Stenting

The stenotic lesion of FMD is typically quite amenable to PTRA. Balloon angioplasty enlarges the arterial lumen in FMD by breaking the septa and stretching the arterial wall, leading to separation of the intima from the media, fracture of the media, and stretch of the adventitia beyond its elastic recoil. Subsequent changes include smooth muscle cell necrosis, fibrosis, and some degree of neointimal formation. In the vast majority of cases, PTRA provides good results; pressure gradients are completely abolished, and there is no indication

for stent placement. Also, given the relative youth of patients with FMD, stenting should be avoided; it is also reported to give a high rate of restenosis.⁶¹ Surgical intervention may be more appropriate in cases of complex stenosis and should not be made more difficult with stent placement.

Indications for stenting of FMD lesions include severe procedural complications and perhaps suboptimal results with persistent pressure gradients after repeated angioplasty attempts or small aneurysms in the renal artery.

Procedure-Related Complications

Puncture-site hematoma is the most common complication of PTRA in FMD, reported in 3% to 26% of cases.^{62,63} The trend toward using micropuncture to optimize puncture-site location and the fact that smaller introducers can be used further reduce this risk. Renal artery dissection occurs rarely (1.4%–6.7%) if the balloons are not too oversized.^{8,62–64} The majority of these dissections are small, and few require treatment. Repeated and prolonged balloon treatment is recommended, and dissections that are not hemodynamically significant can be left alone without jeopardizing the kidney. However, an extensive dissection that is limiting flow should be treated with stent deployment.

Rupture of the renal artery is uncommon in medial or perimedial dysplasia. Rupture is reported to occur in 2% to 6% of cases and is more common in patients with FMD who have complex stenoses.⁸ Some small ruptures stop leaking after prolonged balloon treatment; others require stents, covered stents, or emergency open surgery after the balloon provides initial hemostasis. Both endovascular rescue equipment and resources for emergency operative repair must be available if complex stenoses are being treated.

Branch occlusion can be caused by guide wire misadventures or by dissection during balloon treatment close to a branch takeoff. Branch occlusion is seen in 1% to 5% of patients with FMD after PTRA procedures.^{8,62} Still, most of these patients seem to have a favorable outcome.

Early and Late Outcomes

The favorable results of endovascular treatment of main renal artery FMD lesions are noted in most reports and follow-up information varies from less than 1 year up to 9 years in the different series.^{60–62,65–67} PTRA can today be performed with good results even when branch arteries are affected. However, patients with branch artery involvement show less pronounced blood pressure responses and less optimal long-term effects after PTRA.⁸

Comparisons of published series are difficult because of the large variation in selection criteria and length of follow-up. The hypertension outcomes of “cure,” “improvement,” and “benefit” are not uniformly defined according to current guidelines. In a systematic review by Trinquart et al., the cure rate was around 65% for 30-year-old patients while 55-year-old patients had only about a 20% cure rate.⁶⁵ This striking decline in cure rate with age is also reported by others.⁶⁷ The

review also reports a decline in cure rate from about 60% in series from 1980 to 1985, to about 30% in more recent series.⁶⁵ Another limitation in comparing series is that it may be unclear whether diuretics and nitrates were considered to be blood pressure-lowering drugs. When evaluating treatment, attention to 24-hour blood pressure measurements is essential because effects on nocturnal blood pressure are important.

Alhadad and coworkers found that 34% of their patients required a second PTRA procedure; however, the majority of these were either planned contralateral PTRAs or redo operations within 6 months of an initial suboptimal PTRA.⁸ In the majority of cases, the restenosis lacks clinical significance. Savard et al. analyzed 1-year cure rates depending on the angiographic type of FMD and found that 15 of 28 (54%) patients with unifocal FMD versus only 13 of 50 (26%) with multifocal FMD were cured.³¹ Today most centers perform control angiography only if the initial PTRA procedure was suboptimal or if branches were treated.^{8,62} In summary, in patients with a main-artery string-of-beads appearance and a good initial effect after PTRA, the long-term durability is good; for more complex lesions and branch vessel lesions, results are acceptable but reinterventions are needed more frequently.

Surveillance with renal artery duplex ultrasound may include a postangioplasty study (usually within 1 month) and every 6 months for 24 months, then yearly, to detect findings suggestive of restenosis.³ Imaging may be obtained more frequently in the setting of unexplained increase in blood pressure and/or decline in renal function.

SURGICAL MANAGEMENT

Patient Selection

Surgical revascularization in patients with FMD is currently reserved for patients with severe PTRA complications such as thrombosis, perforation, or dissection that cannot be handled with endovascular techniques. Another option in most of these cases is the use of a stent or a stent graft; the choice of treatment depends on the extension of the lesion and the current renal flow situation. It is therefore important that PTRA procedures be performed only in institutions where such complications can be handled. Open surgery should also be considered after repeated failure or restenosis of PTRA. In a series of 19 patients with FMD and failed PTRA, Wong and associates reported one emergent surgical revascularization due to thrombosis.⁶⁸ Among the remaining patients, two underwent nephrectomy and one was revascularized with aortorenal bypass. Among groups experienced with operative treatment after PTRA failure, the results are favorable.^{35,68–71} Patients with FMD and large aneurysms should also be considered for open surgery; in cases of pediatric RAS (see the section entitled Pediatric RAS and Arterial Dysplasia, further on, and Chapters 128, Renovascular Disease: Open Surgical Treatment and 131, Renovascular Disease: Aneurysms and Arteriovenous Fistulae), a careful choice between open and endovascular treatment should be made.

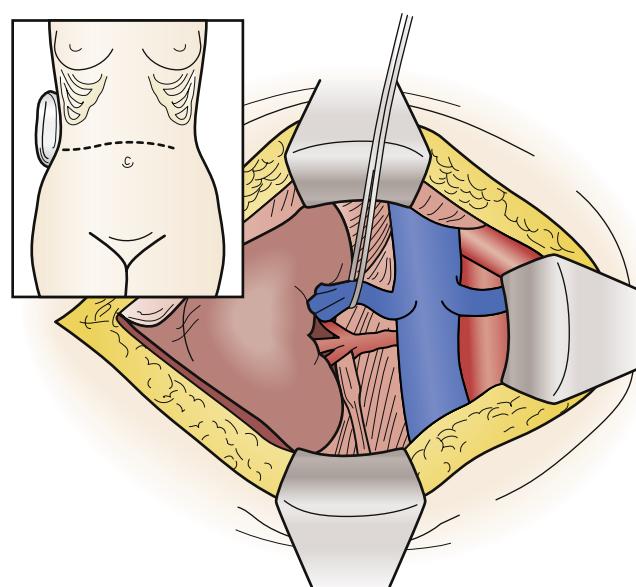


Figure 143.6 Operative approach through a transverse supraumbilical abdominal incision, with an extraperitoneal dissection and reflection of the colon and foregut structures providing exposure of the renal and great vessels.

Techniques

Aortorenal Bypass

Ostial lesions are normally seen in atherosclerotic disease; the technique for the operative repair of these lesions is covered elsewhere (see Ch. 128, Renovascular Disease: Open Surgical Treatment). In patients with FMD requiring open surgery, lesions are most commonly located in the distal portion of the main artery, often combined with branch artery stenosis, and are normally repaired with *in situ* techniques. Many institutions use transverse, subcostal incisions and expose the kidney retroperitoneally or transperitoneally, depending on how much exposure of the aorta is required (Fig. 143.6). In most patients with FMD the aorta or iliac arteries can be used for proximal anastomosis without atherosclerosis limiting its placement.

Graft material for the reconstruction may be either saphenous vein or arterial homograft. In the treatment of FMD, autologous vein grafts are usually preferred for reconstructions in adults, and autologous hypogastric artery grafts are favored for bypass in children.^{35,72} The hypogastric artery may also be used in adults, especially if several branches must be reconstructed.⁷⁰ Dacron or expanded polytetrafluoroethylene grafts can be used in renal artery lesions but are not the first choice. After resection even of a short part of a renal artery, direct anastomosis is often not possible in adult patients with FMD.

Before renal circulation is clamped proximally, adequate diuresis must be established. Mannitol 12.5 to 20 g is administered intravenously before renal ischemia to optimize diuresis. Mannitol also acts as a specific hydroxyl free radical scavenger. A generous anastomotic circumference of the saphenous vein can be achieved by using a branch to widen the anastomotic area (Fig. 143.7). The choice of retrocaval or antecaval positioning of the right renal bypass should be made on a case-by-case basis. Some authors prefer not to pressurize the proximal anastomosis until reconstruction is complete. In patients

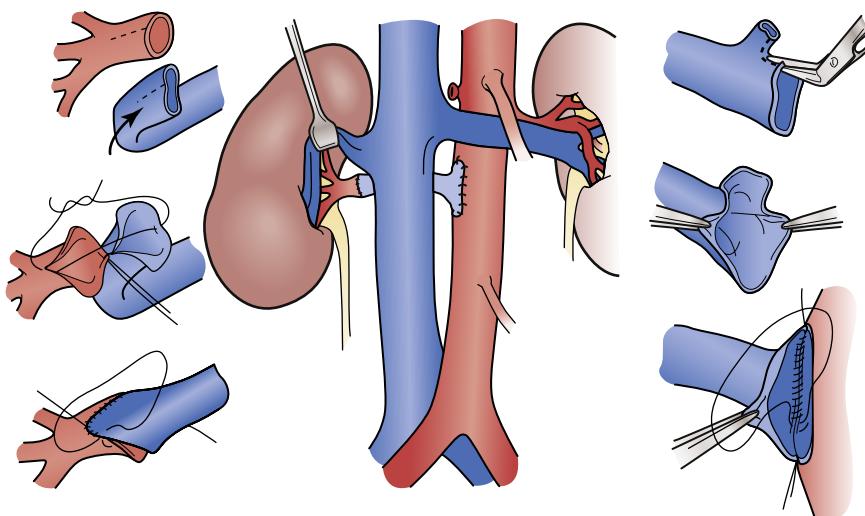


Figure 143.7 Techniques of an end-to-end spatulated renal artery anastomosis and retrocaval placement of the vein graft, with use of a branch of the vein graft to create a wide posteriorly oriented aortic anastomosis.

undergoing *in situ* reconstructions, some surgeons use cool perfusion during renal ischemia. However, it is challenging to maintain cooling intra-abdominally, and such an effort does not convincingly optimize the outcome for the kidney. After the renal anastomosis is made, Intraoperative assessment of the reconstruction is imperative; DUS is reported to be valuable.⁷⁰ Most centers do not routinely perform early post-reconstruction angiography.

In hypertensive patients with FMD in whom an aneurysm constitutes part of the indication for surgery, suturing of the aneurysm (aneurysmorrhaphy) is normally not adequate. A saphenous vein graft interposition is usually required.

Autotransplantation

Autotransplantation and renal repair in patients with FMD should be considered in the following situations: reoperation for failed renal artery repair, failed complex endovascular reconstruction after several attempts, multisegmental arterial dysplasia, and a single kidney and stenosis in several renal arteries.

Current indications for autotransplantation after *ex vivo* repair have changed somewhat owing to refinements in endovascular techniques. PTRA has shown acceptable results in branch artery stenoses. Autotransplantation of the kidney was originally devised as a method for managing patients with high ureteric injury, and it was first used in renovascular hypertension in 1964. Today when renal FMD is treated surgically, it is usually for very complex disease, with a multi-segmental distribution in not only first-order but also second-order branches. *Ex vivo* repair and autotransplantation, placement of the kidney in the iliac fossa may be required in the same manner as in renal homotransplantation.^{69,73,74}

Many institutions preferentially use transverse left or right subcostal retroperitoneal exposure for mobilization of the kidneys. Adequate access may also be obtained with a median or paramedian incision. The renal vasculature is exposed, and the ureter with its pedicle is freed to the level of the iliac vessels. The ureter can be divided and reimplanted in the bladder. This

allows optimal separate benchwork after the renal vessels are divided and the kidney is cooled with perfusate. The right kidney has a shorter vein, and a small patch of surrounding vena cava facilitates later vein anastomosis without causing any significant stenosis of the vena cava. The right renal artery is exposed on the back side of the vena cava as long as required. The artery is ligated first; thereafter, the vein is controlled.

The kidney is perfused with saline, Ringer's, or Wisconsin solution, normally at a temperature of 4°C, until the venous effluent is clear. This normally requires 300 to 500 mL of perfusate. All renal arteries should be perfused. The kidney is kept in Ringer's solution at 4°C and some ice slush; thereafter, further meticulous dissection can be undertaken.

Dissection into the renal hilum should be avoided if possible, because the numerous small veins may constitute a challenge. Depending on the type of repair that is planned, further autologous material for vessel repair must be harvested: parts of the proximal "healthy" renal artery, saphenous vein with or without branches, or internal iliac artery with several branches. The risk of unidentified renal arteries is reduced today with better imaging, but during cool perfusion of the kidney especially, the renal poles should be controlled so that blanching of the entire kidney is achieved.

After reconstruction of the renal vessels, reimplantation of the kidney in the left or right iliac fossa is performed. If the ureter has not been divided, it is important to avoid rotating the kidney while positioning it in the iliac fossa. Normally the vein anastomosis is performed first; the reconstructed renal artery is then anastomosed either end to side to the external or common iliac artery or end-to-end to the internal iliac artery (Fig. 143.8).

Results of Open Surgery

The published series on open surgery include various reports on aortorenal bypass, branch artery reconstructions, and autotransplantation. With each of these different techniques, the early outcome is excellent.

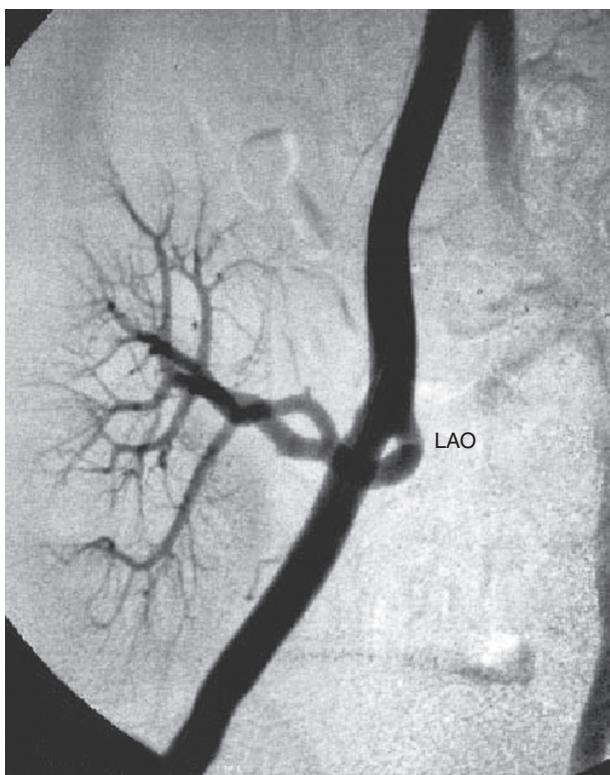


Figure 143.8 Control angiogram after autotransplantation with an arterial allograft (internal iliac artery) and three-branch reconstruction. Slight, insignificant hemodynamic stenosis is seen at the proximal reanastomosis of the internal iliac artery.

The proportion of cured patients has been somewhat lower during the last 10 years, however, owing to older patients, longer duration of hypertension before surgery, and more complex lesions, because PTRA is now used for main artery lesions. A recent review reported a reduction in cure rate with the increasing age of patients with FMD and also with open surgery.⁶⁵ Likewise, cure rate has decreased in recent publications probably due to more refined definitions of cure. The different failure rates among series can be explained by the varying complexity of the cases reported, but it may also reflect an overly optimistic expectation that reconstruction should be successful in patients with small kidneys with branch artery or multi-segmental lesions. The number of nephrectomies required is low.^{71,75}

Complications of Open Surgery

Only a few fatal outcomes have been reported after FMD surgery in adults. Overall morbidity from surgery is between 19% and 28%, mainly caused by minor complications such as urinary tract infection and postoperative pneumonia.^{40,68}

Early postoperative occlusion after FMD reconstructions is seen in 3.8% to 13% of cases, and it occurs more often with venous grafts than with arterial autografts.^{41,71,72,75} It is more frequent after the repair of small renal arteries. Optimal intraoperative assessment of the reconstruction is of the utmost importance to ensure that no technical defects will induce graft thrombosis.⁷⁰



Figure 143.9 Ectatic vein bypass after an aortorenal bypass 6 years earlier. No further dilation has occurred during the 10-year follow-up.

If pain over the kidney increases postoperatively, diuresis is reduced (which is often hard to evaluate because mannitol has been given and ischemia time differs), or episodic hypertension occurs during the postoperative course, graft occlusion should be ruled out. This can be achieved with ultrasound, conventional angiography, CTA or MRA. Symptoms may be minor, however, which is reflected by the fact that Reiher and coworkers found nine unsuspected thromboses in 90 reconstructed patients on routine postoperative angiography.⁷¹ If occlusion is found, reestablishment of the renal circulation should be attempted, depending on both the time elapsed between the supposed occlusion and its diagnosis and the collateral circulation, which often helps in delaying irreversible ischemia. Rescue surgery can be considered several days after an occlusion if the renal parenchyma is enhanced by contrast examinations.

Late restenosis has become less common because most anastomoses are now made in an ovoid shape. Restenosis has been reported in 0% to 16% of patients^{41,71,72} and in less than 8% of vein graft bypasses and even less in arterial allografts.⁷⁶

The need for redo procedures in patients with FMD differs depending on the technique used and the complexity of the initial lesion.^{41,71,72} Secondary treatment using endovascular technology has shown good results, perhaps because a restenosis is more fibrotic.^{8,70,71}

Late vein graft dilations were documented in 20% to 44% of patients in early series of aortorenal bypasses in adults.^{76,77} Normally a nonprogressive increase in vein diameter is seen (Fig. 143.9). Vein graft dilation has not been reported in series from the last decade, perhaps reflecting the fact that patients

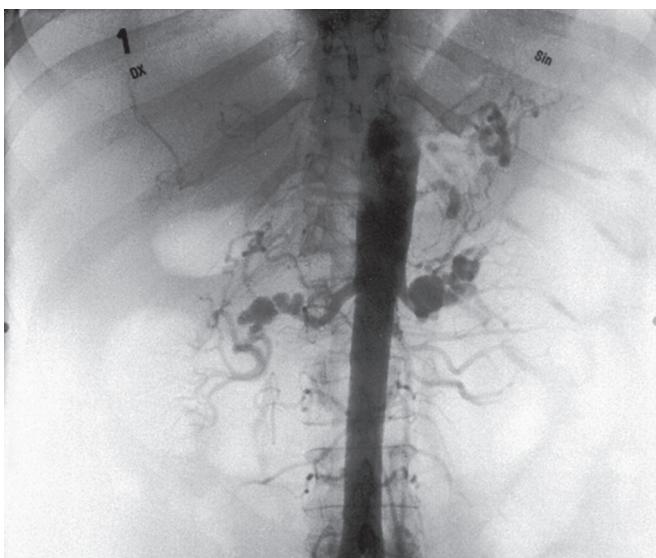


Figure 143.10 Bilateral fibromuscular multifocal dysplasia and aneurysm formation in both renal arteries. Hypertension was fairly well controlled on two drugs. No progression of the aneurysms or hypertension has been seen during 18 years of conservative treatment.

with FMD are now older and have a longer duration of hypertension before diagnosis and treatment than in early series. Renal failure is very uncommon after surgery in patients with FMD.

FIBROMUSCULAR DYSPLASIA AND ANEURYSM

A large proportion of patients with FMD exhibit the string-of-beads appearance, with small aneurysmal areas interspaced by webs in the renal artery. “Macroaneurysms” with obvious aneurysmal development are not infrequent, however; in the U.S. Registry, 25 of 294 patients with renal artery FMD had aneurysmal changes.¹⁶ The University of Düsseldorf group reported on 11 cases of renal artery aneurysm among 101 patients with FMD with renovascular hypertension and treated 48 patients with FMD for renal artery aneurysm. Vuong and associates found that of 131 histologically examined renal arteries in patients with FMD, 35 specimens showed aneurysms measuring 0.5 to 2 cm.¹⁰ Most renal artery aneurysms have a low risk of rupture and only a few ruptured FMD lesions have been reported. The handling of FMD-related aneurysms measuring 1 to 2 cm is unclear at present. Conservative treatment may be successful (Fig. 143.10). If additional risk factors are present, treatment may be justified. Aneurysms larger than 2 cm should probably be excluded.^{70,71} Among pediatric patients with FMD undergoing open surgery, renal artery aneurysms are reported in 5% to 12%.^{35,78}

Endovascular experience is limited. In some patients with renovascular hypertension, small aneurysms may shrink after successful PTCA of stenotic areas (Fig. 143.11). Favorable outcomes have been reported with both embolization and the use of stent grafts.⁷⁹



Figure 143.11 Female patient with a fibromuscular dysplastic multifocal lesion treated with endovascular dilation. The medium-sized aneurysm at the branch site decreased in size during follow-up, and the hypertension has clearly improved.

PEDIATRIC RENAL ARTERY STENOSIS AND ARTERIAL DYSPLASIA

Renovascular disease is among the most common causes of hypertension in children, after thoracic aortic coarctation and renal parenchymal disease (Fig. 143.12).³⁵ Approximately 8% to 10% of all pediatric cases of secondary hypertension are due to renovascular disease, and pediatric RAS may occur in many different conditions, including FMD, developmental RAS, vascular neurofibromatosis type 1, moyamoya, Takayasu disease, Alagille syndrome, and Williams syndrome.^{35,80} Up to 40% of children with renovascular hypertension have developmental renal artery lesions with midaortic syndrome and coexisting lesions in both the mesenteric and carotid arteries (see Ch. 132, Renovascular and Aortic Developmental Disorders).⁸⁰

Endovascular Treatment in Children

Technical success rates are high in published series, with cure or improvement reported in more than 80% of cases.^{35,80,81} Because children have a greater tendency than adults for vasoconstriction during endovascular procedures, many centers give small doses of nitroglycerin at every exchange of catheters or wires to minimize this problem.

The string-of-beads type of lesion is not frequent in children. After ballooning of a stenosis, the frequency of recoil is high. If this persists after more prolonged dilation, oversized or cutting balloons should not be used until it has been determined whether the artery is dysplastic or hypoplastic. Patients with a suspected hypoplastic renal artery or a complex stenosis should be considered for open surgical repair. Long-term data on PTCA in children demonstrate variations in outcome. Restenosis is reported in up to one-third of patients. Follow-up examinations are recommended, especially if the initial treatment was for a complex or branch stenosis. A high rate of failure is also reported after treatment of multisegmental stenosis.

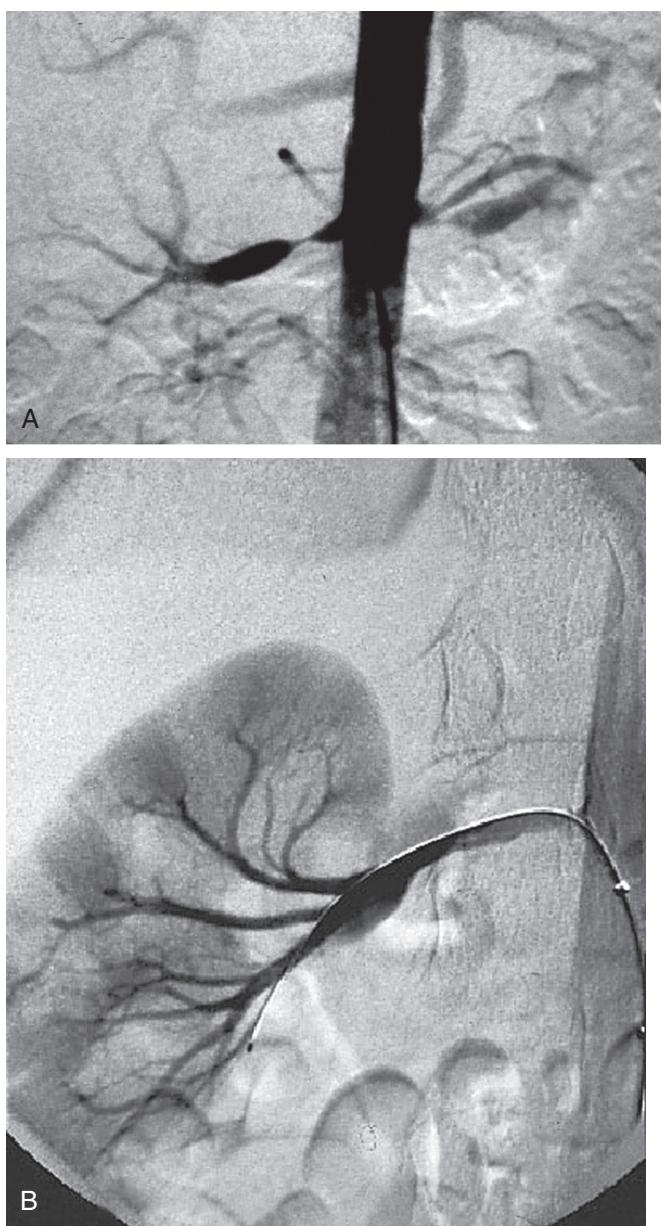


Figure 143.12 (A) Bilateral renal artery unifocal stenosis in a 6-year-old boy with tapered narrowings close to the takeoff from the aorta. Hypoplasia was ruled out. (B) He was treated first on the right side, after which the left stenosis was treated. He required a redo of the right lesion 4 years after the initial treatment.

Overall, the results may be encouraging, but they must be weighed against the results of open surgical repair in children. Because series are small, centralization of treatment is recommended. Treatment of very young children to achieve a moderate improvement may allow open surgery to be delayed until they are older, when the procedure can be performed with better long-term results.

Open Surgery for Pediatric Renovascular Hypertension

A high proportion of pediatric patients with FMD have ostial lesions. In the University of Michigan Pediatric

Renovascular Group's report, 12 of 97 children undergoing open operation had multisegmental disease, 6 had aneurysms, 70 had ostial lesions, 15 had main artery changes, and 18 had branch involvement.³⁵ Unilateral stenosis was seen in 65 children and bilateral stenosis in 47. Few girls younger than 10 years of age were treated; at that age, boys were three times more likely than girls to be affected. For children between the ages of 10 and 17, no gender difference was noted. Eleven children with irreparable renal disease required planned and one child unplanned nephrectomy due to technical failure of the reconstruction. The Michigan group has avoided aortorenal bypass with saphenous vein grafts owing to aneurysm formation in 6 of 25 pediatric vein bypasses.^{77,80} Huang and colleagues reported on one case of aneurysm development among 12 pediatric venous bypasses requiring redo procedures.⁸² Centers of excellence advocate direct aortorenal anastomosis if feasible, and the University of Michigan experience showed that direct anastomosis was possible in 41 of 58 recent reconstructions.³⁵ Arterial allograft is recommended, and the internal iliac artery is usually preferred over a saphenous vein bypass.

The procedural mortality after renal surgery in children is low, and few children develop renal impairment requiring dialysis. Long-term follow-up shows excellent results, with minimal restenosis and reintervention rates following reconstruction in spite of the children's growth. Centralization of the operative treatment of children is required.

EXTRACRANIAL CEREBROVASCULAR FIBROMUSCULAR DYSPLASIA

FMD is most commonly believed to affect the renal arteries and less frequently the carotid and vertebral arteries; however, data on the first 447 patients in the U.S. Registry show the extracranial carotid and vertebral arteries to be nearly as often involved as the renal arteries, primarily in middle-aged women.¹⁶ Carotid FMD is associated with cerebral aneurysms and FMD involving the renal arteries.

Epidemiology

Although the prevalence in the general population is not well known, the incidence of carotid FMD was 0.42% in 3600 patients undergoing cerebral arteriographic examination in one study.⁸³ Many of these examinations were performed for suspected cerebrovascular disease, and thus the true frequency of carotid FMD in the general population is probably lower. In one series of 2000 carotid operations, FMD was the identified pathology in 3.4% of cases.⁸⁴ Carotid FMD is bilateral in 35% to 85% of reported cases.^{1,2,84} Women 40 to 60 years of age predominate in most series, constituting 60% to 90% of patients.^{1,2,84,85} This lesion is rare in African Americans. As described in the earlier section entitled Renal Artery Fibromuscular Dysplasia, a patient may have evidence of FMD in a single artery or in multiple vascular beds; therefore, appropriate diagnostic evaluation is recommended.

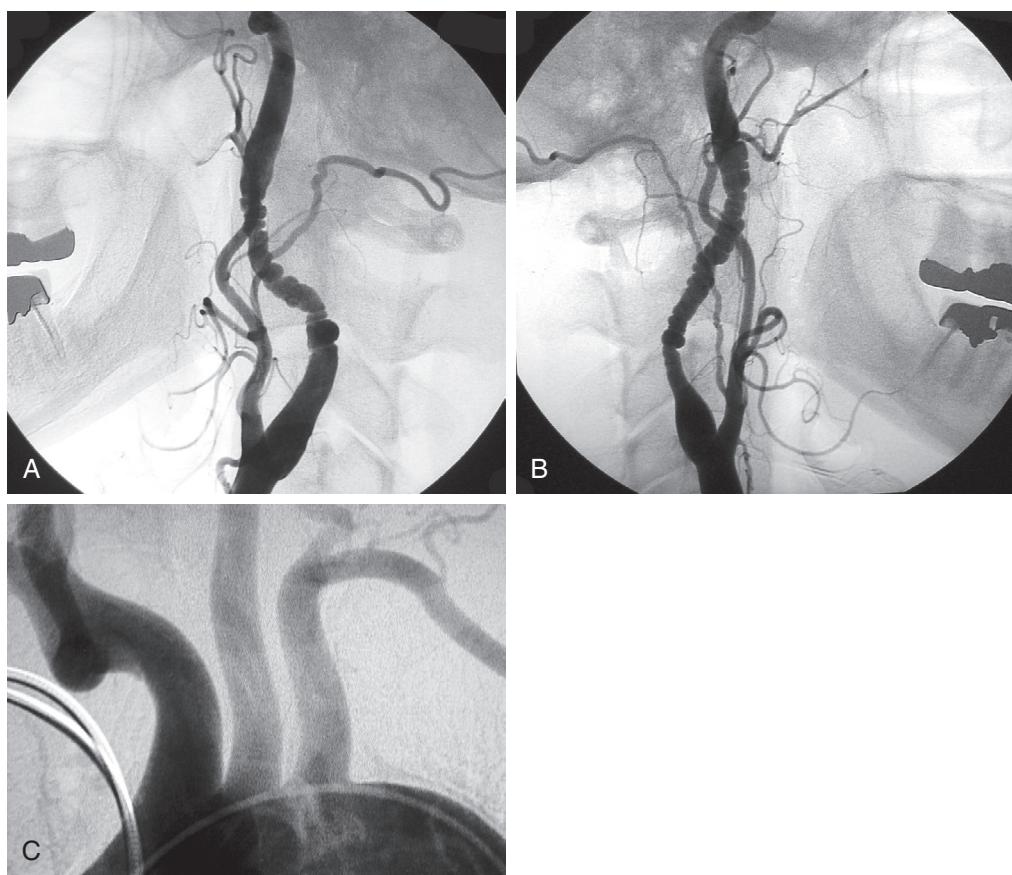


Figure 143.13 (A and B) Carotid arteriograms demonstrating the classic appearance of fibromuscular dysplasia in the usual location opposite the C1–C3 vertebral bodies and intervening disks. Note the low bifurcation and long internal carotid artery. The lesions are present bilaterally in this 43-year-old woman. (C) The aortic arch shows no evidence of disease.

Pathophysiology

This topic is discussed earlier in this chapter, under Pathogenesis of Fibromuscular Dysplasia. Complications occurring with carotid FMD include encroachment on the arterial lumen, causing reduced perfusion, cerebral embolization of thrombus, and dissection leading to stenosis or aneurysmal dilation and possible rupture. These complications occur in less than 10% of cases.

Among the four types of FMD, the internal carotid artery is most often affected by medial fibroplasia, which results in an arteriographic appearance resembling a string of beads (Fig. 143.13), seen in 80% to 95% of the lesions.^{1,2,84,85} The arterial segments involved tend to be more distal than in the case of arteriosclerosis; they are located in the middle and distal segments of the extracranial internal carotid artery without any appearance of disease at the carotid bifurcation. The serial stenoses are frequently evident on examination of the external surface of the artery (Fig. 143.14). The artery is often elongated and tortuous, and kinking occurs in approximately 5% of cases (Fig. 143.15). Similar disease of the external carotid artery or the intracerebral arteries is rare.

Concurrent pathology that frequently complicate the management of carotid FMD include the following:

1. Atherosclerotic occlusive disease at the carotid bifurcation is seen in as many as 20% of individuals with carotid FMD.^{84,86}

2. Extracranial carotid artery aneurysms. In the U.S. Registry, carotid aneurysms (including the extracranial and intracranial internal carotid artery and the ophthalmic artery) were reported in 16 (21.1%) of 76 patients with carotid FMD.¹⁵
3. Carotid artery dissection. In the U.S. Registry, carotid dissection was identified in 14.8% of 447 patients enrolled. Carotid artery dissection was prevalent in patients with carotid FMD and was seen in 68 of 88 (75.0%) patients.¹⁶ The prevalence of FMD in individuals with cerebrovascular dissection is roughly 5% but may be as high as 15%–20% considering vascular beds beyond the cerebrovascular circulation were not evaluated for FMD in the majority of these cases.^{87–89}
4. Vertebral artery FMD. This is identified in 7% to 38% of patients with carotid lesions and is occasionally an isolated finding.^{84,90} Vertebral artery disease is usually located at the level of the C2 vertebral body and does not extend intracranially.⁸⁵
5. Intracranial aneurysms and occlusive disease. This is found in at least 10% of patients with FMD in general and as many as 51% of patients with internal carotid FMD in particular.^{1,2,85,90} Solitary intracranial aneurysms are present in 80% of these patients, but multiple aneurysms occur in the remaining 20%. In the U.S. Registry, intracranial FMD, manifesting primarily as intracranial aneurysms, was reported in 8.3% of patients.¹⁶ These aneurysms tend to be



Figure 143.14 Medial fibrodysplasia of the extracranial internal carotid artery. Operative exposure of the artery reveals an external beaded appearance due to serial narrowing.

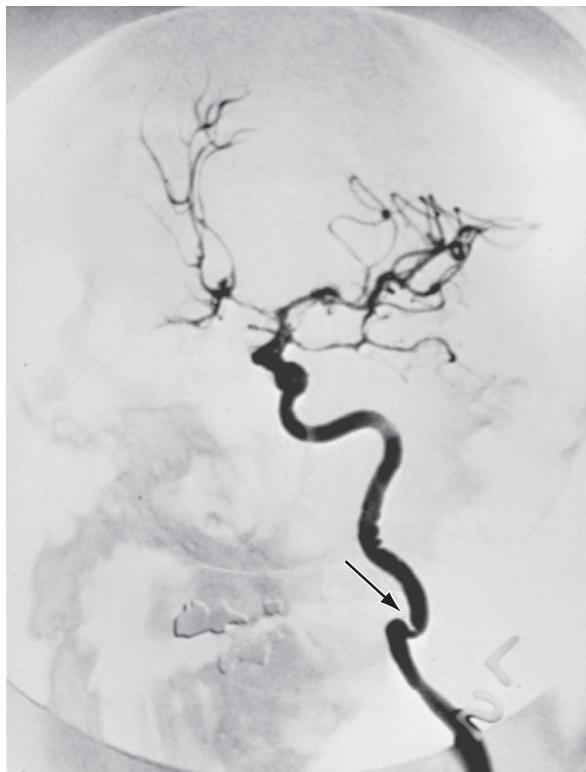


Figure 143.15 Medial fibrodysplasia of the extracranial internal carotid artery, with angulation and stenosis (arrow) affecting a tortuous elongated segment. (From Stanley JC, et al. Extracranial internal carotid and vertebral artery fibrodysplasia. *Arch Surg*. 1974;109:215–222.)

on the same side as the extracranial carotid FMD. They pose an independent threat of rupture and hemorrhage, and their natural history has the potential to be worsened by relief of a proximal stenosis.

6. Renal artery FMD coexists with carotid FMD in 8% to 40% of patients.^{1,2,84}
7. An entity named “carotid web” or “carotid bulb diaphragm” has been classified as atypical FMD of the carotid bulb, though is still believed to be distinct from the clinical syndrome of FMD.³ These diaphragms are endoluminal webs or spurs that can be visualized as linear defects on CTA or MRA. This entity seems to be associated with a high risk of ischemic stroke, likely via an embolic mechanism, which may justify carotid stenting or endarterectomy in the setting of recurrent ischemic events despite medical treatment.

Natural History

Our understanding of the natural history of FMD of the carotid circulation is not complete. Many series have documented the potential for carotid FMD to cause symptoms, as discussed earlier, but the natural history of asymptomatic lesions is less well documented. In one series of 79 patients, most of whom were found to have carotid FMD incidentally on cerebral angiography (0.6% of the total), only 3 (4%) subsequently suffered a cerebral ischemic event during an average follow-up of 5 years.⁹¹ When small groups of asymptomatic patients were studied prospectively, less than 10% went on to experience new neurologic symptoms. Roughly one-third of carotid FMD lesions demonstrate significant angiographic progression with time.^{2,90,91} Most cases of asymptomatic carotid FMD are known to remain clinically silent, and there is no optimal method of noninvasive follow-up of these lesions to reliably grade progression. None of the existing studies has included a significant number of patients with high-grade asymptomatic stenoses, a group in which the risk for stroke would be expected to be higher.

Clinical Presentation

Extracranial cerebral artery FMD may be either an incidental finding without symptoms or the cause of neurologic events. Symptomatic manifestations in large, contemporary series of treated patients include TIA, stroke, and disability. Stroke is the initial finding in 12% to 27% of patients. Hemispheric TIA occurs in 31% to 42%, and amaurosis fugax in 22% to 28%.^{84,90–92}

Physical examination findings at the time of enrollment were available for 414 patients (92.6%) in the U.S. Registry. Findings consistent with Horner syndrome (pupil abnormality or ptosis) were reported in 12.4% of patients. Cranial nerve abnormalities were reported in 9.4%, and other focal neurologic deficits in 13.6%. Bruits were reported over the carotid arteries (30.5%; 18.1% bilateral), epigastrium (17.5%), and flanks (6.1%). Among 306 patients with reported imaging of the extracranial circulation (carotid and vertebral) and a documented physical examination for carotid bruits, 227 (74.2%) had FMD. The sensitivity of a carotid bruit for extracranial

FMD was 103 of 227 (45.4%), and the specificity was 74 of 79 (93.7%).¹⁶

Patients can also present with nonspecific symptoms or signs that frequently occur with carotid or vertebral artery FMD, such as dizziness, long-standing headaches, altered mentation, pulsatile tinnitus, neck pain, headache, wooziness, and a swishing (swooshing, whooshing) sound in the ears. Such symptoms should trigger diagnostic evaluation for carotid FMD, especially in younger patients with no classic risk factors for atherosclerotic disease. Patients can report significant disability because of the constant noise in their ear and they seek support and help with others who are similarly afflicted.^{4,93}

More focal and specific neurologic signs and symptoms may be related to one or more of the following mechanisms: (1) severe stenosis producing hypoperfusion, (2) embolization, (3) thrombosis, (4) dissection, and (5) aneurysm rupture.^{94,95}

Other than this process occurring in a relatively young, mostly female population, the history and physical findings may be notable for the absence of additional identifying factors. There may be no particular history or inciting factors. The presence of atherosclerotic risk factors is variable. Physical examination may detect bruits in other locations.

Diagnostic Evaluation

Most asymptomatic patients with carotid bruit and those with hemispheric or nonfocal neurologic symptoms undergo carotid duplex ultrasound (DUS; see Ch. 91, Cerebrovascular Disease: Diagnostic Evaluation). DUS may reveal elevated velocity as a result of FMD, but the lesion may be missed because it is located more distally than the usual atherosclerotic plaque.^{86,96} If the lesion is detected, the DUS study may not be able to evaluate the artery distal to the lesion because FMD may involve the artery all the way to base of the skull. Standard arteriography is excellent at delineating the anatomic features of FMD of the extracranial cerebral arteries. Many cases of carotid FMD are discovered during arteriography.⁸⁵ Severe tortuosity in the distal carotid arteries, an interesting finding, is seen in patients with FMD. This may occur in the absence of other findings such as beading. However, it is unclear whether this represents another manifestation of FMD.^{4,93}

CTA may replace standard catheter-based arteriography in the evaluation of carotid FMD when enough experience has been gained for clinical and anatomic correlation, just as CTA has done in relation to other vascular beds and disease processes. When carotid FMD is identified, the intracranial vascular anatomy should be evaluated to check for the presence of intracranial aneurysms as well as contralateral carotid stenosis and vertebral artery disease. In fact and as described in a previous section, the extra- and intracranial anatomy should be evaluated for any FMD diagnosis. MRA has not been particularly useful in the diagnostic evaluation of carotid FMD because of the tendency for signal dropout with tight lesions and the propensity to produce a “beaded” appearance in normal conduit arteries, which may be confused with FMD. MRA may be beneficial in the follow-up of known FMD. Computed tomography or magnetic resonance imaging of the brain should be

performed in patients with carotid FMD to look for evidence of infarction as well as for cerebral aneurysms.

Treatment Selection

Given the generally benign behavior of asymptomatic disease, patients with asymptomatic carotid FMD should be monitored and treated medically, with antiplatelet therapy for primary stroke prevention. There is no evidence to suggest a role for lipid-lowering therapy in patients with isolated FMD, although it should be considered as part of a primary prevention strategy in those with abnormal low-density lipoprotein cholesterol (LDL) levels and evidence of atherosclerotic occlusive disease.

Most reported cases of symptomatic carotid FMD have been treated with dilation of the responsible artery. There is no study in which a large number of patients with carotid FMD and focal cerebral ischemic events were treated medically. In a small series, 13 patients with either TIA (10 patients) or stroke (3 patients) did not undergo surgical intervention; only 1 patient remained symptomatic.⁹⁷

Another rare potential indication for invasive therapy in patients with carotid FMD includes disabling intractable headaches. Percutaneous interventions have been offered to such patients, although the pathogenesis of headache in such patients is not known. The key lies in careful patient selection, reserving invasive therapy for patients with severe disabling symptoms after other common etiologies have been evaluated and ruled out and conservative therapies have been exhausted.^{4,93}

At present we are left with a rare cause of focal cerebral ischemic events – extracranial carotid stenosis – which can be repaired with a fairly simple open operation or with percutaneous balloon dilatation.

Therapeutic Challenges

Because of the lack of sophisticated data on carotid FMD, the following challenges frequently arise in its management and must be considered during the treatment planning stage:

1. One of the key driving factors in the treatment of atherosclerosis of the carotid bifurcation, the degree of stenosis, cannot be determined with any reliability in carotid FMD. This problem makes the severity of the disease in a given patient extremely difficult to assess. The indication for mechanical treatment is driven primarily by the development of cerebral ischemia. The problem also compromises the follow-up of asymptomatic patients.
2. It is not always possible to determine which of two concurrent lesions is causing the cerebral symptoms, as is the case with coexistent carotid FMD and significant atherosclerotic disease of the carotid bifurcation. These lesions are usually treated simultaneously. Carotid FMD may also be associated with a coexistent cerebral aneurysm, presenting the same dilemma of competing suspected lesions.
3. When symptomatic carotid FMD is treated, it can be a challenge to decide how to manage a contralateral severe but asymptomatic lesion. Although asymptomatic lesions seem to have a generally benign course, such may not be the case

- in a patient who suffered a stroke on the contralateral side from the same pathology.
4. Patients with carotid FMD often have nonfocal symptoms, some of which may be due to global ischemia. The indications for intervention in this situation are ambiguous.
 5. The presence of an intracranial aneurysm may alter the treatment sequence or the surgical approach.
 6. The presence of hypertension secondary to renal artery FMD may complicate any procedure performed for carotid FMD.

Clinical Considerations

Because of the relative safety and effectiveness of mechanical intervention (see the section titled Mechanical Repair, further on), dilation of the artery is appropriate for lesions causing focal ischemic events (hemispheric or ocular) or episodes of cerebral hypoperfusion. A lesion causing a focal cerebral ischemic event should be considered for treatment because it remains a significant threat. Hypoperfusion is rare but can occur in the setting of critical bilateral carotid FMD or even unilateral disease when there is a significant defect in the circle of Willis. Percutaneous transluminal angioplasty (PTA) has been successful in the treatment of renal artery FMD, and carotid angioplasty with stenting has a growing role in the management of carotid disease; however, the results and durability of balloon angioplasty for carotid FMD with or without stent placement are not known. Symptomatic patients should be considered for balloon angioplasty using a transcervical approach with proximal clamping and a reversed flow circuit (TCAR approach) or percutaneous balloon angioplasty if the anatomy allows the use of cerebral protection devices.

Anatomic Considerations

Cerebral protection

The lesion requiring treatment in carotid FMD is usually a series of webs with intervening pockets, in between which platelet thrombi and cellular debris have accumulated. Disruption of the webs, whether by balloon dilatation or rigid dilatation, produces potentially embolic debris. Some type of cerebral protection is warranted. Carotid FMD tends to involve the carotid artery for several centimeters distal to the bifurcation and may affect the length of the artery to the base of the skull, thus precluding a “landing zone” for an embolic filter to be placed during the procedure. Most distal filters require a few centimeters of straight, healthy artery proximal to the petrous portion of the carotid artery to be functional and safely placed. Cerebral protection using a flow reversal circuit (common carotid artery to femoral vein) and proximal occlusion of the common carotid artery may be the best method of protection during percutaneous intervention.

Stents

It is not clear whether carotid balloon angioplasty should be accompanied by stent placement in FMD. Stent placement is not usually required after PTA in renal artery FMD because the results are excellent without stents and the patients are

usually otherwise young and healthy with good life expectancies. However, stents are routinely placed when atherosclerotic stenosis of the carotid bifurcation is treated percutaneously, and there is some likelihood that stent placement after PTA helps stabilize flaps and disrupted dysplastic tissue. Experience with PTA for carotid FMD is limited, and there are even fewer cases of carotid stent placement for FMD. In light of this paucity of cases, more time will be required to determine the role of PTA with or without stenting in the treatment of patients with carotid FMD.

Medical Management

Patients with asymptomatic carotid stenosis secondary to FMD should be started on a regimen of antiplatelet agents. Diagnostic evaluation should be undertaken to rule out other arterial pathology. If associated conditions are identified, either in the carotid circulation (e.g., carotid aneurysm) or in other vascular beds (e.g., RAS), they should be treated as needed. Management of cervical artery dissection (see Chs. 96, Cerebrovascular Disease: Carotid Artery Dissection, and 100, Vertebral Artery Dissection and Other Conditions) or stroke (see Ch. 95, Endovascular Management of Large Vessel Occlusion in Acute Ischemic Stroke) associated with FMD should be similar to that of patients without FMD.

Carotid FMD should be monitored at intervals of 6 months with a noninvasive study such as DUS, CTA, or MRA. If DUS follow-up is used, the internal carotid artery must be interrogated as distally as possible. If symptoms develop or there is a significant change in the pathologic lesion (e.g., dissection), mechanical repair of the artery should be considered. There is no established role for anticoagulation or for anti-inflammatory medications such as steroids in carotid FMD. Chiropractic manipulation of the neck should be avoided, as should sports that are likely to produce whiplash-type neck injuries.

Mechanical Repair

Methods of mechanical intervention for the treatment of carotid FMD include open surgical graduated rigid dilatation, open common carotid artery access for balloon dilation (with or without stent placement) with proximal clamping and neuroprotection with a reversed flow circuit to avoid embolization, and transfemoral PTA (with or without stent placement or cerebral protection devices). Although open surgical exposure of the bifurcation and rigid dilatation has been successfully used in the past, balloon therapy with flow reversal represents the optimal current approach. Surgical therapy or endovascular therapy with stents or coils may also be needed for patients with concomitant aneurysms or with aneurysmal complications.

Open surgical dilation

The usual fibrohyaline lesion encountered in the internal carotid artery responds to mechanical dilation. Over the past several decades such treatment has been performed with relative success and safety by means of rigid dilators of progressively enlarging size passed antegrade into the internal carotid artery with arterial control.^{1,8,27,31,32} This approach permits gentle

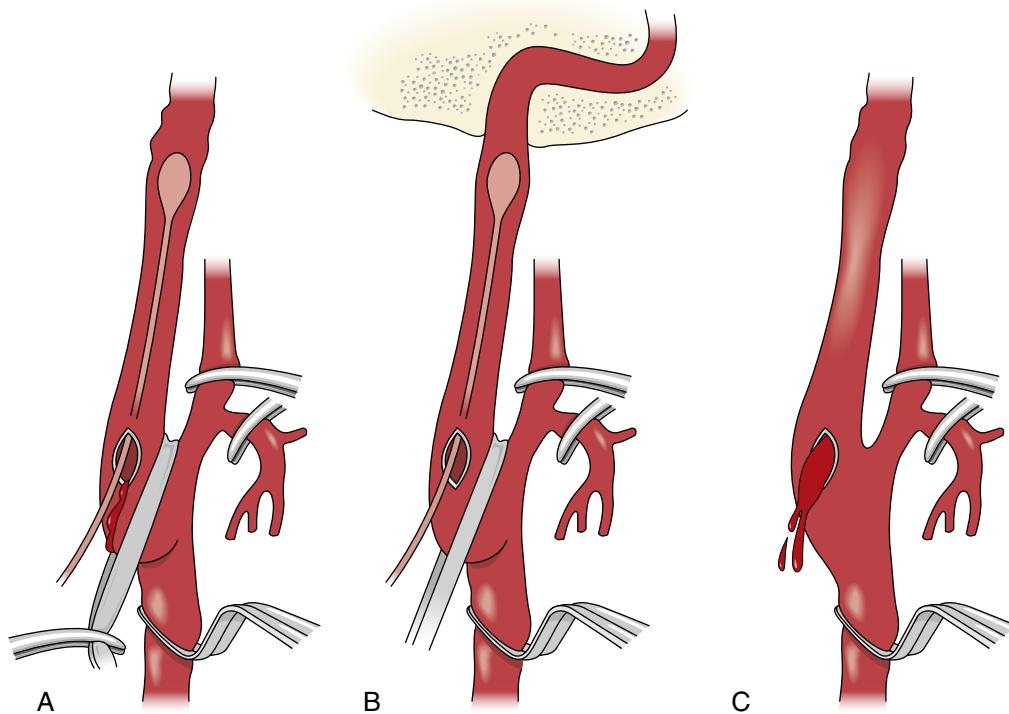


Figure 143.16 Drawings showing the main features of the open surgical technique. (A) Straightening of the carotid artery with downward traction on a polymeric silicone (Silastic) sling. (B) Gentle, graduated dilation of the internal carotid artery from 2 to 4 mm. Passage of the dilator to the bony canal at the base of the skull is shown. (C) Back-bleeding of the artery to remove dislodged debris. (From Wylie EJ, et al. Nonatherosclerotic diseases of the extracranial carotid arteries. In: Eggers R, ed. *Manual of Vascular Surgery*, New York: Springer-Verlag; 1986:184–185.)

disruption of the obstructive webs while allowing associated debris to be flushed out of the artery and has been shown over the years to have reasonable results.

The main disadvantages of this approach are that it is performed without imaging of the luminal surface and it requires full, open exposure of the carotid bifurcation. The length of the arterial segment to undergo treatment must be estimated. Kinks and coils must be managed by “feel” without direct guidance. There is no simple method of assessing the results of treatment in real time, the way interval arteriography can guide a procedure during endovascular treatment.

Exposure for the open approach is similar to that for carotid endarterectomy except that higher internal carotid artery exposure is usually required to ensure that dilation is carried out under direct vision and that the extracranial carotid artery can be safely straightened during passage of the dilator. The posterior belly of the digastric muscle may be divided (see Ch. 57, Cerebrovascular Exposure). The normal arterial segment above the highest point of involvement is apparent with direct inspection, and the internal carotid artery is encircled at this point. This approach should not be used if the distal internal carotid artery is not accessible.

Determination of stump pressure or electroencephalographic monitoring is not ordinarily needed for this brief procedure but may be indicated if a more extensive procedure is planned (e.g., bifurcation endarterectomy, correction of redundancy, interposition grafting). Heparin is administered (75–100 U/kg) before flow is interrupted. The common carotid artery is

cross-clamped. Traction on a polymeric silicone (Silastic) sling placed around the internal carotid artery just above the bifurcation is performed to straighten the artery. A short arteriotomy is made in the internal carotid artery at the base of the bulb. Graduated metal dilators are then gently passed up the straightened internal carotid artery, beginning with a probe 1.5 mm in diameter and progressing up to a 3.5-mm diameter probe or, occasionally, one 4.0 mm in diameter (Fig. 143.16). A series of “giving” sensations is usually felt as each septal stenosis is gently fractured, but such sensations are not felt thereafter.

The procedure is terminated after the segment has been gently stretched to full diameter throughout its course. This step can usually be observed under direct vision. It is important not to exceed this gentle stretching and therefore not to proceed beyond a 4-mm diameter. Back-bleeding after passage of the dilators should be thorough because large debris is sometimes retrieved. The short arteriotomy is closed rapidly with a simple running suture of 6-0 polypropylene. Careful interrogation of the entire segment with a Doppler ultrasound probe or DUS scanner after restoration of flow ensures patency without turbulence and residual defect.

There are three large series of surgically managed patients.^{19,98,99} These reports consist primarily of patients undergoing rigid carotid dilation but also include some instances of carotid replacement and vertebral revascularization. The incidence of perioperative stroke during surgical treatment in these series ranged from 1.4% to 2.6%. TIA occurred in 1.4% to 7.7%, and perforation occurred twice in 318 operations

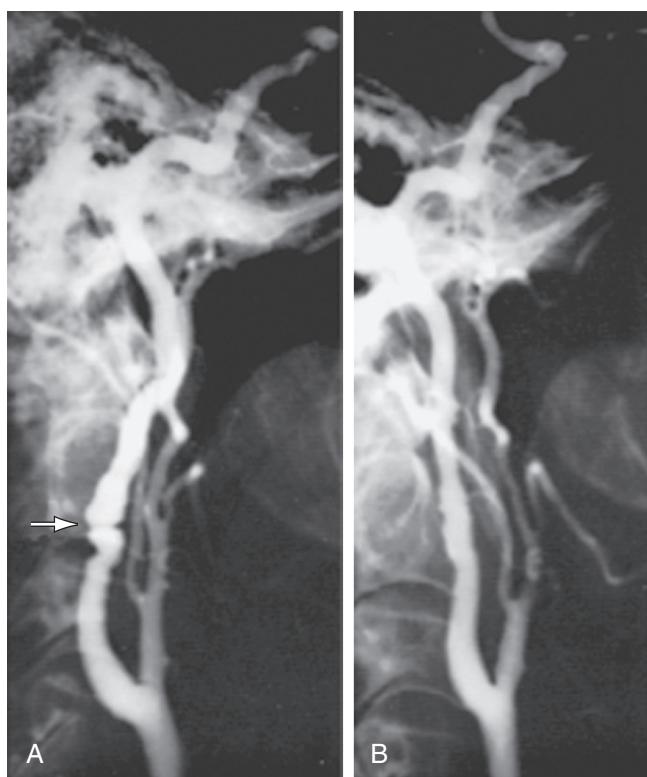


Figure 143.17 (A) Preoperative right carotid arteriogram showing a localized zone of fibromuscular dysplasia characterized by an intraluminal diaphragm (arrow). (B) Postoperative right carotid arteriogram after graduated intraluminal dilation. The carotid lumen is now widely patent.

(0.6%). Cranial nerve injuries, most of which were transient, resulted from extensive distal operative exposure of the internal carotid artery and were reported to occur in 5.1% to 16.7% of cases.

Excellent long-term follow-up data are available. Late stroke developed in 1.2% to 3.8% of patients, and nearly all late deaths (up to 22 years) were due to non-neurologic causes. In one series, 94% of patients underwent DUS scanning (mean follow-up, 7 years).⁹⁸ Actuarial rates of primary patency, survival, and stroke-free survival were 94%, 96%, and 94%, respectively, at 5 years and 94%, 82%, and 88%, respectively, at 10 years. When follow-up angiography is performed, it usually demonstrates a normal-sized lumen (Fig. 143.17).

Balloon angioplasty

The rationale for this approach is based on the success of PTA in the treatment of renal artery FMD. Balloon angioplasty of carotid FMD may be performed using three different approaches; each one has an associated method of access and a method of cerebral protection.

The first method is an open but limited exposure of the very proximal common carotid artery just distal to the clavicle with insertion of an 8-F sheath. The arterial sheath is connected to a circuit and filter that flows into the common femoral vein, using a TCAR approach. TCAR, or transcarotid artery revascularization, was developed to treat atherosclerotic disease of the carotid bifurcation (as described in Ch. 94, Carotid Artery Stenting) and these techniques lend themselves well to the

management of FMD. The common carotid artery at the access site is usually healthy in these patients. The bifurcation is not usually affected by FMD, so the external carotid artery may be used for placement of an exchange guide wire during the process of sheath placement. After the common carotid artery sheath is placed and the flow circuit is connected, with flow into the low resistance femoral vein, very robust cerebral protection can be obtained after the common carotid artery is cross-clamped. This permits continual back-bleeding and washout of any potential debris and also provides the opportunity for interval arteriogram and the ability to respond to the results of treatment or manage other lesions. If stent placement is required, there is excellent access for stent placement using this platform. If an atherosclerotic carotid bifurcation disease requires treatment it can be treated simultaneously using this approach. Although there is no data yet using this approach, this may be the best way to introduce an angioplasty balloon because of the excellent cerebral protection and control of the procedure.

A second method for performing balloon angioplasty utilizes open surgical exposure of the bifurcation for arterial control, as described under Open Surgical Dilation. Results in a small number of patients in several reports appear acceptable.^{100,101} The benefit of this approach is the opportunity for controlled dilation with interval arteriography while maintaining the ability to back-bleed the artery and avoid embolization of debris from the dilated lesion. The disadvantage is that the cerebral protection is achieved with intermittent back-bleeding, and without continuous flow reversal.

A third method of balloon angioplasty is with the use of percutaneous transfemoral access and placement of a sheath in the common carotid artery. Because these patients tend to be younger and healthier than those who undergo intervention for atherosclerotic disease, the aortic arch and common carotid arteries are less likely to be diseased and may be amenable to safe passage of a sheath and proximal balloon occlusion at the bifurcation. The carotid arteries frequently arise from the superior aspect of the arch rather than on the upslope of the proximal arch (see Fig. 143.13). The carotid artery sheath may be placed in the distal common carotid artery because the bifurcation is not usually diseased (Fig. 143.18).

Some technical aspects of angioplasty, regardless of access and approach, are included here. Heparin is administered to achieve an activated clotting time >250 seconds. The external carotid artery is generally normal in appearance and can be used as a place to anchor a stiff exchange guide wire for sheath placement. After the stiff exchange guide wire is placed, the carotid sheath is advanced. Because internal carotid artery lesion may extend to the base of the skull, the image intensifier must be placed so that the operator can observe the distance from the tip of the sheath inferiorly to the area distal to the lesion superiorly. Cerebral protection varies with each approach, as discussed previously. The preferred approach is a transcarotid artery approach with robust flow reversal. The intolerance rate is quite low and cerebral protection is continuous. In a percutaneous approach, if there is no safe landing zone for a distal protection device, the patient should undergo

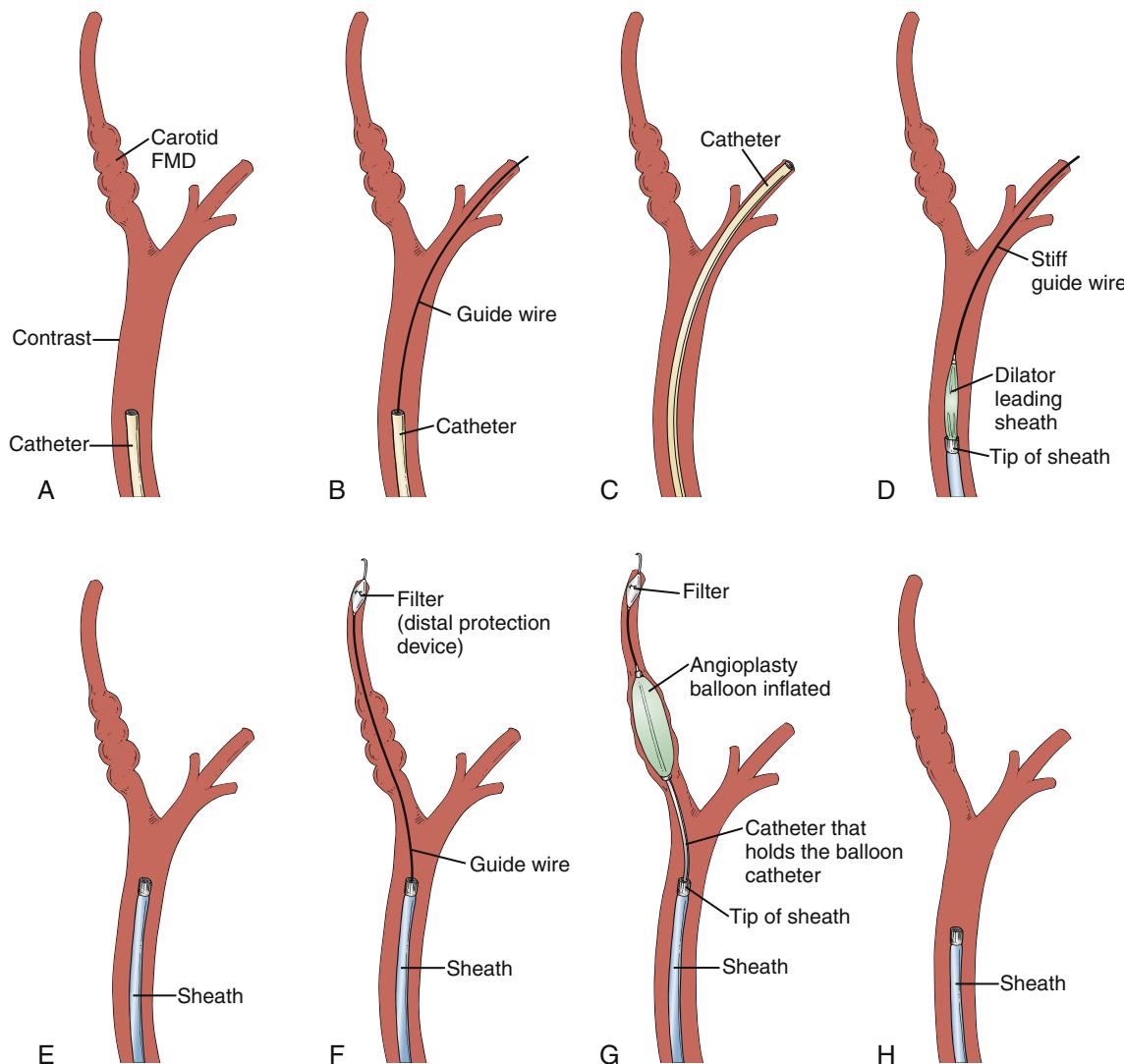


Figure 143.18 Endovascular Technique. (A) Internal carotid artery narrowed by fibromuscular dysplasia (FMD). An arteriogram was performed through a carotid catheter. (B) Guide wire placed in the external carotid artery through use of a road-map arteriogram of the carotid bifurcation. (C) Cerebral catheter advanced into the external carotid artery. (D) Stiff guide wire advanced into the external carotid artery. The carotid access sheath is advanced over this exchange guide wire. (E) Carotid sheath in place with the tip of the sheath in the distal common carotid artery. (F) Cerebral protection device in place in the distal internal carotid artery. (G) Balloon angioplasty of the fibromuscular lesion in the internal carotid artery. (H) After balloon angioplasty, the lumen improved significantly.

treatment using a proximal occlusion balloon with aspiration. Wire passage should be performed with an atraumatic, steerable, 0.014-in diameter guide wire. It is not always possible to identify the lumen as it passes through each web. Patience and persistence may be required to safely cross the lesion. In addition, an angled catheter may be used to support and direct the guide wire as it traverses the web-like internal carotid artery lesions, which sometimes have only pinhole openings. As the guide wire passes through each lesion, the responsiveness and directionality of the guide wire decreases.

If stent placement is anticipated, the nose cone on the stent delivery catheter typically requires at least 2 cm of clearance. Care must also be taken to avoid interactions of the guide wire with any associated intracranial pathology that may be present.

If stent placement is performed, avoid extending the stent as far distally as the petrous portion. An intervening segment of flexible artery should be left if possible. FMD generally covers a longer distance of the internal carotid artery than carotid atherosclerosis and may therefore require a longer balloon. It is best to dilate the entire lesion with a single balloon inflation. The balloon should be slightly undersized with regard to the intended diameter of the artery to help avoid dissection or rupture. Fortunately, the most frequently encountered extracranial carotid FMD pathologic lesion is medial fibroplasia, which is amenable to dilation and less likely to include aneurysmal dilation. For FMD lesions that contain aneurysmal segments, PTA is probably not advisable and they may be better treated with open arterial replacement.

Given a track record of success with PTA of FMD lesions in other locations, primary stent placement is probably not warranted, at least without more data. In addition, FMD tends to occur in a younger group of patients with a long life-expectancy, and the performance of carotid stents over many decades is not known. Lesions that show some evidence of dissection should be considered for stent placement. Self-expanding stents are used and diameters are sized for the distal internal carotid artery (5 or 6 mm). No more than the minimum length of artery required to cover the disease should be stented because stents confer stiffness and create compensatory bends or even kinks in the more relaxed, non-stented segment of artery. Stent placement in a kink should be performed cautiously because the extra curvature is usually transferred to another segment of the artery and may exacerbate a kink in that area. Stent placement in a coil should be avoided altogether.

Unfortunately it is not possible at present to provide a comprehensive assessment of the results of PTA because few data are available regarding perioperative complications or longer-term success.⁴ Periprocedural complications are rare and may include dissection or stroke. No follow-up is available beyond the perioperative period.

FIBROMUSCULAR DYSPLASIA IN OTHER ARTERIAL BEDS

Fibrodysplasia is considered a systemic arteriopathy; although it may be clinically overt when it affects the renal and extracranial carotid, it can frequently be identified in lower limb vessels (mainly iliac arteries) and less frequently in the visceral and coronary arteries.^{4,7,16,98} As discussed earlier, a good clinical examination and imaging of all vessels from brain to pelvis at least once is recommended after FMD has been diagnosed in one vascular bed.³

Although fibrodysplasia is usually asymptomatic, presenting symptoms of lower extremity involvement include claudication or other atypical lower extremity symptoms.¹⁰² In the viscera, FMD usually involves more than one vessel. Although typically asymptomatic, mesenteric ischemia can occur, but owing to extensive collateralization rarely results in infarction.¹⁰³ Epicardial coronary artery involvement has rarely been

reported and has a strong female predilection. Among men and women presenting with acute coronary syndrome undergoing coronary angiography, spontaneous coronary artery dissection (SCAD) is reported in ~1%. In women under the age of 50, SCAD accounts for 10% to 25% of acute myocardial infarctions, 50% of those occurring in the postpartum period. Coronary FMD typically appears as a well-demarcated long smooth lesion in the distal portion of the artery. There is an abrupt transition from an angiographically normal coronary artery to the abnormal area. Rarely, the string-of-beads appearance will be noted in the coronary arteries.^{4,104}

SELECTED KEY REFERENCES

- Chiche L, Bahnini A, Koskas F, Kieffer E. Occlusive fibromuscular disease of the arteries supplying the brain: results of surgical treatment. *Ann Vasc Surg.* 1997;11:496–504.
- Large and thoroughly evaluated surgical series with good long-term data on patency and stroke prevention.*
- Gornik HL, Persu A, Adlam D, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens.* 2019;37:229–252.
- International consensus document on fibromyodysplasia.*
- Lacombe M, Ricco J-B. Surgical revascularization of renal artery after complicated or failed percutaneous transluminal renal angioplasty. *J Vasc Surg.* 2006;44:537–544.
- Open surgery after failed endovascular treatment is possible, with good results.*
- Moreau P, Albat B, Thevenet A. Fibromuscular dysplasia of the internal carotid artery: long-term results. *J Cardiovasc Surg.* 1993;34:465–472.
- Best long-term follow-up of treated patients available.*
- Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004;350:1862–1871.
- Comprehensive summary of fibromuscular dysplasia and its manifestations.*
- Stanley JC, Criado E, Upchurch Jr GR, et al. Michigan Pediatric Renovascular Group. Pediatric renovascular hypertension: 132 primary and 30 secondary operations in 97 children. *J Vasc Surg.* 2006;44:1219–1229.
- Largest series of arterial fibrodysplasia in children.*
- Trinquart L, Mounier-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery atenosis caused by fibromuscular dysplasia: a systemic review and meta-analysis. *Hypertension.* 2010;56:525–532.

A complete reference list can be found online at www.expertconsult.com.

REFERENCES

1. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004;350:1862–1871.
2. Zhou W, Bush RL, Lin PL, Lumsden AB. Fibromuscular dysplasia of the carotid artery. *J Am Coll Surg.* 2005;200:807.
3. Gornik HL, Persu A, Adlam D, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens.* 2019;37:229–252.
4. Olin JW, Sealeve BA. Diagnosis, management, and future developments of fibromuscular dysplasia. *J Vasc Surg.* 2011;53:826–836.e1.
5. Persu A, et al. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens.* 2014;32:1367–1378.
6. Kadian-Dodov D, et al. Dissection and aneurysm in patients with fibromuscular dysplasia: findings from the U.S. Registry for FMD. *J Am Coll Cardiol.* 2016;68:176–185.
7. Olin JW, et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. *Circulation.* 2014;129:1048–1078.
8. Alhadad A, Mattiasson I, Ivancev K, et al. Revascularisation of renal artery stenosis caused by fibromuscular dysplasia: effects on blood pressure during 7-year follow-up are influenced by duration of hypertension and branch artery stenosis. *J Hum Hypertens.* 2005;19:761–767.
9. Sotiriou V, Fry WJ, Stanley JC. Ultrastructural characteristics of experimental arterial medial fibroplasia induced by vasa vasorum occlusion. *J Surg Res.* 1978;24:167–177.
10. Vuong PN, et al. Fibromuscular dysplasia of the renal artery responsible for renovascular hypertension: a histological presentation based on a series of 102 patients. *Vasa.* 2004;33:13–18.
11. Kaufman JJ, Maxwell MH. Upright aortography in the study of nephroptosis, stenotic lesions of the renal artery, and hypertension. *Surgery.* 1963;53:736–742.
12. Hagg A, Aberg H, Eriksson I, et al. Fibromuscular dysplasia of the renal artery—management and outcome. *Acta Chir Scand.* 1987;153:15–20.
13. Leung DY, Glagov S, Mathews MB. Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. *Science.* 1976;191:475–477.
14. Fievez ML. Fibromuscular dysplasia of arteries: a spastic phenomenon? *Med Hypotheses.* 1984;13:341–349.
15. Nicholson JP, et al. Cigarette smoking and renovascular hypertension. *Lancet.* 1983;2:765–766.
16. Olin JW, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. *Circulation.* 2012;125:3182–3190.
17. Bigazzi R, Bianchi S, Quilici N, et al. Bilateral fibromuscular dysplasia in identical twins. *Am J Kidney Dis.* 1998;32:E4.
18. Rushton AR. The genetics of fibromuscular dysplasia. *Arch Intern Med.* 1980;140:233–236.
19. Pannier-Moreau I, et al. Possible familial origin of multifocal renal artery fibromuscular dysplasia. *J Hypertens.* 1997;15:1797–1801.
20. Plouin P-F, et al. Fibromuscular dysplasia. *Orphanet J Rare Dis.* 2007;2:28.
21. Bofinger A, et al. Polymorphisms of the renin-angiotensin system in patients with multifocal renal arterial fibromuscular dysplasia. *J Hum Hypertens.* 2001;15:185–190.
22. Persu A, et al. Diagnosis and management of fibromuscular dysplasia: an expert consensus. *Eur J Clin Invest.* 2012;42:338–347.
23. Schievink WI, Limburg M. Angiographic abnormalities mimicking fibromuscular dysplasia in a patient with Ehlers-Danlos syndrome, type IV. *Neurosurgery.* 1989;25:482–483.
24. Pontes TC, Rufino GP, Gurgel MG, et al. Fibromuscular dysplasia: a differential diagnosis of vasculitis. *Rev Bras Reumatol.* 2012;52:70–74.
25. Schievink WI, Bjornsson J, Piepras DG. Coexistence of fibromuscular dysplasia and cystic medial necrosis in a patient with Marfan's syndrome and bilateral carotid artery dissections. *Stroke.* 1994;25:2492–2496.
26. Hudgins LB, Limbacher 2nd JP. Fibromuscular dysplasia in Alport's syndrome. *J Tenn Med Assoc.* 1982;75:733–735.
27. Booth C, Preston R, Clark G, Reidy J. Management of renal vascular disease in neurofibromatosis type 1 and the role of percutaneous trans-luminal angioplasty. *Nephrol Dial Transplant.* 2002;17:1235–1240.
28. Gutmann DH, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *J Am Med Assoc.* 1997;278:51–57.
29. Germain DP. The vascular Ehlers-Danlos syndrome. *Curr Treat Options Cardiovasc Med.* 2006;8:121–127.
30. Lacolley P, et al. Disruption of the elastin gene in adult Williams syndrome is accompanied by a paradoxical reduction in arterial stiffness. *Clin Sci.* 2002;103:21–29.
31. Savard S, et al. Association between 2 angiographic subtypes of renal artery fibromuscular dysplasia and clinical characteristics. *Circulation.* 2012;126:3062–3069.
32. Cragg AH, et al. Incidental fibromuscular dysplasia in potential renal donors: long-term clinical follow-up. *Radiology.* 1989;172:145–147.
33. Andreoni KA, et al. Incidence of donor renal fibromuscular dysplasia: does it justify routine angiography? *Transplantation.* 2002;73:1112–1116.
34. Blondin D, et al. Fibromuscular dysplasia in living renal donors: still a challenge to computed tomographic angiography. *Eur J Radiol.* 2010;75:67–71.
35. Stanley JC, et al. Pediatric renovascular hypertension: 132 primary and 30 secondary operations in 97 children. *J Vasc Surg.* 2006;44:1219.
36. Pascual A, Bush HS, Copley JB. Renal fibromuscular dysplasia in elderly persons. *Am J Kidney Dis.* 2005;45:e63–e66.
37. Mancia G, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2007;28:1462–1536.
38. Davis BA, Crook JE, Vestal RE, et al. Prevalence of renovascular hypertension in patients with grade III or IV hypertensive retinopathy. *N Engl J Med.* 1979;301:1273–1276.
39. Labropoulos N, Ayuste B, Leon LRJ. Renovascular disease among patients referred for renal duplex ultrasonography. *J Vasc Surg.* 2007;46:731–737.
40. Zeller T. Renal artery stenosis: epidemiology, clinical manifestation, and percutaneous endovascular therapy. *J Interv Cardiol.* 2005;18:497–506.
41. Anderson CA, et al. Renal artery fibromuscular dysplasia: results of current surgical therapy. *J Vasc Surg.* 1995;22:206–207.
42. Warchol-Celinska E, et al. Systematic and multidisciplinary evaluation of fibromuscular dysplasia patients reveals high prevalence of previously undetected fibromuscular dysplasia lesions and affects clinical decisions. the ARCADIA-POL study. *Hypertension.* 2020;75:1102–1109.
43. Shroff R, et al. Angioplasty for renovascular hypertension in children: 20-year experience. *Pediatrics.* 2006;118:268–275.
44. Bayazit AK, et al. Renovascular hypertension in childhood: a nationwide survey. *Pediatr Nephrol.* 2007;22:1327–1333.
45. Higashi Y, et al. Endothelial function and oxidative stress in renovascular hypertension. *N Engl J Med.* 2002;346:1954–1962.
46. Alhadad A, et al. Renal angioplasty causes a rapid transient increase in inflammatory biomarkers, but reduced levels of interleukin-6 and endothelin-1 1 month after intervention. *J Hypertens.* 2007;25:1907–1914.
47. Mounier-Vehier C, et al. Parenchymal consequences of fibromuscular dysplasia renal artery stenosis. *Am J Kidney Dis.* 2002;40:1138–1145.
48. Safan RD. Atherosclerotic renal artery stenosis. *Curr Treat Options Cardiovasc Med.* 2003;5:91–101.
49. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. *Urol Clin North Am.* 1984;11:383–392.
50. Ropponen KM, Alafuzoff I. A case of sudden death caused by fibromuscular dysplasia. *J Clin Pathol.* 1999;52:541–542.
51. Mestres CA, et al. Improvement of renal function in azotaemic hypertensive patients after surgical revascularization. *Br J Surg.* 1988;75:578–580.

52. Gavalas M, Meisner R, Labropoulos N, et al. Renal infarction complicating fibromuscular dysplasia. *Vasc Endovascular Surg.* 2014;48:445–451.
53. Textor SC. Secondary hypertension: renovascular hypertension. *J Am Soc Hypertens.* 2014;8:943–945.
54. Vasbinder GB, et al. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med.* 2001;135:401–411.
55. De Bruyne B, et al. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol.* 2006;48:1851–1855.
56. Mancia G, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens.* 2009;27:2121–2158.
57. James PA, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *J Am Med Assoc.* 2014;311:507–520.
58. Weinberg I, Gu X, Giri J, et al. Antiplatelet and antihypertension medication use in patients with fibromuscular dysplasia: results from the United States Registry for fibromuscular dysplasia. *Vasc Med.* 2015;20:447–453.
59. Cotroneo AR, et al. Cutting balloon angioplasty (CBA) for the treatment of renal artery fibromuscular dysplasia (FMD) in six patients: 5-year long-term results. *Cardiovasc Interv Radiol.* 2017;40(4):546–552.
60. Tanaka R, Higashi M, Naito H. Angioplasty for non-arteriosclerotic renal artery stenosis: the efficacy of cutting balloon angioplasty versus conventional angioplasty. *Cardiovasc Interv Radiol.* 2007;30:601–606.
61. Barrier P, et al. Technical and clinical results after percutaneous angioplasty in nonmedial fibromuscular dysplasia: outcome after endovascular management of unifocal renal artery stenoses in 30 patients. *Cardiovasc Interv Radiol.* 2010;33:270–277.
62. de Fraissinet B, et al. Percutaneous transluminal angioplasty of dysplastic stenoses of the renal artery: results on 70 adults. *Cardiovasc Interv Radiol.* 2003;26:46–51.
63. Birrer M, Do DD, Mahler F, Triller J, et al. Treatment of renal artery fibromuscular dysplasia with balloon angioplasty: a prospective follow-up study. *Eur J Vasc Endovasc Surg.* 2002;23:146–152.
64. Sos TA, et al. Percutaneous transluminal renal angioplasty in renovascular hypertension due to atheroma or fibromuscular dysplasia. *N Engl J Med.* 1983;309:274–279.
65. Trinquart L, Mounier-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. *Hypertension* 2010;56:525–532.
66. Mousa AY, et al. Short- and long-term outcomes of percutaneous transluminal angioplasty/stenting of renal fibromuscular dysplasia over a ten-year period. *J Vasc Surg.* 2012;55:421–427.
67. Davies MG, et al. The long-term outcomes of percutaneous therapy for renal artery fibromuscular dysplasia. *J Vasc Surg.* 2008;48:865–871.
68. Wong JM, et al. Surgery after failed percutaneous renal artery angioplasty. *J Vasc Surg.* 1999;30:468–482.
69. Lacombe M. Surgical treatment of renovascular hypertension in children. *Eur J Vasc Endovasc Surg.* 2011;41:770–777.
70. Carmo M, et al. Surgical management of renal fibromuscular dysplasia: challenges in the endovascular era. *Ann Vasc Surg.* 2005;19:208–217.
71. Reiher L, Pfeiffer T, Sandmann W. Long-term results after surgical reconstruction for renal artery fibromuscular dysplasia. *Eur J Vasc Endovasc Surg.* 2000;20:556–559.
72. Novick AC, et al. Trends in surgical revascularization for renal artery disease. Ten years' experience. *J Am Med Assoc.* 1987;257:498–501.
73. Marekovic Z, Mokos I, Krhen I, et al. Long-term outcome after surgical kidney revascularization for fibromuscular dysplasia and atherosclerotic renal artery stenosis. *J Urol.* 2004;171:1043–1045.
74. Sevmis S, Karakayali H, Boyvat F, et al. Renal autotransplantation for the treatment of complex renovascular hypertension. *Transplant Proc.* 2006;38:3412–3415.
75. Jakubowski HD, Eigler FW, Montag H. Results of surgery in fibrodysplastic renal artery stenosis. *World J Surg.* 1981;5:859–861.
76. Dean RH, Wilson JP, Burko H, et al. Saphenous vein aortorenal bypass grafts: Serial arteriographic study. *Ann Surg.* 1974;180:469–478.
77. Stoney RJ, Silane M, Salvatierra OJ. Ex vivo renal artery reconstruction. *Arch Surg.* 1978;113:1272–1278.
78. Piercy KT, et al. Renovascular disease in children and adolescents. *J Vasc Surg.* 2005;41:973–982.
79. Serter S, Oran I, Parildar M, Memis A. Fibromuscular dysplasia-related renal artery stenosis associated with aneurysm: successive endovascular therapy. *Cardiovasc Interv Radiol.* 2007;30:297–299.
80. Stanley JC, Zelenock GB, Messina LM, et al. Pediatric renovascular hypertension: a thirty-year experience of operative treatment. *J Vasc Surg.* 1995;21:212–217.
81. Angus A, et al. Outcomes of percutaneous transluminal angioplasty for pediatric renovascular hypertension. *J Ped Surg.* 2017;52:395–399.
82. Huang Y, et al. Renal artery intervention in pediatric and adolescent patients: a 20-year experience. *Vasc Endovascular Surg.* 2007;41:490–499.
83. Stanley JC, Fry WJ, Seeger JF, et al. Extracranial internal carotid and vertebral artery fibrodysplasia. *Arch Surg.* 1974;109:215–222.
84. Moreau P, Albat B, Thevenet A. Fibromuscular dysplasia of the internal carotid artery: long-term surgical results. *J Cardiovasc Surg (Torino).* 1993;34:465–472.
85. Furie DM, Tien RD. Fibromuscular dysplasia of arteries of the head and neck: imaging findings. *AJR Am J Roentgenol.* 1994;162:1205–1209.
86. Stahlfeld KR, Means JR, Didomenico P. Carotid artery fibromuscular dysplasia. *Am J Surg.* 2007;193:71–72.
87. Southerland AM, Meschia JF, Worrall BB. Shared associations of nonatherosclerotic, large-vessel, cerebrovascular arteriopathies: considering intracranial aneurysms, cervical artery dissection, moyamoya disease and fibromuscular dysplasia. *Curr Opin Neurol.* 2013;26:13–28.
88. Debette S. Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts? *Curr Opin Neurol.* 2014;27:20–28.
89. Bejot Y, et al. Characteristics and outcomes of patients with multiple cervical artery dissection. *Stroke.* 2014;45:37–41.
90. So EL, Too JF, Dalal P, Moody DM. Cephalic fibromuscular dysplasia in 32 patients: clinical findings and radiologic features. *Arch Neurol.* 1981;38:619–622.
91. Corrin LS, Sandok BA, Houser OW. Cerebral ischemic events in patients with carotid artery fibromuscular dysplasia. *Arch Neurol.* 1981;38:616–618.
92. Collins GJJ, Rich NM, Clagett GP, et al. Fibromuscular dysplasia of the internal carotid arteries. Clinical experience and follow-up. *Ann Surg.* 1981;194:89–96.
93. Poloskey SL, Olin JW, Mace P, Gornik HL. Fibromuscular dysplasia. *Circulation.* 2012;125:e636–e639.
94. Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. *N Engl J Med.* 1994;330:393–397.
95. Haneline MT, Croft AC, Frishberg BM. Association of internal carotid artery dissection and chiropractic manipulation. *Neurologist.* 2003;9:35–44.
96. Arning C. Nonatherosclerotic disease of the cervical arteries: role of ultrasonography for diagnosis. *Vasa.* 2001;30:160–167.
97. Russo CP, Smoker WR. Nonatheromatous carotid artery disease. *Neuroimaging Clin N Am.* 1996;6:811–830.
98. Chiche L, Bahnnini A, Koskas F, et al. Occlusive fibromuscular disease of arteries supplying the brain: results of surgical treatment. *Ann Vasc Surg.* 1997;11:496–504.
99. Schneider P. *Vascular Surgery: Principles and Practice.* McGraw-Hill; 1994.

100. Brown MM. Balloon angioplasty for cerebrovascular disease. *Neurology Res.* 1992;14:159–163.
101. Ballard JL, Guinn JE, Killeen JD, et al. Open operative balloon angioplasty of the internal carotid artery: a technique in evolution. *Ann Vasc Surg.* 1995;9:390–393.
102. Brinza E, et al. Lower Extremity Fibromuscular Dysplasia. *Angiology.* 2017;68(8):722–727.
103. Sekar N, Shankar R. Fibromuscular dysplasia with multiple visceral artery involvement. *J Vasc Surg.* 2013;57:1401.
104. Pate GE, Lowe R, Buller CE. Fibromuscular dysplasia of the coronary and renal arteries? *Catheter Cardiovasc Interv.* 2005;64:138–145.

Nonatheromatous Popliteal Artery Disease

THOMAS L. FORBES and AHMED KAYSSI

INTRODUCTION	1911
POPLITEAL ARTERY ENTRAPMENT SYNDROME	1912
Epidemiology	1912
Pathogenesis	1912
<i>Etiology</i>	1912
<i>Classification</i>	1913
TYPE I	1913
TYPE II	1913
TYPE III	1913
TYPE IV	1913
TYPE V	1913
TYPE VI	1913
<i>Pathology</i>	1914
Clinical Presentation	1914
Diagnostic Evaluation	1915
<i>Noninvasive Testing</i>	1915
<i>Angiography</i>	1915
<i>Computed Tomography and Magnetic Resonance Imaging</i>	1916
Treatment	1916
<i>Type I to V, Normal Popliteal Artery</i>	1916
<i>Types I to V, Abnormal Popliteal Artery</i>	1918
<i>Type VI, Symptomatic</i>	1918
<i>Type VI, Asymptomatic</i>	1918
<i>Treatment Outcomes</i>	1918
ADVENTITIAL CYSTIC DISEASE	1919
Epidemiology	1919
Pathogenesis	1920
<i>Etiology</i>	1920
<i>REPETITIVE TRAUMA THEORY</i>	1920
<i>GANGLION THEORY</i>	1920
<i>SYSTEMIC DISORDER THEORY</i>	1920
<i>DEVELOPMENTAL THEORY</i>	1920
<i>ARTICULAR (SYNOVIAL) THEORY</i>	1920
<i>Pathology</i>	1920
Clinical Presentation	1920
<i>Arterial</i>	1920
<i>Venous</i>	1921
Diagnostic Evaluation	1921
<i>Noninvasive Testing</i>	1922
<i>Angiography</i>	1922
<i>Computed Tomography and Magnetic Resonance Imaging</i>	1922
Treatment	1922
<i>Nonresectional Methods</i>	1922
TRANSLUMINAL ANGIOPLASTY	1922
CYST ASPIRATION	1924
CYST EXCISION AND EVACUATION	1924
<i>Resectional Methods</i>	1924
<i>Treatment Outcomes</i>	1925
CHAPTER ALGORITHM	1925

INTRODUCTION

Most lower extremity ischemic symptoms occur in patients with atherosclerotic occlusive disease. Nonatheromatous causes must be considered, however, in the absence of significant atherosclerotic risk factors, especially in younger individuals. The two most common nonatheromatous causes of popliteal artery disease are

popliteal artery entrapment syndrome (PAES) and adventitial cystic disease (ACD). These patients can be asymptomatic but clinical symptoms associated with these pathologies range from claudication to chronic limb-threatening ischemia (CLTI). Given their rarity and the younger age of presentation, these conditions are often not diagnosed in a timely fashion, resulting in prolonged disability and occasional progression to CLTI.

POPLITEAL ARTERY ENTRAPMENT SYNDROME

Epidemiology

PAES was first described in 1879 by University of Edinburgh medical student Anderson Stuart.¹ It was not until 1965, however, that Love and Whelan at the Walter Reed Army Medical Center in Washington, D.C., coined the term “popliteal artery entrapment syndrome” to describe this clinical entity.^{2,3} The anatomic abnormalities associated with PAES have been observed in 3.5% of individuals in a post-mortem study,⁴ and up to 60% of young individuals with claudication symptoms suffer from this syndrome.⁵ Those affected tend to be active and otherwise healthy, which has led some clinicians to describe PAES as the “jogging disease.”

The majority (up to 80%) of reported cases are in men, with a median age of 32 years (range, 20.7–41 years).⁶ Cases of PAES have also been described in children, teenagers, women, and siblings, but are unusual.^{7–9} While the anatomic variant in affected individuals is developed *in utero*, several decades are sometimes necessary before symptoms develop. Bilateral lower-extremity symptoms in PAES have been described in approximately 30% of cases, and two-thirds of patients with unilateral symptoms were found to have bilateral anatomic abnormalities.¹⁰ Rare instances of bilateral popliteal artery occlusion secondary to popliteal artery entrapment have also been reported,¹¹ and concurrent entrapment of the popliteal and anterior tibial arteries has been described.^{10,12}

Pathogenesis

Etiology

The anatomical variations observed in PAES are best understood by considering the embryologic development of the structures within the popliteal fossa.

The lower extremity arterial system arises from two arteries, the axial and external iliac arteries, which originate from the umbilical artery. The femoral artery originates from the external iliac artery and progresses distally in the anterior compartment, whereas the axial artery elongates distally in the posterior compartment. At approximately 42 days of intrauterine life, the axial artery is divided into three segments, depending on its relationship to the popliteus muscle: proximal, deep, and distal. A bridging artery, the ramus communicans superius, joins the femoral artery and the proximal segment of the axial artery through the adductor hiatus. During the following week of development, the proximal component of the axial artery gives rise to a branch that runs superficial to the popliteus muscle and joins with the distal segment of the axial artery. The deep segment of the axial artery involutes, and the fully developed popliteal artery results from the fusion of these arterial elements (Fig. 144.1).²

Initially, both heads of the gastrocnemius muscle originate from the proximal tibia. With development, they migrate cranially along the femur to different extents. The final position of the medial head of the gastrocnemius muscle is more proximal to that of the lateral head and immediately caudal to the adductor hiatus, with the popliteal artery lying immediately lateral.² These dynamic processes of muscle

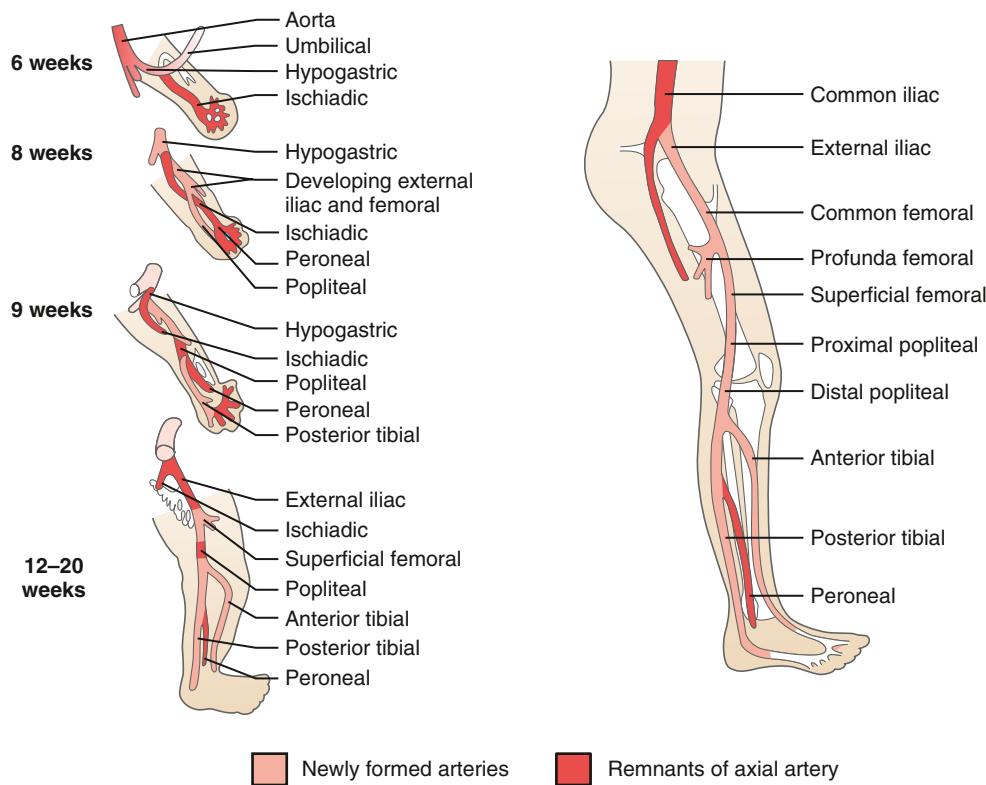


Figure 144.1 Embryologic derivation of the popliteal and other lower limb arteries. Remnants of the axial artery and arteries that develop with later differentiation are indicated. (From Levien LJ, Benn CA. Adventitial cystic disease: a unifying hypothesis. *J Vasc Surg*. 1998;28:193–205.)

and arterial development create the potential for various anatomic variations that can lead to popliteal artery entrapment (Fig. 144.2).

Classification

The current PAES classification system consists of six variants and is based on the Heidelberg classification. It accounts for variations in the anatomy of the popliteal fossa (Fig. 144.3).¹³

Type I

The popliteal artery completes its development before migration of the medial head of the gastrocnemius muscle, which then pushes the artery medially during migration. This results in the popliteal artery's medial deviation to a normally situated gastrocnemius muscle.¹⁰

Type II

The artery is displaced medially, but the medial head of the gastrocnemius muscle has an abnormal attachment on the lateral aspect of the medial femoral condyle or intercondylar area. In this case, the artery forms prematurely and partially arrests the migration of the gastrocnemius muscle, resulting in the artery positioned medially to an abnormally attached muscle. In contrast to the normal position of gastrocnemius muscle insertion in type I entrapment, type II is defined by an abnormal femoral insertion site.

Type III

This type is caused by an abnormal muscle slip or fibrous band that arises from either the medial or lateral femoral condyle.¹⁰

Type III entrapment occurs when embryologic remnants of the gastrocnemius muscle remain posterior to the popliteal artery or when the artery develops within this muscle mass. Occasionally, a double origin of the gastrocnemius muscle can surround and compress the popliteal artery.

Types I to III represent the same anatomic variant, the degree of which depends on the temporal relationship between popliteal artery development and migration of the medial head of the gastrocnemius muscle.

Type IV

The mechanism resulting in type IV entrapment is fundamentally different from that causing types I to III. Type IV entrapment occurs with persistence of the axial artery as the mature distal popliteal artery. This artery remains in its embryologic position, deep to the popliteus muscle or fibrous bands.¹⁰

Type V

Both the popliteal artery and vein are involved or entrapped by any of the previously described mechanisms. This subtype has been estimated to occur in approximately 10% to 15% of cases.^{14,15}

Type VI

An additional type of entrapment – previously known as functional entrapment, or type F – is now commonly referred to as type VI entrapment. Patients present with the typical features of PAES in the absence of an explanatory anatomic abnormality.¹⁰ It has been proposed that the anatomic abnormality in type VI entrapment is an especially lateral attachment of the

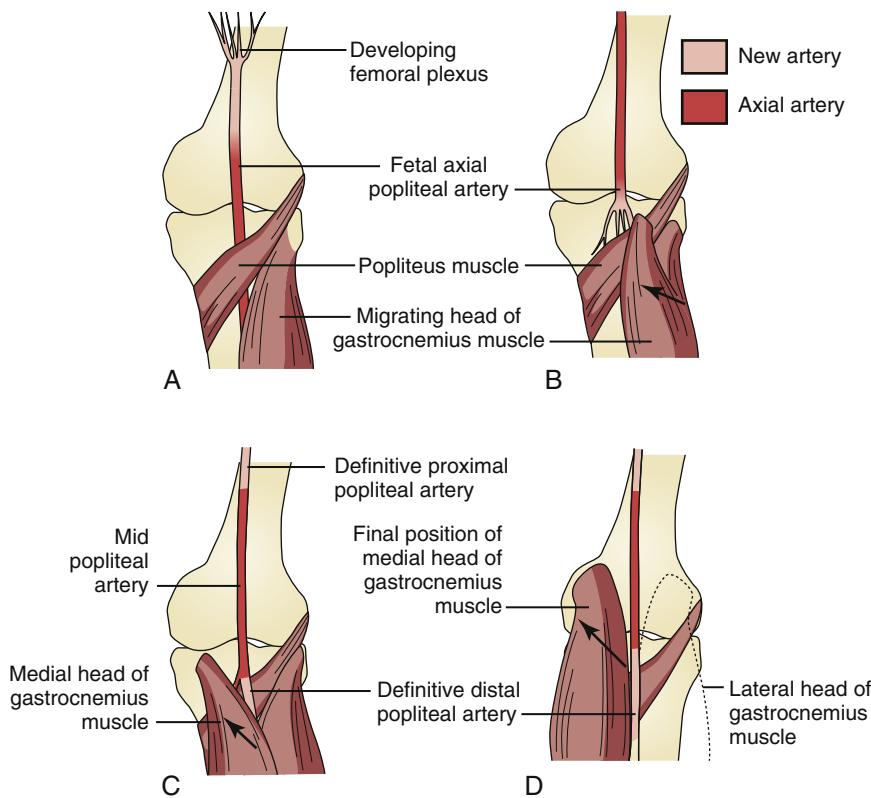


Figure 144.2 Migration of the medial head of the gastrocnemius muscle through the popliteal fossa during formation of the popliteal artery. (A) The medial head of the gastrocnemius muscle begins to migrate from the region of the fibula. At this stage, the axial distal popliteal artery lies deep to the popliteus muscle. (B) The distal portion of the popliteal artery involutes as the medial head of the gastrocnemius muscle passes from lateral to medial. The proximal popliteal artery is derived from fusion with the developing femoral plexus, whereas the midportion of the popliteal artery is formed from the persistent axial artery remnant. (C) A new or nonaxial distal popliteal artery now forms superficial to the popliteus muscle, after the medial head has migrated through the popliteal fossa. (D) Normal definitive popliteal anatomy. (From Levien LJ, Veller MG. Popliteal artery entrapment syndrome: more common than previously recognized. *J Vasc Surg*. 1999;30:587–598.)

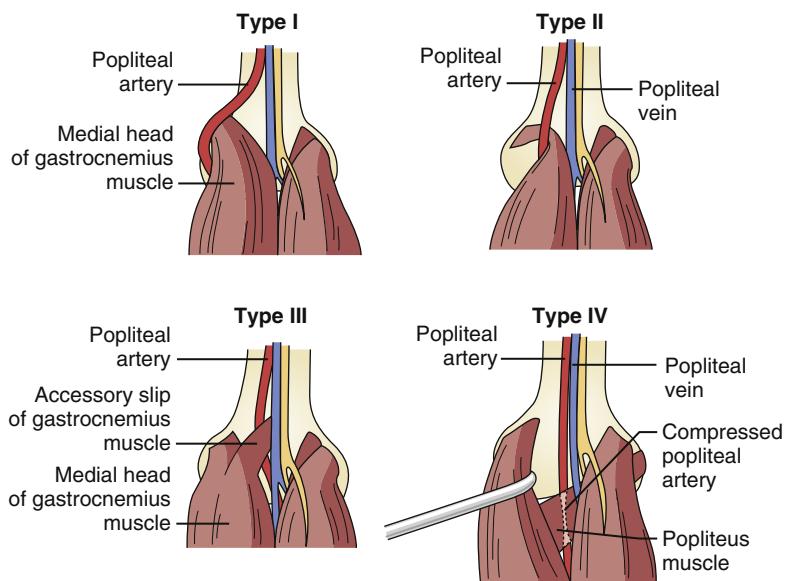


Figure 144.3 Types of popliteal artery entrapment syndromes. (From Levien LJ, et al: Popliteal artery entrapment syndrome: more common than previously recognized. *J Vasc Surg*. 1999;30:587–598.)

medial head of the gastrocnemius muscle to the posterior aspect of the medial femoral condyle. Alternatively, hypertrophy of gastrocnemius following regular exercise is thought to result in compression of the posteromedial aspect of the popliteal artery. When subjected to MRI examination, individuals with type VI PAES and popliteal artery occlusion with stressor maneuvers tend to have a more extensive midline position of the medial head of the gastrocnemius muscle. Compared with normal controls, patients with type VI PAES have more of this muscle attached toward the supracondylar femoral midline, around the lateral border of the medial femoral condyle, and within the intercondylar fossa.¹⁶

Recent advancements in imaging technologies have led to the discovery of other etiologies for popliteal artery entrapment, such as anomalous slips of the lateral head of the gastrocnemius or plantaris muscles.^{17–19} Such cases are extremely rare and have not warranted a modification of the current classification system.

Pathology

The pathological classification of PAES describes the continuum of histological changes that result with chronic popliteal compression, from fibrosis of the various arterial layers to complete occlusion and thrombosis.¹⁰ In stage 1, the fibrosis is confined to the adventitia. In stage 2, it extends into the media, which may result in post-stenotic dilatation or aneurysm formation. In stage 3, the artery may become thrombogenic as the fibrosis extends to the intimal layer.¹⁵ The degree of arterial damage does not appear to be related to the duration of compression or popliteal entrapment.

Clinical Presentation

PAES patients are typically young, physically active men who present with lower-extremity claudication. However, a range in the severity of symptoms, along with a grading scale for their description, has been described (Table 144.1).²

TABLE 144.1

Classification of Popliteal Artery Entrapment Syndrome Symptoms

Class	Description
0	Asymptomatic
1	Pain, paresthesia, and cold feet after physical training (e.g., jogging, heavy work)
2	Claudication while walking (>100 m)
3	Claudication while walking (<100 m)
4	Rest pain
5	Necrosis

From di Marzo L, Cavallaro A. Popliteal vascular entrapment. *World J Surg*. 2005;29:S43–S45.

Claudication symptoms may be atypical and paradoxical, worsening with standing or walking and improving with more vigorous exercise, or they may occur immediately, rather than after walking for a long distance. Patients occasionally describe symptoms of coldness, blanching, and numbness. All types of entrapment (except type VI) can involve the tibial nerves and result in paresthesia. A minority of patients (10%) present with signs and symptoms of chronic CLTI, and even fewer present with acute limb ischemia. Venous entrapment (type V) is suggested by calf cramping or symptoms more typical of a compartment syndrome, including swelling and a feeling of fullness.¹⁵

Pedal pulses are typically palpable and normal at rest, but disappear with passive dorsiflexion or active plantar flexion of the foot. These maneuvers tense the gastrocnemius muscle against the entrapped artery, temporarily occluding the patent lumen. They should also be performed on the contralateral asymptomatic limb. If left untreated, chronic entrapment causes progressive fibrosis of the popliteal artery, resulting in a thrombogenic intimal surface and eventual arterial thrombosis and occlusion.¹⁰ Occlusion of the popliteal artery can be heralded

TABLE 144.2 Differential Diagnosis of Nonatherosclerotic Peripheral Artery Disease

	Age	Sex	Key Features	Diagnosis	
Popliteal artery entrapment syndrome	Young adults	M > F	Exertional claudication pain, paresthesias, and poikilothermia after exertion External compression of popliteal artery from muscles and ligaments in popliteal fossa	Loss of Doppler signaling with provocative maneuvers Demonstration of compression on active pedal plantar flexion against resistance CT/MRI to demonstrate entrapment of vascular structures	
Adventitial cystic disease	4th and 5th decades	M > F	Exertional claudication with extended recovery time compared to aPAD Symptoms caused by compression of arterial lumen by mucinous containing cystic lesion within the adventitia	Loss of pedal pulses with sharp knee flexion (Ishikawa sign) CT/MRI	
Iliac artery endofibrosis	2nd and 3rd decades	M = F	Competitive athletes, common in cyclists Intimal thickening by collagen fibers, fibrous tissue, and smooth muscle proliferation Femoral bruit with hip flexion	Arterial duplex ultrasound and digital subtraction angiography with hip flexion and extension Intravascular ultrasound with intraarterial translesional pressure gradients	
Fibromuscular dysplasia	2nd to 5th decades	F > M	“String of beads” appearance Symptoms based on vascular bed involved	Digital subtraction angiography with intravascular ultrasound	
TAO (Buerger disease)	<50 years		Tobacco smokers, intermittent claudication, Raynaud phenomenon, superficial thrombophlebitis, skipped lesions and corkscrew collaterals	CT/MRI digital subtraction angiography	
Medium and large vessel vasculitis	TA GCA Behcet	15–30 years >50 years <30 years	F > M M = F M = F	Asian and Latin descent Pulseless upper extremity Headache, jaw claudication, visual disturbances Recurrent mucosal ulcers, uveitis, pathergy	Elevated inflammatory markers Duplex ultrasound CTA MRA temporal artery biopsy (GCA)
Chronic exertional compartment syndrome		>40	M = F	Athletes Typically bilateral Complete symptom resolution 10–20 min after rest	Imaging to rule out other causes Elevated intra-compartment pressures before and after exercise

aPAD, atherosclerotic peripheral artery disease; CTA, computed tomographic angiography; GCA, giant cell arteritis; MRA, magnetic resonance angiography; TA, Takayasu arteritis; TAO, thromboangiitis obliterans.

From Mintz AJ, Weinberg I. Nonatherosclerotic PAD: Approach to Exertional Pain in the Lower Extremities. *Curr Cardiol Rep*. 2015;17(8):66.

by the sudden onset of more severe calf claudication and absent pedal pulses. This can occur after an episode of strenuous exercise, and should result in a high degree of suspicion for PAES when it occurs in a young adult with no risk factors for atherosclerosis. Post-stenotic dilatation or aneurysmal degeneration of the popliteal artery, when it occurs, can be a source of distal emboli.¹⁰

Diagnostic Evaluation

The differential diagnosis for nonatherosclerotic lower-extremity peripheral arterial disease is outlined in Table 144.2.²⁰

Noninvasive Testing

Exercise treadmill testing is commonly performed as an initial investigation. The patient is instructed to walk or jog until symptoms develop. Ankle-brachial pressure measurements are obtained before and following the treadmill test and should drop significantly.²¹ Subsequently, duplex segmental pressures are taken with the Doppler probe placed on the posterior tibial

artery. Active plantar flexion and passive dorsiflexion of the ankle with the knee in full extension results in gastrocnemius muscle contraction.¹⁴ Readings are repeated several times, and care should be taken to avoid moving the probe during muscle contractions. Similarly, duplex studies are performed with visualization of the popliteal artery during calf muscle contraction and relaxation. The duplex interrogation must be repeated several times because the popliteal artery can be pushed deeper into the popliteal fossa during muscle contraction, negatively affecting visualization and volume recordings. A positive duplex test with provocative maneuvers should prompt further investigative studies. While some investigators have had excellent results with duplex ultrasound,²² others have reported high (72%) false-positive studies, resulting in an overestimation of popliteal artery compression.¹⁵

Angiography

Angiography remains the mainstay of investigation at many centers, with a reported median sensitivity of 97% (range 85%–100%).⁶ Generally, the diagnosis of PAES should be

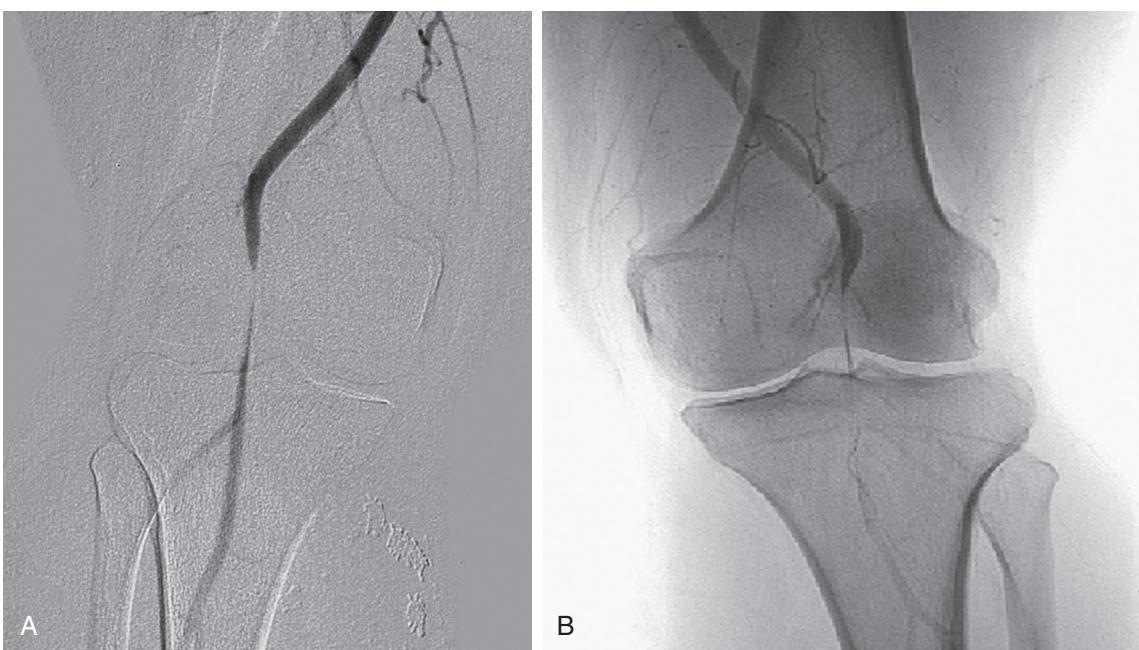


Figure 144.4 Angiogram reveals popliteal artery occlusion with plantar flexion of the foot. (From Causey MW, Singh N, Miller S, et al. Intraoperative duplex and functional popliteal entrapment syndrome: strategy for effective treatment. *Ann Vasc Surg.* 2010;24:556–561.)

considered when at least two of the following angiographic features are present²:

- Medial deviation of the proximal popliteal artery.
- Focal occlusion of the mid-popliteal artery.
- Post-stenotic dilatation of the distal popliteal artery.

Angiography has the additional advantage of delineating tibial artery anatomy following embolization from a post-stenotic dilatation of an entrapped popliteal artery or a thrombogenic entrapped artery. Angiographic views should be obtained in the neutral position and during provocative maneuvers (Fig. 144.4). Angiography is useful to distinguish PAES from ACD of the popliteal artery. In contrast to PAES, the arterial stenosis or compression from adventitial cysts is readily visible in the neutral position.

Computed Tomography and Magnetic Resonance Imaging

Less invasive imaging alternatives such as computed tomography (CT) or magnetic resonance imaging (MRI) can be particularly useful in cases of popliteal artery entrapment syndrome when the artery is occluded because they illustrate the anatomic relationships between the vessels and muscles in the popliteal fossa and identify anomalous muscular insertions (Fig. 144.5). Some investigators believe that MRI is superior to CT in this regard, and should be the diagnostic test of choice in young patients presenting with intermittent claudication.¹⁵

Treatment

In most cases of symptomatic PAES, surgical intervention is indicated and should be offered. This is especially true for types

I to V entrapment, and depends on the severity of symptoms in type VI entrapment. The approach to treatment is dictated by the patient's anatomy, clinical presentation, and the status of the popliteal artery (Table 144.3).

Generally, early intervention allows for a more limited operation with myotomy alone, rather than arterial reconstruction. Because the natural history of PAES progresses from arterial fibrosis to thrombosis and eventual occlusion, most authors advocate surgical correction of types I to V PAES to prevent arterial degeneration. The principles of surgical treatment include release of arterial entrapment, restoration of normal anatomy, and restoration of arterial flow.¹⁵

The role of endovascular therapies is limited because they do not address the underlying muscular entrapment. There have been reports of small numbers of patients with occluded popliteal arteries undergoing endoluminal interventions and thrombolysis followed by myotomy several weeks later. These patients were anticoagulated for various periods.²³ However, anticoagulation and the preservation of a potentially thrombogenic popliteal artery are suboptimal treatment options in this young and active patient population.

Type I to V, Normal Popliteal Artery

In the absence of arterial fibrosis in an otherwise normally appearing popliteal artery, musculotendinous release alone is sufficient to restore normal anatomy.¹⁵ Musculotendinous release can be performed through either a posterior or a medial approach. Proponents of the posterior approach highlight the operative flexibility that it offers the surgeon, the wider degree of inspection possible, the greater ease of identifying and addressing the specific anatomic abnormality, and an adequate exposure to complete an arterial reconstruction if necessary.^{15,24} Following

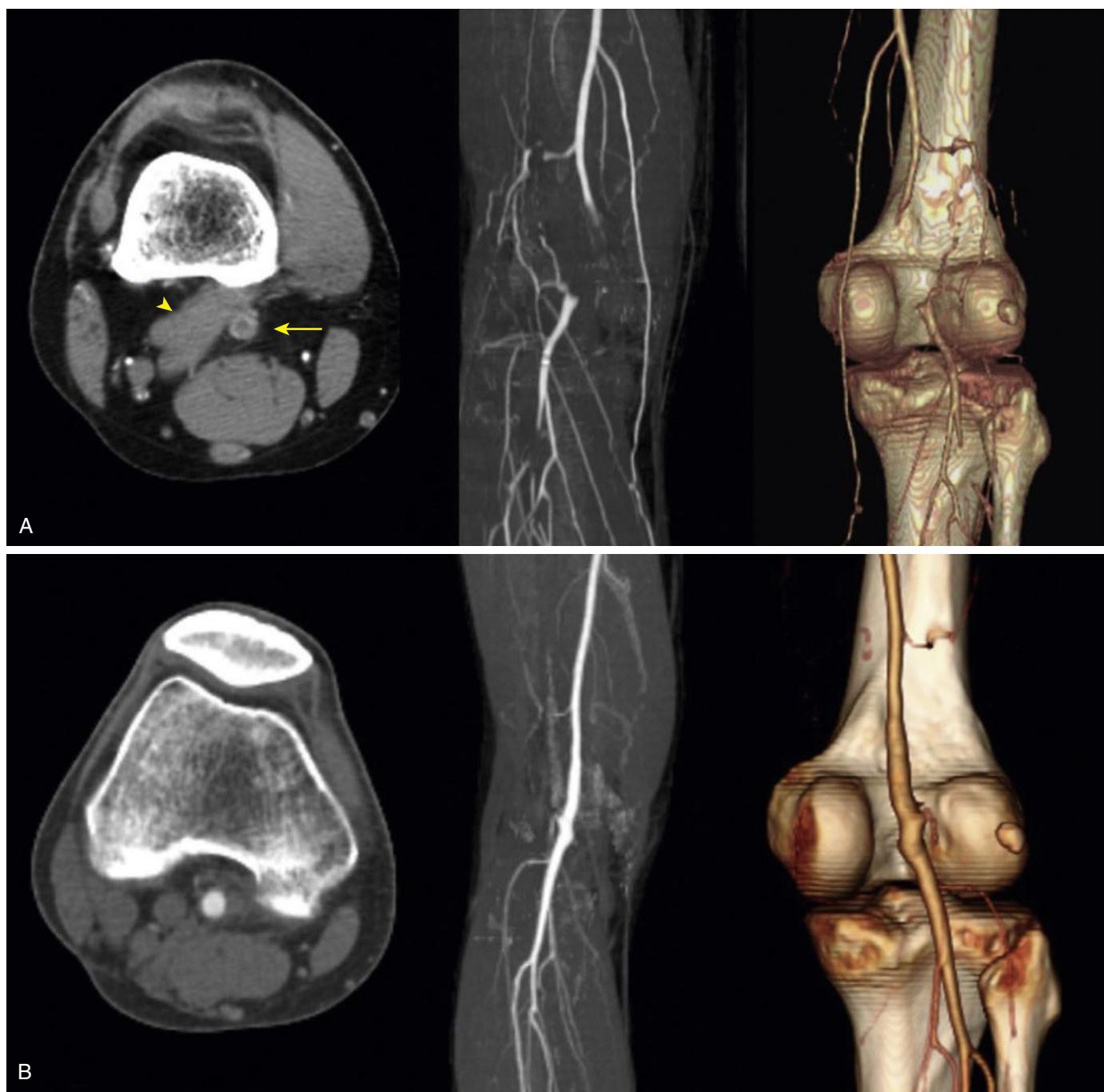


Figure 144.5 Popliteal entrapment syndrome type I. (A) Medial head of gastrocnemius muscle (arrowhead) occludes popliteal artery (arrow). (B) Patent artery following musculotendinous resection and popliteal artery interposition venous graft. (From Kim SY, Min SK, Ahn S, et al. Long-term outcomes after revascularization for advanced popliteal artery entrapment syndrome with segmental arterial occlusion. *J Vasc Surg*. 2012;55:90–97.)

an S- or Z-shaped incision, flaps are raised to expose the deep fascia, which is incised longitudinally, avoiding injury to the median cutaneous sural nerve. Sacrifice of the lesser saphenous vein can facilitate exposure. As the vessels are approached, the tibial nerve is encountered and mobilized. The popliteal vein is identified, passing between the heads of the gastrocnemius muscle deep in the popliteal fossa. The popliteal artery, which is not in its normal position, is identified higher in the popliteal space and followed distally. The artery's abnormal course can be medial to

the medial head of the gastrocnemius muscle or entrapped by anomalous muscular structures or tendinous tissue.²⁴

Through this posterior exposure, the medial head of the gastrocnemius muscle or the entrapping musculotendinous bands are completely divided, with no adverse functional sequelae, even in these young, active patients.²⁵ In entrapment types III and IV, mobilization of the muscular portion of the medial head of the gastrocnemius off of the posterior aspect of the femoral condyles usually suffices to relieve compression of the artery.

TABLE 144.3**Management Options for Popliteal Artery Entrapment Syndromes**

Status of Artery	Entrapment Type	Operation	Surgical Approach
Normal	I and II	Myotomy	Medial
	III and IV	Myotomy	Posterior
	V	Myotomy	Medial or posterior
	VI	Myotomy if symptomatic	Medial or posterior
Abnormal (occluded, stenosed, or post-stenotic dilatation or aneurysm)	I to VI	Decompression and arterial resection and replacement or exclusion and bypass	Medial or posterior

The medial operative approach is most suited for PAES types I and II and is less appropriate for types III and IV, where it may be more difficult to delineate the arterial and muscular anatomy. Entrapment types III and IV can best be explored via the posterior approach. Type V entrapment can be explored through either route, depending on the underlying muscular abnormality. The medial approach seems to result in a quicker return to normal athletic activities in these active patients and less incision-related morbidity.¹⁰ Similar to the posterior approach, the medial head of the gastrocnemius muscle is divided when approached from its medial aspect, permitting complete arterial decompression.

Types I to V, Abnormal Popliteal Artery

Arterial bypass or replacement is indicated in cases of complete thrombosis, arterial wall degeneration from the chronic entrapment, thrombus formation on the intimal surface, fibrotic narrowing of the artery, and post-stenotic dilatation or aneurysm formation. When the popliteal artery demonstrates evidence of chronic damage, even if the extent is only minimal fibrosis, it should be replaced or bypassed in its entirety. Early reports of this syndrome described numerous instances of thromboendarterectomy with or without vein patch angioplasty. This approach produced inferior results, with a higher incidence of arterial thrombosis and re-occlusion compared with arterial replacement with an autogenous conduit.¹⁵

Intraoperative duplex ultrasound can be useful for determining the need for arterial bypass. White and colleagues proposed the following intraoperative duplex ultrasound criteria for performing an interposition graft bypass in PAES patients: peak systolic velocity of 250–275 cm/s or greater, velocity ratio of 2 or greater, arterial occlusion, or aneurysmal (post-stenotic) degeneration.²⁶

The entrapment is first relieved by dividing the muscle or tendinous segment causing the arterial compression. Resection of the thrombosed artery and a short interposition vein graft are then performed. Alternatively, a short venous bypass graft

can be performed, with exclusion of the occluded artery to prevent distal thromboemboli. If post-stenotic dilatation or aneurysm formation has occurred, arterial resection and replacement with a vein are performed.

Arterial reconstruction can be performed through a posterior or a medial approach. The posterior approach is less useful in cases requiring a more distal reconstruction. Conversely, the medial approach allows for the harvesting of the more proximal great saphenous vein if a conduit of larger caliber is required. Additionally, it is much easier to expose the more distal popliteal artery, or tibial arteries, through a medial exposure if a more distal revascularization is required. This may be the case with extensive post-stenotic dilatation or with tibial artery occlusion secondary to thromboemboli from the entrapped popliteal artery.

Type VI, Symptomatic

Most authors support surgical intervention for symptomatic type VI PAES.²⁷ Hislop and colleagues in Australia have advocated for the injection of botulinum toxin (Botox BTX-A) as an initial intervention in these patients.²⁸ Botox's proposed mechanism of action is through paralyzing the slip of muscle responsible for the dynamic arterial occlusion, inducing muscle atrophy that increases the space available for the popliteal artery, and relaxing the arterial smooth muscle which results in popliteal vasodilation. However, this treatment remains untested in prospective studies.

Other authors have advocated for the use of surgical decompression for these patients, either through a medial or a posterior approach. Transection and resection of the muscular portion of the medial head of the gastrocnemius muscle, with preservation of the tendon, is usually sufficient to relieve symptoms.¹⁵ To ensure adequate decompression, one must take care to completely transect the muscular fibers from the posterior aspect of the lateral femoral condyle and the intercondylar area. Adequacy of the extent of the myectomy can be determined with intraoperative duplex. Before resection, arterial systolic velocities are measured and compared with post-myectomy velocities in neutral, plantar, and dorsiflexion positions. Myectomy is continued until no further changes in velocity are observed.²⁹

Type VI, Asymptomatic

Up to half the normal, asymptomatic population may exhibit signs of popliteal artery compression with provocative measures such as active plantar flexion and passive dorsiflexion of the foot. When these individuals are truly asymptomatic, little evidence supports prophylactic operative intervention, and these asymptomatic patients are best followed.¹⁵

Similarly, although bilateral popliteal artery entrapment is common, often only one extremity is symptomatic (43% of cases).³⁰ These asymptomatic contralateral extremities should be investigated, but surgical exploration is seldom indicated in the absence of symptoms.⁴

Treatment Outcomes

Myotomy alone for the management of PAES with a normal popliteal artery is associated with excellent results. In one large

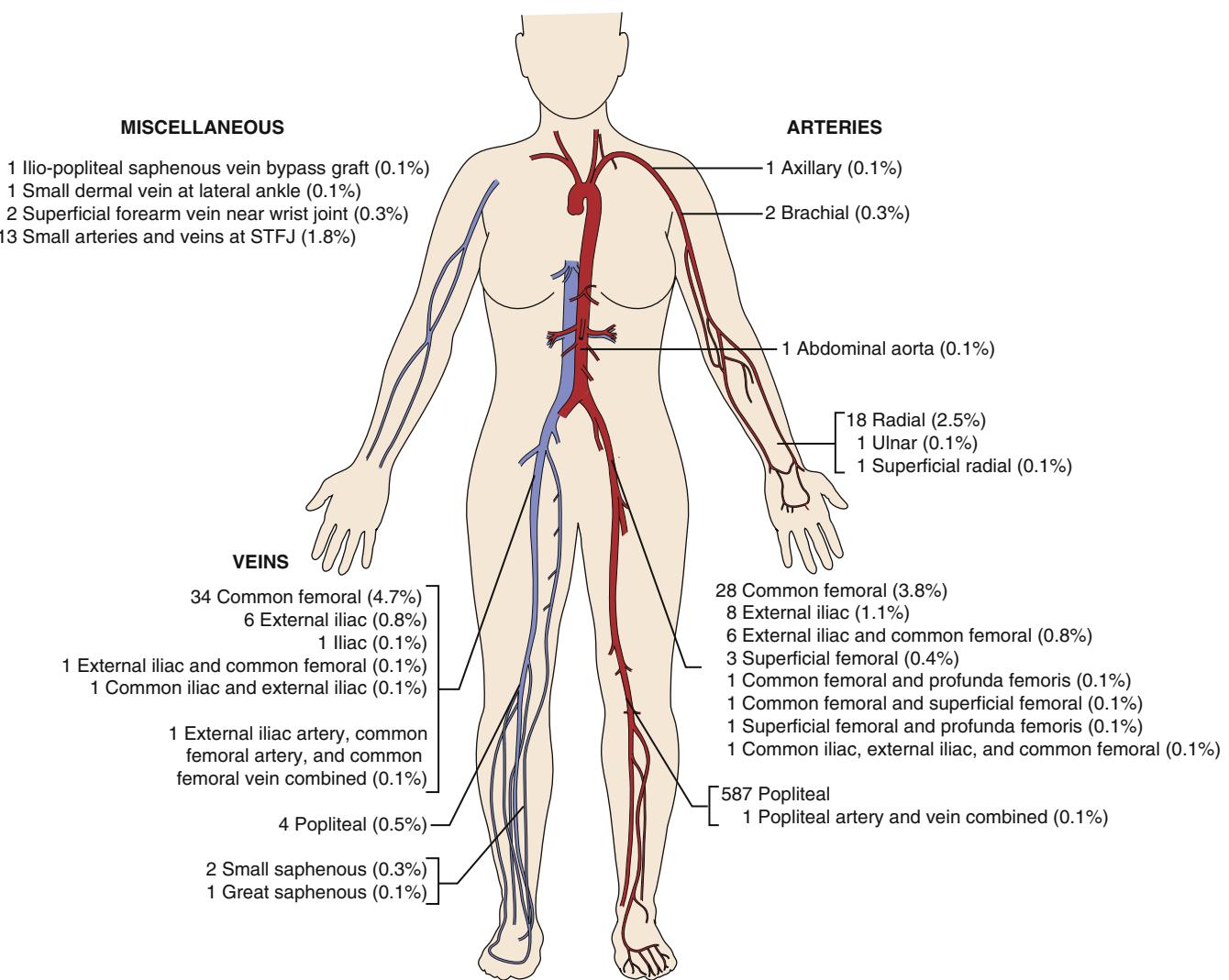


Figure 144.6 Artistic drawing demonstrating the various sites of adventitial cystic disease. STFJ, superior tibiofibular joint. (From Desy NM, Spinner RJ. The etiology and management of cystic adventitial disease. *J Vasc Surg*. 2014;60:235–245, 45.e—11.)

series, patients were able to return to their prior sports activities, did not require any further interventions, and maintained arterial patency at 10 years of follow-up.¹⁰

Bypass surgery with vein graft for PAES with an abnormal popliteal artery is associated with 65%–100% graft patency at 10 years of follow-up.^{31–33} Interposition grafts have better patency rates compared with long bypass grafts.³⁴ Reports of outcomes after hybrid procedures that combine angioplasty with musculotendinous resection and popliteal artery release are limited, but Ozkan and colleagues from Turkey reported primary and secondary patency rates of 60% at a median follow-up of 5 years.³⁵

ADVENTITIAL CYSTIC DISEASE

Epidemiology

ACD was first reported in 1947 by Atkins and Key in London. The patient was a 40-year-old policeman with claudication and ACD of the external iliac artery.³⁶ It was not until 1954,

however, that Ejrup and Hiertonn from Sweden described the first case involving the popliteal artery.³⁷ Since then, over 700 cases have been reported, with the popliteal artery most commonly affected (80.5% of cases).³⁸

ACD accounts for 0.1% of lower-extremity claudication.³⁹ In the majority of cases, popliteal artery involvement is unilateral, and only five cases of bilateral lesions have been reported.³⁸ The next most commonly involved arteries are the external iliac and femoral arteries,^{40,41} but the disease has been reported in most of the arteries lying adjacent to joint spaces (Fig. 144.6).^{42,43} Although it is most commonly a disorder of the arterial system, ACD of the iliofemoral and saphenous veins has also been described.⁴⁴

ACD affects males predominantly, with a male to female ratio of 5 to 1, and patients are typically in their mid-40s.³⁸ Some investigators have reported a slightly older age at diagnosis in women.⁴⁵ Cases of pediatric patients (5 to 15 years old) have also been described.³⁸ It must be emphasized, however, that the diagnosis is often delayed because of the relatively young