Best Practice & Research Clinical Gastroenterology 31 (2017) 49–57

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

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Diagnosis and treatment of chronic mesenteric ischemia: An update

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Keywords:
Chronic mesenteric ischemia
Mesenteric artery stenosis
Mesenteric circulation
Diagnosis
Treatment

A B S T R A C T

Although the prevalence of mesenteric artery stenoses (MAS) is high, symptomatic chronic mesenteric ischemia (CMI) is rare. The collateral network in the mesenteric circulation, a remnant of the extensive embryonal vascular network, serves to prevent most cases of ischemia. This explains the high incidence of MAS and relative rarity of cases of CMI. The number of affected vessels is the major determinant in CMI development. Most subjects with single vessel mesenteric stenosis do not develop ischemic complaints. Our experience is that most subjects with CA and SMA stenoses with abdominal complaints have CMI. A special mention should be made on patients with median arcuate ligament compression (MALS). There is ongoing debate whether the intermittent compression, caused by respiration movement, can cause ischemic complaints. The arguments pro and con treatment of MALS will be discussed. The clinical presentation of CMI consists of postprandial pain, weight loss, and an adapted eating pattern caused by fear of eating. In end-stage disease more continuous pain, diarrhea or a dyspepsia-like presentation can be observed.

Workup of patients suspected for CMI consists of three elements: the anamnesis, the vascular anatomy and proof of ischemia. The main modalities to establish mesenteric vessel patency are duplex ultrasound, CT angiography or MR angiography. Assessing actual ischemia is still challenging, with only tonometry and visual light spectroscopy as tested candidates.

Treatment consists of limiting metabolic demand, treatment of the atherosclerotic process and endovascular or operative revascularisation. Metabolic demand can be reduced by using smaller and more frequent meals, proton pump inhibition. Treatment of the atherosclerotic process consists of cessation of smoking, treatment of dyslipidemia, hypertension, hyperglycaemia, and medication with trombocyte aggregation inhibitors.

Epidemiology

Although chronic mesenteric ischemia (CMI) is rare, the incidence of mesenteric artery stenoses (MAS) is quite common, A number of relatively small studies showed an increasing prevalence with age going from 6% at age 40, to 14% at 60 years [1], and between 18% and 67% in those over 75 years of age [1,2]. These figures are comparable to those in peripheral artery disease (PAD) [3,4], the cerebrovascular disease (CVD) [5–7], and coronary artery disease (CAD) [8]. Development of actual ischemia in PAD was up to 50% after 5 years in studies where subjects with incidentally found ileofemoral stenoses were followed [3]. For CVD, the development of ischemia, TIA or stroke, was seen in 10–20% after 5 years [5–7]. For MAS, these figures seem to be far lower. In multivessel MAS it was reported that up to 6% developed CMI or acute mesenteric ischemia (AMI) after 3–6 years [2,9]. In our cohort, we just finished an analysis of the incidence and prevalence of CMI and noted 1) that the incidence keeps rising in our region and 2) now ranges between 5 and 6 per 100.000 annually with a prevalence of approximately 30 per 100.000 (paper in preparation). That the prevalence may be higher could be appreciated from an autopsy study that showed an incidence of AMI at autopsy or operation, of

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http://dx.doi.org/10.1016/j.bpg.2017.01.003
1521-6918/

Abbreviations

AMI	acute mesenteric ischemia
BMI	body mass index
CVD	cardiovascular disease
CA	celiac artery
CACS	celiac artery compression syndrome (syn: MALS)
CVD	cerebrovascular disease
CMI	chronic mesenteric ischemia
CTA	computed tomography angiography
CT	computed tomography scintigraphy
DM	diabetes mellitus
DSA	digital subtraction angiography
DUS	duplex ultrasonography
GI	gastro-intestinal
IMA	inferior mesenteric artery
ICU	intensive care unit
LDH	lactate dehydrogenase
MAS	mesenteric artery stenosis
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NOMI	non-occlusive mesenteric ischemia
PTA	percutaneous transluminal angioplasty
PAD	peripheral arterial disease
PV	portal vein
PPI	protein pump inhibitors
SMA	superior mesenteric artery
SMV	superior mesenteric vein
VLS	visible light spectroscopy

12 per 100.000 inhabitants [10]. Still, compared to the estimated prevalence for PAD of 3–10% [11], CAD of 4.5% and CVD of 2.4% (Source: volksgezondheidenzorg.nl), the CMI prevalence of 0.03% (30 per 100.000) is still very low. This low CMI–MAS ratio is explained by the abundant collateral circulation, a remnant of the complex embryonal network that renders the GI tract quite flexible to prevent ischemia from stenoses in most cases.

The physiology of the mesenteric circulation

Three vessels form the mesenteric arterial circulation, the celiac artery (CA), superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA). The CA, with a normal diameter of 6 mm, comes from the aorta at the level of the crux of the diaphragm. It normally branches off the splenic artery, the left and right gastric artery, the gastroduodenal artery, and the common hepatic artery. It delivers blood to the stomach, the first and second part of the duodenum, the upper part of the pancreas and liver and spleen. The SMA originates from the aorta 2 cm below the CA, has a diameter of app. 7 mm, and gives off jejunal and ileal branches, the right and middle colic artery, ileocolic and appendicular artery. It delivers blood from the lower part of the pancreas, the second part of the duodenum, the small bowel, and the right colon of the transverse colon. The IMA, with a normal diameter of 2 mm, provides the distal part of the colon, usually starting at the splenic flexure.

The normal gastrointestinal blood flow under fasting conditions accounts for some 20% of the total blood flow [12]. In an elegant study Someya et al. showed that baseline blood flow in CA of mean 450 ml/min increased after meals to 700 ml/min with a peak within 10 min of the meal. The SMA blood flow increased from mean baseline 400 to over 800 ml/min, peaking after 40 min [13]. The increase in SMA blood flow may persist for up to 3 h [14].

This increase in blood flow depends on volume and constitution of the meal, with the largest and longest postprandial peaks observed after fat containing meals [15]. Proteins cause the smallest increase in blood flow, with carbohydrates in between fat- and protein responses [16]. The trigger for the increased blood flow is increased oxygen consumption for increased motility and secretions to process the ingested foods.

The major trigger to reduce mesenteric blood flow is an increased adrenergic drive caused by circulatory stress [17]. The most common cause is reduced circulating blood volume, or (pre)-shock conditions. At these conditions of low flow, the mesenteric vasculature shows early and profound vasoconstriction, which serves to preserve blood flow to the immediately vital organs (brain, heart, kidneys) [18]. Even before actual hypotension ensues, gastrointestinal ischemia can already be observed when measured with tonometry, an early specific marker for mesenteric ischemia [19]. A decrease in mesenteric perfusion has also been observed in severe psychological stress [20], similar to stress-induced cardiac dysfunction [21].

Etiology of CMI

The main cause of MAS consists of atherosclerotic narrowing of the arteries. Other causes include vasculitis, fibromuscular dysplasia, or compression by the median arcuate ligament, referred to as MALS (median arcuate ligament syndrome). The other term in literature is celiac axis compression syndrome (CACS) or Dunbar syndrome. In the latter condition the median arcuate ligament, part of the diaphragm, with important anatomic function in the lower esophageal sphincter, either compresses the celiac artery during inspiration, or expiration (Fig. 1 figure PanVascular Medicine). The atherosclerotic process in CMI is driven by the same risk factors as in other vascular beds [22,23], and include hypertension, hyperlipidemia, overweight, and nicotine abuse. A major difference with PAD, CAD, and CVD is the striking female preponderance in CMI [22,23]. A distinct form of CMI is the so-called non-occlusive mesenteric ischemia (NOMI). It is characterized by mesenteric ischemia despite normal mesenteric vessels. NOMI is a frequent complication of low-flow states especially in critically ill, or operative patients [17], and can be seen in endurance athletes as well [24]. In the outpatient setting it has been demonstrated in patients with heart failure, even after optimal treatment [25]. The same holds true for patients with end-stage pulmonary failure, where the diminished oxygen delivery may lead to redistribution of blood flow and consequently mesenteric vasoconstriction and ischemia. NOMI was also demonstrated in outpatients with typical CMI complaints, normal vessels and abnormal function test. In these patients, it is often accompanied by vasospastic disorders like migraine or Raynaud's phenomenon [26].

Clinical presentation

The clinical presentation of CMI has been established from several, relative small patient series.

The most typical complaint is postprandial pain, usually starting after the meal has finished. It has been reported in over 90% of patients in most series [27]. The duration of pain is usually between 30 min and 2 h. Pain for shorter duration, or lasting longer than 4–6 h are rarely seen in CMI. This pain often leads patients to take smaller meals, more frequently, and typically avoid fatty ingredients [28]. Ultimately, this may lead to weight loss, and is the

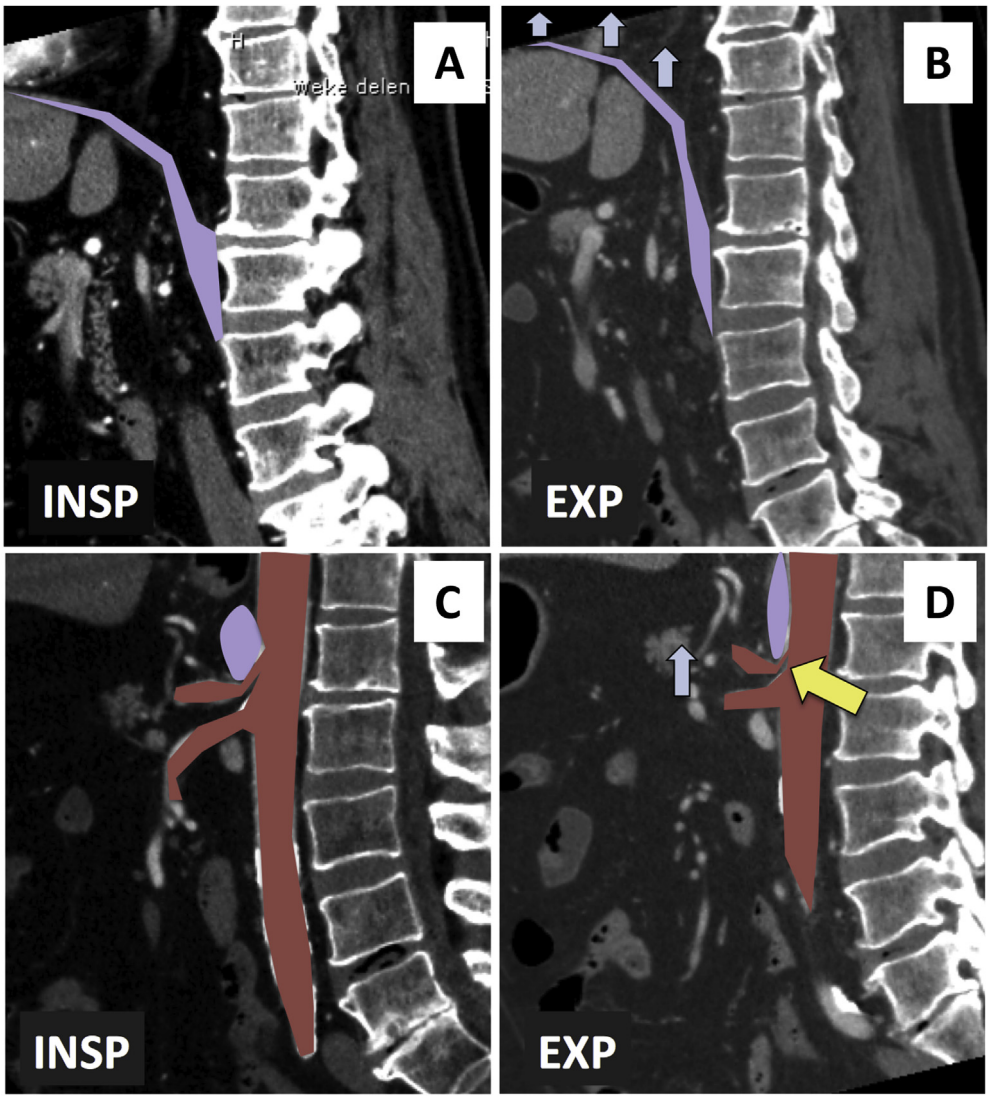

Fig. 1. Median arcuate ligament syndrome: compression of the celiac artery. The diaphragm, on CT scan some cm's beside the midline, moves down on inspiration (A) pushing down the abdominal organs. On expiration (B), the abdominal organs move upward. In the midline the effect on the celiac artery can be seen. In this case, the celiac artery is hardly compressed on inspiration (C). On expiration, the celiac artery kinks across the arcuate ligament leading to significant narrowing. Purple: diaphragm. Blue arrows: movement of the diaphragm on. Red: aorta and celiac artery. Yellow arrow: celiac axis compression (from Kolkman et al. PanVascular Medicine [53].

basis of the so-called fear of eating. Unexplained diarrhea was also observed in 7–35% of CMI patients [28,29]. Although diarrhea has been considered a sign of end-stage CMI, it has also been observed in the earlier stages of CMI. Other complaints, like pain after stress or with exercise can also be seen in CMI [28,30,31], although they were found in MAS-patient without ischemia as well [28]. Sometimes postprandial abdominal fullness is reported, although that is less typical for CMI, and may point to functional dyspepsia (FD), irritable bowel syndrome (IBS), or gastroparesis. The problem is of course that abdominal pain, related to meals, weight loss and diarrhea, are symptoms of a variety of more common gastrointestinal disorders. These include peptic ulcer disease, chronic pancreatitis, inflammatory bowel disease, FD and IBS. The latter is often accompanied by distended abdomen, flatulence and a changed pain perception before or after defecation. The presence of these complaints reduces the probability of CMI as explanation, or that IBS or FD may co-exist.

That the typical CMI complaints (postprandial pain, adapted eating pattern, fear of eating, weight loss) may be missed often as diagnostic clue for CMI can be derived from two findings. First, the duration of complaints before CMI diagnosis was 20–25 months in two large series [30,31]. Second, in studies to AMI patients, it was observed that 25–84% of them previous complaints indicative of CMI in the preceding months to years [32,33].

Of note, many of the patients referred to our center for suspected CMI have never been asked why the lost weight (typical CMI answer: because I eat less, because it hurts too much) and how it is if they don't eat (typical CMI answer: great, no pain, but I can't live without eating).

The clinical presentation between single vessel CMI, multivessel CMI, and MALS did not differ significantly in our cohort [34]. There is one exception: in patients with end-stage multivessel CMI, the clinical presentation gets less typical: pain is more continuous, the postprandial pain may last for many hours, and lack of energy and diarrhea is presented more often. The pathophysiological mechanism is that the now severely diminished blood flow is not even sufficient to sustain basal metabolism. These patients are at risk for development of acute bowel infarction and should therefore be considered as imminent AMI, or as they are now called acute-on-chronic mesenteric ischemia (A-O-CMI).

CMI can also present as unexplained persistent gastroduodenal ulcers or right-sided colitis. Therefore, in patients with peptic ulcers in whom no cause, Helicobacter pylori or non-steroidal anti-inflammatory drugs, can be identified CMI should be considered. In patients with right-sided colon ischemia, which can be very hard to distinguish from Crohn's disease, a SMA stenosis should be considered. This should be considered especially in patients of advanced age who present with a first presentation of right-sided Crohn's colitis. In some cases patients were treated for weeks to months with unresponsive colitis before CMI was considered and they were finally referred to our center.

Diagnosing chronic mesenteric ischemia

The diagnosis of chronic mesenteric ischemia depends on three elements: 1] medical history compatible with insufficient blood flow to the mesenteric organs, 2] mesenteric artery stenosis exceeding 70%, most often in at least two but sometimes in only a single vessel, 3] actual proof of mesenteric ischemia.

As discussed, the clinical presentation of chronic mesenteric ischemia is far from specific. Many other diseases may present postprandial pain, weight loss or diarrhea. As in all medical diagnosis, much depends on the prevalence of the disorder in the population that is investigated. In this sense, a huge difference seems to exist between patients with single-vessel MAS and those with multivessel MAS. First, in our series we found that among patients referred for CMI the diagnosis was made in one third of patients with single-vessel MAS and in almost 90% of those with multivessel MAS [paper in preparation]. This may indicate that in patients with otherwise unexplained abdominal complaints and significant multivessel MAS a diagnosis of CMI is rather likely in the absence of other disorders. There would be no need for functional testing with this very high pre-test probability. In contrast, in patient with single-vessel MAS, even in our nation-wide referral center only one third had CMI. In non-tertiary centers the proportion of symptomatic single-vessel MAS patients will probably be even lower, and in the general physician's population only a very small minority of patients with single-vessel MAS will have CMI. Our impression is that this is becoming an increasingly large problem: the availability and quality of both CT scan and duplex ultrasound result in, among other things, more and more asymptomatic MAS findings who are then referred for analysis, or worse, treatment. Selecting those patients who will benefit from treatment is therefore a task which will not get easier in the coming years. The need for an accurate ischemia function test may become indispensable in our view.

Medical history

As indicated above the main questions to be asked are: 1. Is the pain postprandial, 2. Is there no pain without eating, 3. Is there weight loss (if so, was it for fear of eating), 4. Has the eating pattern changed (more frequent, smaller and less fat containing meals), 5. Does the patient have unexplained diarrhea. In a recently published model, duration of symptoms and concomitant cardiovascular disease also had predictive value [35]. Still, medical history alone was a poor predictor of CMI [28,30,35].

Assessment of stenoses

The assessment of vessel anatomy should include the degree of stenosis of the artery, the nature of the stenosis (atherosclerosis, soft plaques, or external compression), and the presence and type of collaterals [36]. Also, the likelihood of CMI depends largely on which artery is stenosed at what degree. As can be derived from Fig. 2, the total vessel surface is reduced by approximately 20% when the CA is 70% stenosed, whereas a 70% stenosis in CA and SMA leads to a 75% reduction in flow surface. Because the flow resistance in vessels increases in proportion to the fourth power of the diameter [37], the actual decrease of blood flow probably exceeds this 75%. Although most stenoses are seen in the origin of the arteries, assessing the remaining artery for atherosclerotic changes is crucial when planning treatment. Several techniques are available to sufficiently establish these parameters. Ideally, information on the flow characteristics and pressure changes in the artery could be very important. Still, at this moment techniques to assess these are not widely available. The main diagnostic tools for vascular assessment will be briefly reviewed.

Duplex ultrasonography

Duplex ultrasonography is an established screening tool in patients suspected of MAS. It is patient friendly, has no radiation burden, and is in experienced hands quite reliable (accuracy of over 80%). The main disadvantage of duplex ultrasonography is that is very operator dependent and that the reported accuracy figures will probably not be reached in centers with less exposure and or experience. Duplex ultrasonography is also very useful in follow-up of patients that underwent endovascular treatment. It should be kept in mind that normal systolic and diastolic flow velocities in patients with stents are higher than in normal vessels. When the flow velocity in the treated vessel increases over time physicians should be aware that a critical stenosis may be developing, and that recurrence of pain should result in analysis and treatment of the stenosis.

CT angiography

CT angiography has become the standard of diagnosis of the mesenteric vasculature. It combines anatomical resolution with possibilities of three-dimensional reconstructions, and provides important information on non-vascular structures as well. Moreover, it is investigator independent, and it can be performed in most sites almost 24/7, even in very sick patients. The main disadvantage is the high radiation burden of CT angiography. Of note, state-of-the-art CTA should include an arterial phase with slice thickness of maximum 1 mm, and venous phase slices of maximum 3 mm.

MR angiography

MR angiography has the potential advantage of zero radiation burden. However, there are very limited validation studies comparing MRA with for example DSA or CTA [38,39]. In one small study, direct comparison CTA proved superior over MRA [40]. With further improvements in MRA technique, both in software and in hardware, MRA may regain some ground currently lost to the CTA as diagnostic tool for MAS. A potential extra value of MRA is that it allows measurement of flow velocity, and flow volume [41]. Some small studies suggested that reduction of portal and superior mesenteric vein blood flow could be used as an indirect measure of mesenteric hypoperfusion [42]. Commonly used stents are often not compatible to standard MR angiography imaging due to creation of various artefacts and loss of signal by the stents, and thus, making assessment of stented arterial segments impossible. Still, the current role of MRA in MAS assessment is that of second-best after CTA, especially when CTA is contra-indicated, for example in renal failure.

DSA

DSA (digital subtraction angiography) has long been the gold standard to assess the mesenteric vasculature. For diagnostic purposes, it has been surpassed by CTA, and is now mainly used to treat MAS via the endovascular route. In our experience, it has some

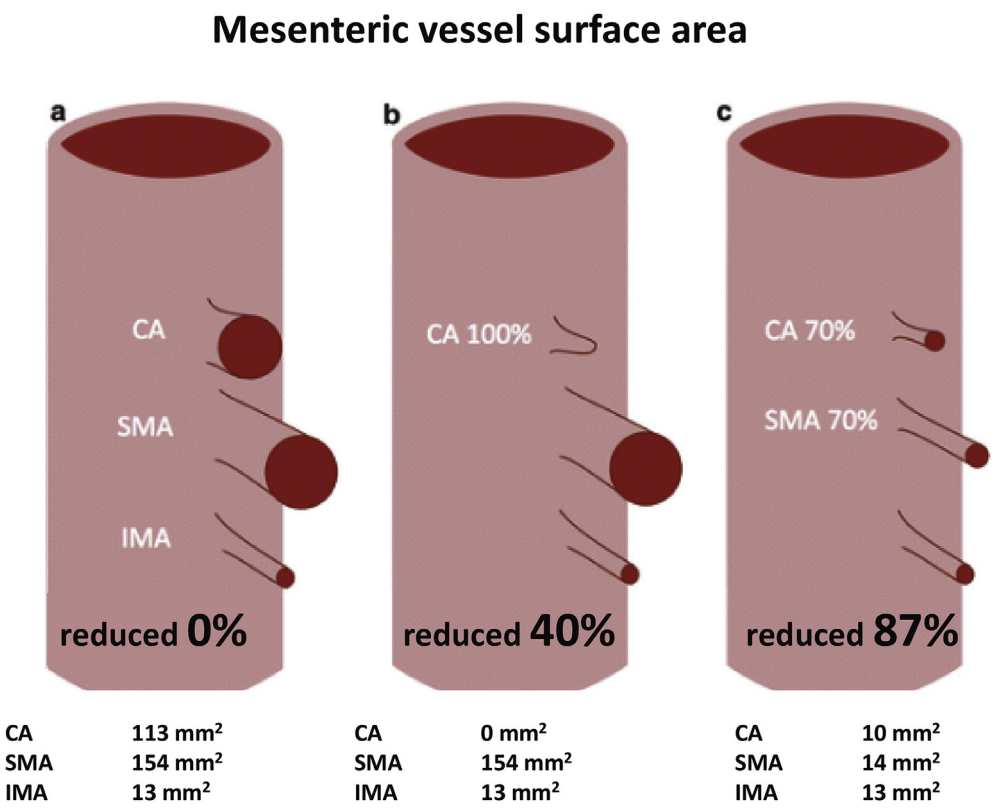

Fig. 2. Vessel surface area in single- and multi-vessel MAS. Stenosis degree, vessel diameter, and vessel surface area. (a) Normal situation: two large vessels, the AC and AMS, provide the largest diameter for blood entering the GI tract. (b) With complete single-vessel CA occlusion, the vessel surface area is reduced by 40%. (c) With 'mild' multi-vessel stenosis of 70% of CA and SMA, the calculated reduction in vessel surface area is 87%. (Copyright© 2014 JJ Kolkman); adapted from Ref. [53].

value in patients with MALS in the preoperative evaluation as it can show the length of the compressing ligament and demonstrate the influence of respiration on the stenosis guiding the retroperitoneal endoscopic approach [43].

Ischemia functional testing

Function testing is extensively covered in this issue by van Noord et al. In short, two function tests have been evaluated in patients with CMI: PCO2 tonometry [44–46] and visual light spectroscopy [47,48]. PCO2 tonometry has the advantage that it can be used with a provocative test (eating or exercise), but is laborious, and the technique is sparsely available. VLS has the advantage that it is widespread available and can be used during endoscopy; its main disadvantages include poor specificity, uncertainty about reproducibility, and the short measurement time that makes use with a provocative test complicated. Although small studies to serological markers, especially i-FABP, have been published and the potential seems quite good [49], large validation studies are so far lacking. The presence of otherwise unexplained ulcers in the stomach, duodenum or right-colon can also be regarded as proof of ischemia. In those cases, functional ischemia testing is not indicated.

Treatment

Conservative treatment

The simplest way to reduce metabolic amount in patients with CMI is to reduce the size meals as well as the fat content, and take more frequent meals. Many patients have already changed their eating habits accordingly, because it reduces their pain. The consequence of this adapted eating pattern is weight loss; it may also lead to vitamin and mineral deficiencies. Therefore, it is advisable to refer these patients to a dietitian to maintain vitamin and mineral, not caloric, intake at optimal levels. Increasing the caloric intake in multi-vessel CMI patients before revascularization Amy pose the risk of worsening ischemia, or even provoke AMI. A second way to decrease metabolic demand is to prescribe proton pump inhibitors (PPI). Acid secretion in the stomach is a major energy consuming activity, and PPIs decreased energy expenditure whilst at the same time maintaining gastric perfusion. The next thing is to advise patients to abandon smoking. Apart from the effects of nicotine on atherosclerosis, it has some direct effects mesenteric ischemia as well. Nicotine causes both reduced mesenteric blood flow [50], and reduces the oxygen delivery capacity of the blood, both increasing mesenteric ischemia. The effect of an e-cigarette on mesenteric blood flow is unknown.

Preventing the progression of atherosclerosis mainly consists of treatment of hypertension, hyperlipidemia, diabetes, as well as cessation of smoking and changing lifestyle on the mainstays. Concerning hyperlipidemia, we have previously shown that in patients with CMI the prevalence of hyperlipidemia is lower than those with PAD, CAD and CVD [22]. It is likely that the changes in eating pattern [28], caused this difference. This usually changes after successful treatment of the MAS; now the postprandial pain disappears and patients resume a normal diet, with normal fat-content. They therefore may be at increased risk for progressive atherosclerosis after treatment.

The blood pressure should be kept below 140/90 mmHg. This can be achieved by lifestyle adjustments and medication. The most important lifestyle measures are to prevent overweight, increase

physical activity, and moderate both alcohol and sodium intake, and eat a healthy diet (more fruit, vegetables and less carbohydrates and red meat).

Hyperlipidemia

Although there is discussion about the threshold values for cholesterol there is convincing data that reducing cholesterol levels is a positive effect on cardiovascular events. The most used target values for LDL are below 2.6 mmol/l for those with average risk, and below 1.8 mmol/l in high-risk patients. The latter was defined as patients with atherosclerosis and uncontrolled or poorly controlled risk factors like ongoing nicotine use, presence of metabolic syndrome, a recent cardiovascular event. In most patients, a statin will be initiated.

Physical exercise

It seems reasonable to motivate patients to perform 30 min of moderate exercise at least five times a week. This can be achieved by brisk walking for example.

Body weight

Has been shown that a body mass index between 18.5 and 25 kg/m^2 with an abdominal circumference less than 89 cm in women and less than 102 cm in men reduces the risk of further atherosclerosis.

Diabetes

Diabetes mellitus type II is associated with the metabolic syndrome and is strongly associated with atherosclerosis development. Reducing blood glucose levels reduces this process; as guidance, anHbA1c below 7% is advised.

Vascular treatment: approach to the patient

Because the large majority of MAS patients do not develop CMI, treatment will be performed in a minority of MAS patients. The first question is therefore to decide which patient may benefit from treatment. The next question is what treatment should be offered. In this issue, others will go into detail on the treatment, both for acute and chronic mesenteric ischemia. For this discussion, the focus will be on the decision who to treat, and what arguments and criteria can be of help. Four clinical scenarios will be covered, because the diagnosis CMI or AMI only follows after analysis, we refer to them as single- or multi-vessel MAS patients in this part. The scenarios are: (1) the symptomatic single-vessel MAS and MALS patient, (2) the symptomatic multivessel MAS patient, (3) the patient with chronic NOMI, and (4) the asymptomatic MAS patient.

The symptomatic single-vessel patient, including MALS

Because most patients with single vessel MAS are asymptomatic, and the complaints typical for ischemia are not very specific for the disease, diagnosing CMI is a challenge. Our center has used tonometry as ischemia test for over 20 years and found it useful for selecting patients for treatment [31,45]. It also helps patients who had normal tonometry, to accept that treatment is no option. In a short period that the catheters were not available, we felt quite helpless in deciding who to treat and who not to treat. The problem is that tonometry has never gained popularity and is hardly available anymore. Alternative tests, including visible light spectroscopy or i-FABP after meals may prove useful, but need further evaluation. Without a functional test our approach, only patients with very typical presentation without other explanation after extensive investigations, would be treatment candidates.

For MALS patients, the situation is essentially the same. It has been shown that with proper selection (anamnesis, function test and proof of celiac artery compression) durable release of symptoms of 80–85% are achievable [36,45]. The current approach using endoscopic techniques via the retroperitoneal route had a low complication rate. Still, in our experience in almost 200 patients we had two major complications: one iatrogenic renal artery occlusion and one patient with persisting lymph leakage due to an iatrogenic damage of the thoracic duct.

Taken together, treatment in single-vessel MAS is indicated in patients with typical complaints and a functional test showing ischemia. When a functional ischemia test is not available, as will be the case in many centers, extra precautions should be made to exclude more common causes of abdominal complaints, and that the patient is informed that the treatment is more or less a shot in the blind with success rates up to 50%.

The symptomatic multi-vessel MAS patient

In our cohort, most patients with multivessel MAS, defined as stenosis in both the CA and SMA >70%, had CMI. In these patients, a functional test will be of little extra value, and would rarely change the treatment decision. With less severe stenoses, or ischemia-atypical complaints, an ischemia function test could be useful to assess the potential benefit of treatment. An abnormal function test would strengthen the case for treatment, whereas as normal ischemia function test would favor a wait-and-see strategy.

Special attention should be given to patients with severe multivessel MAS, especially those with subtotal stenosis or occlusions. In these patients, a gradual transition to acute ischemia can be seen, referred to as acute-on-chronic mesenteric ischemia (A-O-CMI). In these patients, the mesenteric blood flow can be insufficient even under fasting circumstances. Complaints may now last for many hours after meals or even during fasting, patients may complain of fullness, loss of appetite, or diarrhea. These patients should be treated urgently, as discussed in the chapter on acute mesenteric ischemia in this issue. In short, the choice of treatment depends on vessel anatomy and age and comorbidity of the patient. In most cases a percutaneous mesenteric artery stenting (PMAS) will be the first choice (high success rate, low morbidity). The second choice in our opinion would be that retrograde operative mesenteric stenting (high success rate, moderate morbidity). Operative surgical mesenteric artery repair (OSMAR) would be our current last option (high success rate, high morbidity), but can be first choice in “fit” patients because the open approach still has the most convincing long-term primary patency results.

The chronic NOMI patient

NOMI, characterized by normal vessel anatomy and mesenteric ischemia, can be seen in outpatients in four different forms. Of note, because NOMI cannot be diagnosed without a good ischemia function test, and the condition is therefore hardly diagnosed outside centers performing these tests. In our cohort, 132 patients had abdominal complaints, normal vessels and tonometric proof of CMI, compatible with NOMI (Table 1). The largest group in whom the presentation and comorbidity was suspected for vasospasm of the mesenteric circulation, or abdominal migraine, was offered medical treatment. Treatment options consist of vasodilatation by nitrates, ketanserin, nicorandil, or doxazosin, as previously reported [26]. In this cohort, 59 of 75 got medication, of whom 45 reported symptom improvement, or 60% of the abdominal

Table 1
Non-occlusive ischemia in outpatients.

Mechanism	n (%)
Abdominal migraine	75 (57%)
Heart failure – pulmonary failure	25 (19%)
IBS	18 (14%)
Top-class sport	8 (6%)
Other	6 (5%)
Total	132

IBS: irritable bowel syndrome.
Other: threepatients with pancreatic cancer.

migraine group or 77% of those who were treated. The other 16 patients did not receive medical treatment for various reasons. The second largest group consisted of patients with varying degrees or heart or respiratory failure. Because vasodilating drugs are often poorly tolerated in these patients, often our only advice has been to aim for improved cardiac or respiratory function. The third group was patients with all symptoms of irritable bowel syndrome, and ischemia may be secondary to bowel spasm. The fourth group consisted of individuals who develop ischemia during exercise; in most cases the type of exercise was very extensive (marathon running, competitive biking, triathlon, etc.). Here, the NOMI is the consequence of the adaptation of the body to this extreme physical exertion. In most cases the only valuable advice is to reduce the level of exercise. There is some recent data in healthy volunteers, suggesting that using 10 g citrulline before exercise would be beneficial [51], although no studies in symptomatic subjects have been performed.

The asymptomatic MAS patient

As a rule, most experts would agree that there is no indication to treat patients with MAS without ischemic symptoms. This fact alone is important to share with patients in whom a coincidental MAS was found. In our experience, for many of them it is very hard to conceive that a vascular stenosis remains untreated. There may be four exceptions to this rule of “no complaints, no ischemia, no treatment”.

MAS and (pre)-shock. If low-flow states develop, the normal circulatory response is mesenteric vasoconstriction to preserve blood flow in more crucial organs (brain, heart). It is conceivable that MAS patients can develop symptoms or even end-organ damage, during these low-flow states. This mechanism has been observed in patients who were completely asymptomatic before the shock-period, when they developed colonic ischemia or limited small bowel infarct. They recovered spontaneously, or had limited bowel resection, and had no CMI-symptoms after this period. Thus, the presence of these complications in a single vessel MAS patient after a period of circulatory shock, should not automatically lead to vessel treatment. It is advisable to wait for the recovery, and advise the patient to avoid hypovolemia in the future.

MAS and heart failure. A clinically challenging combination is the patient with heart failure, abdominal complaints and MAS. Both the MAS and the reduced cardiac output with accompanied mesenteric vasoconstriction [25] contribute to development of mesenteric ischemia. There is no way to decide which of the two is the predominant factor, and therefore, what the best approach should be. In our experience, endovascular treatment in these patients had disappointing results. Consequently, we are very reluctant in treating these patients and would favor an approach toward improving cardiac output first.

Single-vessel CA or SMA stenosis and major abdominal surgery. We have seen some patients with protracted and complicated course after cholecystectomy, pancreatectomy or partial colonic resection, who had, previously asymptomatic, SMA stenosis. After treatment of the stenosed or occluded SMA, these patients had a remarkable recovery following this intervention. The explanation is probably that these patients may not have had ischemic complaints during the normal life before surgery. However, when extra mesenteric perfusion was needed to heal their surgical wounds they could not meet this demand because of the restricted mesenteric inflow. It is currently unclear if preventive vascular treatment would be of benefit in patients with asymptomatic MAS who are scheduled for major abdominal surgery. We would consider this approach in patients scheduled for especially pancreatic, gastroduodenal, or colonic surgery, with critical stenoses of the providing artery. Indirect support for this approach comes from a recent study that showed a more complicated in-hospital course for a variety of disease in patients with asymptomatic MAS [52].

Multivessel MAS. In patients with multivessel MAS there is data to suggest that a significant proportion of patients will ultimately develop acute mesenteric ischemia [9] with its inherent high mortality. It might be justifiable therefore to offer treatment to patients with multivessel MAS even without symptoms if the reduced risk of treatment outweighs its risks. A reasonable case would be a young patient, with little comorbidity, and subtotal stenoses or occlusions in CA and SMA. The risk in these cases would be an extensive and potentially lethal bowel infarction, whereas the risk of treatment is relatively small.

Taken together, treatment of asymptomatic MAS can be considered in (1) patients with severe multivessel MAS in otherwise good physical condition, (2) patients scheduled for major abdominal surgery with severe MAS especially of the SMA. We would not advise treatment in patients with severe heart failure and single-vessel stenosis, as the NOMI component seems to be the major problem in most patients.

Research agenda

- There is a need for studies that address significant endpoints to assess the success of CMI treatment; ideally they should include patient reported outcomes.
- There is a need for a calculation or grading to assess the risk for CMI in patients with coincidental findings of mesenteric artery stenosis.
- An ischemia function test that is widespread applicable, for AMI it should be 24/7 available.
- An ischemia function test that allows for prolonged measurement during the day, similar to the current tonometry, is needed to diagnose NOMI and abdominal migraine; our results with vasodilating drugs indicates that abdominal migraine is a real disease and can be treated successfully.

Practice points

- Most patients with abdominal discomfort and significant (>70%) stenoses of both SMA and CA have CMI, and are candidates for vascular treatment.
- A minority of patients with single-vessel MAS have CMI; patient selection for vascular treatment is therefore crucial, and an ischemia function test highly desirable.
- Endoscopic release in case of the median arcuate ligament syndrome, previously called celiac axis compression syndrome, is indicated in those with typical complaints and evidence of ischemia, and can lead to durable symptom relief in up to 80%.
- In patients with weight loss, always ask "why did you lose weight"; CMI patients will tell you they eat less because they're afraid of the pain.
- The typical pain for CMI starts after the meal, lasts for 2–3 h, and is absent if the patient is not eating.
- Patients with subtotal stenosis or occlusions of SMA and CA may progress from chronic to acute mesenteric ischemia. Complaints become less typical with prolonged periods of pain, even during fasting (vascular abdominal rest pain), diarrhea and abdominal fullness. Urgent referral and treatment is indicated.

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