State of the Art

Pulmonary Arteriovenous Malformations
A State of the Art Review

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INTRODUCTION

Pulmonary arteriovenous malformations are caused by abnormal communications between pulmonary arteries and pulmonary veins, which are most commonly congenital in nature. Although these lesions are quite uncommon, they are an important part of the differential diagnosis of common pulmonary problems such as hypoxemia and pulmonary nodules. Since their first description at autopsy in 1897 (1), these abnormal communications have been given various names including pulmonary arteriovenous fistulae, pulmonary arteriovenous aneurysms, hemangiomas of the lung, cavernous angiomas of the lung, pulmonary telangiectases, and pulmonary arteriovenous malformations (2). The term "pulmonary arteriovenous malformations" (PAVM) will be used in this review to describe these lesions.

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Abnormal communications between blood vessels of the lung may also be found in a variety of acquired conditions. Right-to-left shunting as a result of communications between pulmonary arteries and pulmonary veins has been reported in hepatic cirrhosis (3–7), and less commonly in schistosomiasis (8), mitral stenosis (9), trauma (9), actinomycosis (9), Fanconi's syndrome (10), and metastatic thyroid carcinoma (11). Communications between bronchial arteries and pulmonary arteries, causing left-to-right shunt, can develop in chronic inflammatory conditions such as bronchiectasis (12). The focus of this review will be congenital PAVM. Although many patients with PAVM have hereditary hemorrhagic telangiectasia (HHT), this review will discuss HHT predominantly as it relates to PAVM. Hereditary hemorrhagic telangiectasia has recently been reviewed in detail (13).

EPIDEMIOLOGY

PAVM are not a common clinical problem. In an autopsy study in 1953 from Johns Hopkins Hospital (2), only three cases of PAVM were detected in 15,000 consecutive autopsies. However, it was noted by the same investigators that small PAVM may easily be missed in routine autopsies. The Mayo Clinic saw 63 cases over 20 yr ending in 1972 (14), and 38 cases over 8.5 yr ending in 1981 (15), for an annual incidence of 3.2 and 4.5 cases/yr, respectively. Smaller, nontertiary care hospitals might expect to see one case every few years.

PAVM occur twice as often in women as in men, but there is a male predominance in newborns (16). Around 10% of cases of PAVM are identified in infancy or childhood, followed by a gradual increase in the incidence through the fifth and sixth decades. Approximately 70% of the cases of PAVM are associated with HHT (Table 1). Conversely, approximately 15 to 35% of patients with HHT have PAVM (17–20). Although Plauchu and coworkers (21) found PAVM in only 4.6% of 324 patients with HHT from an endemic area in France, chest radiographs were not routinely performed. Also known as Rendu-Osler-Weber syndrome, HHT is a condition which is transmitted in an autosomal dominant pattern, and characterized by arteriovenous malformations (AVM) in the skin, mucous membranes, and visceral organs (Figure 1) (21). Depending on the geographic population studied, HHT has been found to occur with an incidence between 1/39,216 and 1/2,351 (13). Penetrance is age-related and is nearly complete by age 40 (22). Although the AVM in HHT are inherited and should be present at birth, they seldom manifest clinically until adult life, after the vessels have been subjected to pressure over several decades (18). The initial manifestations of HHT are usually the appearance of cutaneous telangiectases or epistaxis. Of 80 HHT patients with visceral involvement by AVM, only 9% had visceral signs or symptoms (e.g., dyspnea

TABLE 1

SYMPTOMS AND SIGNS IN PAVM*

	Moyer 1962 (46)	Sluiter-Eringa 1969 (48)	Dines 1974 (14)	Dines 1983 (15)	White 1988 (40)	Jackson 1990 (49)	Puskas 1993 (47)	All Consecutive Case-series†	Literature Review (44)
Number of patients	21	27	63	38	76	16	21	262	138
Symptomatic, %	NR	52	44	87	91	NR	90	72	91
Epistaxis, %	71	56	NR	32	79	NR	29	59	79
Dyspnea, %	62	40	32	47	71	63	67	53	82
Hemoptysis, %	NR	13	10	NR	13	NR	5	11	NR
Telangiectases, %	67	79	NR	34	NR	NR	48	54	69
Bruit, %	NR	67	59	29	NR	25	29	46	87
Clubbing, %	81	54	13	NR	NR	69	33	39	78
Cyanosis, %	76	25	16	NR	NR	69	29	34	79
HHT, %	NR	78	60	47	88	63	57	69	NR

Definition of abbreviations: NR = not reported; HHT = hereditary hemorrhagic telangiectasia.

* Not all patients from each study had evaluation for each feature.

† Data in this column reflect the total number of patients (row 1) and total percentage of patients with a particular feature from the seven consecutive case-series in the preceding columns (14, 15, 40, 46–49).

or gastrointestinal bleeding) as the first manifestation of HHT (21). Because visceral AVM are typically larger than cutaneous and mucosal AVM at the time of clinical appearance, the later onset of visceral manifestations may reflect the additional time needed for further enlargement.

ETIOLOGY AND PATHOGENESIS

The etiology of PAVM is unknown, but recent discoveries about the genetics of HHT may be relevant to the etiology of PAVM in patients with HHT—and perhaps in patients without HHT. Genetic mapping in the last few years has found that HHT is linked to loci on at least three different chromosomes (20, 23–29). Endoglin, the most abundant transforming growth factor beta (TGF-β) binding protein that is found on endothelial cells, has been identified as the HHT gene mapping to locus 9q3, and is presently referred to as the gene for HHT 1 (20, 23–25, 28, 29). Thus far, at least 16 novel mutations of the endoglin gene have been discovered in 17 different families (28–31). Proposed mechanisms by which mutations to the endoglin gene might cause HHT 1 have included a dominant negative effect, a two-hit model, and haploinsufficiency, although recent data seem most consistent with haploinsufficiency (28–31).

Mutations in the gene for activin receptor-like kinase 1 have been mapped to locus 12q and are referred to as the gene for HHT 2 (26, 27). Activin receptor-like kinase 1 is a type I serine–threonine kinase receptor that can bind TGF-β in the presence of its type II receptor and is expressed predominantly on endothelial cells (27). Thus far, at least 12 novel mutations of the activin receptor-like kinase 1 gene have been discovered in 12 different families (26, 27). All 12 mutations have affected the cytoplasmic kinase region, suggesting that the resultant protein would have decreased kinase activity. As

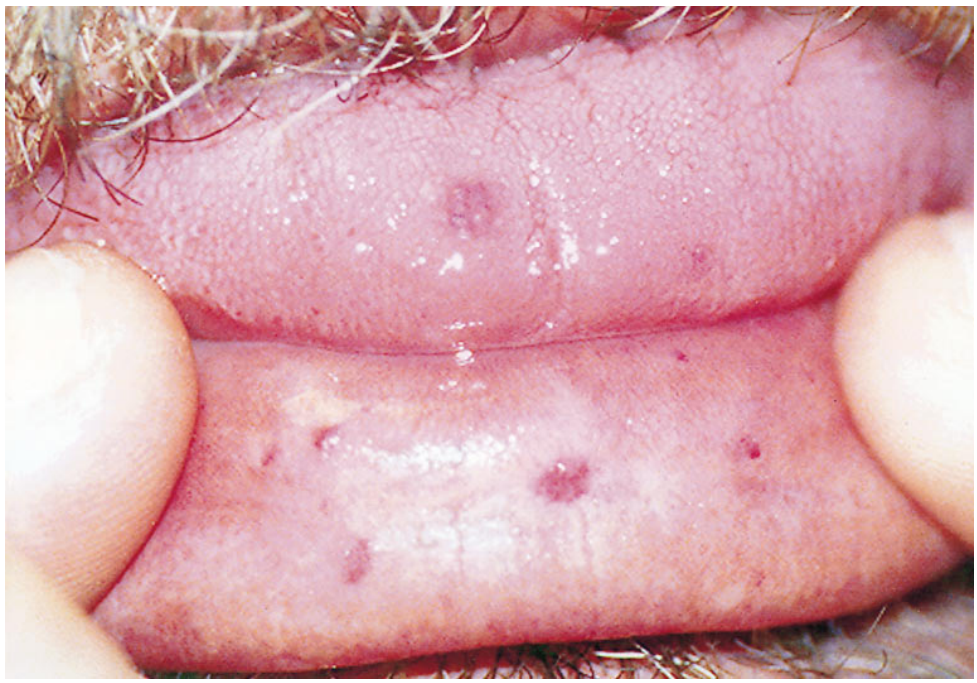

Figure 1. Photograph showing several characteristic telangiectases on the tongue (*upper part of photograph*) and lower lip (*lower part of photograph*) of an asymptomatic 42-yr-old man with HHT and a solitary PAVM.

with the endoglin gene, there is evidence to support the dominant negative, two-hit, and haploinsufficiency mechanisms (27). Preliminary data have suggested a third locus for HHT at 3p22, where the TGF-β II receptor gene is located (28).

Several reports have suggested a possible correlation between the varied phenotypes of HHT and its genetic heterogeneity (20, 25, 30, 32, 33). In a prospective analysis, Berg and coworkers (32) showed that the incidence of PAVM was 29.2% in eight families with HHT 1 (i.e., those with a linkage to endoglin) versus only 2.9% in eight families in which a linkage to endoglin was excluded. Similarly, Shovlin and coworkers (30) found that 41% of HHT patients with endoglin mutations had PAVM compared with only 14% of HHT patients without endoglin mutations. These studies are consistent with the hypothesis that HHT families with endoglin mutations have an increased incidence of PAVM. However, there was no evidence for significant phenotypic variability between the various endoglin mutations—supporting the hypothesis for haploinsufficiency (30, 31).

Therefore, all the known mutations associated with various types of HHT result in potential abnormalities in ligands for TGF-β. Transforming growth factor beta family members are involved in a variety of vascular phenomena including angiogenesis, induction of endothelial cell mitogens, and the interplay between cells, matrix, and external factors during the response to vascular insults (27). McAllister and coworkers (28) have postulated that changes in endoglin might result in endothelial cells that would respond abnormally to TGF-β during the process of vascular remodeling, possibly resulting in the formation of AVM (28). Endoglin and activin receptor-like kinase 1 may even act together to alter repair and remodeling of vascular tissue through changes in expression of matrix proteins (26). While intriguing, these hypotheses remain unproven. The reason for the propensity of families with HHT 1 to develop PAVM is also unknown.

The exact pathogenesis of PAVM is not known either. Some investigators have hypothesized that the cause is a defect in terminal arterial loops which allows dilatation of thin-walled capillary sacs (34). Others have argued that PAVM are the result of incomplete resorption of the vascular septae that separate the arterial and venous plexuses which normally anastomose during fetal development (35). It has also been suggested that multiple small PAVM develop as a result of failure of capillary development during fetal development (35). Hales (36) studied the lungs of two patients with multiple 1-12-mm pulmonary telangiectases by injection of the vascular tree with colored vinylite, followed by digestion of lung tissue with acid. Based on a detailed study of the variable morphology of different telangiectases in these two cases, Hales hypothesized that large saccular PAVM develop by progressive dilation of favored limbs of smaller plexuses. As the favored limbs dilate, the smaller limbs progressively disappear, perhaps due to diversion of blood to the favored limbs. Further enlargement of the favored limbs results in a mass of tortuous loops and U-turns with the formation of multiloculated sacs. Ultimately, the thin vascular walls between these juxtaposed loops may deteriorate or rupture, resulting in formation of a single saccular PAVM. This latter theory has been challenged by White and coworkers (37), who studied PAVM architecture with angiography and found that many small PAVM consisted of a single artery-to-vein connection without an intervening plexus.

PATHOLOGY

Fifty-three to seventy percent of PAVM are found in the lower lobes (2, 14, 38–40). An extensive review of the pathologic anatomy in 350 patients with PAVM found that 75% of patients had unilateral disease, 36% had multiple lesions, and half of those with multiple lesions had bilateral disease (38). Of 110 cases with adequate information, PAVM involved the pleura in 89 (81%) and were totally subpleural in 21 (19%) (38). Individual PAVM are typically from 1 to 5 cm in size, although they are occasionally in excess of 10 cm. There have also been descriptions of PAVM that are spread over the surface of the lung like a Medusa's head (38). However, PAVM may be microscopic in size and are then referred to as telangiectases. Seven to eleven percent of patients have diffuse microvascular PAVM, which are often in combination with larger, radiographically visible PAVM (15, 40). Hales (36) reported a case with several hundred plexiform lesions 1 to 10 mm in diameter that were diffusely scattered through both lungs.

PAVM can be classified as either simple or complex. Eighty to ninety percent of PAVM are of the simple type—defined as those with a single feeding segmental artery and a single draining vein (37, 40, 41). The rest are complex, with two or more feeding arteries or draining veins (37). If one defines simple PAVM as those with a single feeding artery, regardless of drainage, 86 to 92% are classified as simple by 3-D helical computed tomography (CT) scanning (42). The smaller telangiectases are most commonly of the complex type (36). PAVM are supplied by pulmonary arteries in about 95% of cases, and by systemic arteries less frequently (14). There have been cases described with both pulmonary and systemic arterial supply (43). Drainage is usually to the left atrium, but anomalous drainage to the inferior vena cava or innominate veins has been reported (2, 35).

PAVM are pathologically similar to AVM that occur elsewhere in the body. Two basic elements make up these malformations which often have paper-thin walls. The first element is the vascular channels, which are thin-walled and lined with a layer of endothelium (2). The second element is the connective tissue stroma, which is usually scant with no communication with surrounding lung tissue (2). Occasionally the wall is thickened by fibrous tissue and elastic fibers. The malformations may have one of three typical appearances: (*1*) a large, single sac, (*2*) a plexiform mass of dilated vascular channels, or (*3*) a dilated and often tortuous direct communication between artery and vein (35, 36, 38). Uncommonly, there may be mural thrombi or mural calcifications (2).

CLINICAL MANIFESTATIONS

In evaluating the incidence of the various clinical manifestations of PAVM as reported in the literature, it is important to consider whether the particular source is a literature review or a series of consecutive cases from a single institution. Many of the older articles reported on all cases in the literature and therefore overestimated the average severity of illness (2, 39, 44–46). Table 1 shows the incidence of the more common symptoms and signs as reported in seven case-series with 10 or more consecutive patients (14, 15, 40, 46–49) and in a representative literature review (44).

Symptoms

Symptoms in early life may vary from being totally absent to severe with cyanosis, congestive heart failure, and even fulminant respiratory failure (16, 50). In contemporary series, about 72% of patients have symptoms referable to the PAVM or underlying HHT (Table 1). Symptoms related to PAVM often develop between the fourth and sixth decades. In a 1974 study from the Mayo Clinic (14), symptoms were more common in

PAVM patients with HHT than in those without HHT. The presence of symptoms correlated best with lesion size (14). Usually, a single PAVM < 2 cm in diameter does not cause symptoms (14, 18). The incidence of symptoms is said to be greater in patients with multiple rather than single PAVM (44), but not all series have found this to be the case (14, 15). In the Mayo Clinic series (14), symptoms were seen in 37% of patients with single PAVM and in 59% of patients with bilateral PAVM; although this difference was not statistically significant, there was a strong trend ($p < 0.1$ by chi-square analysis). Haitjema and coworkers (51) reported on gas exchange data in 32 patients undergoing embolotherapy; although they did not comment on symptoms, the magnitude of shunt fraction was significantly correlated with the number of PAVM ($p < 0.001$ by linear regression). It therefore seems logical, though unproven, that the presence of symptoms would correlate with the number of PAVM if a large enough sample were analyzed. Patients with diffuse microvascular PAVM are uniformly symptomatic (15).

The most common complaint in symptomatic patients with PAVM is epistaxis, which is caused by bleeding from mucosal telangiectases and reflects the high incidence of HHT in patients with PAVM. Epistaxis is characteristically spontaneous or precipitated by minor trauma. Epistaxis is an early symptom, and in one series of 324 patients with HHT (with or without PAVM), 50% of patients with epistaxis developed it by age 20, and 90% by age 45 (21). Interestingly, epistaxis typically preceded the development of external telangiectases by 10 to 30 yr (21).

Dyspnea is the second most common complaint in patients with PAVM, and the most common complaint referable to the lungs in such patients. Dyspnea is most common in patients with large or multiple PAVM, and is seen in almost all patients who have associated clubbing (44). Interestingly, it has been noted clinically that symptoms such as dyspnea are sometimes strikingly minimal when compared with associated signs such as cyanosis and clubbing (52). Some patients also have platypnea (improvement in breathing on reclining) (53). This phenomenon is believed to be secondary to a decrease in blood flow through PAVM in the dependent portions of the lungs upon assuming the supine position. Though suggestive of PAVM, platypnea may also be seen with the hepatopulmonary syndrome (3, 53) and less commonly following pulmonary embolism or pneumonectomy (54). Hemoptysis is the third most common symptom, but may be a more common presenting complaint (14, 18, 48). Massive hemoptysis may occur, but is rarely fatal (55).

Bleeding from telangiectases on the skin and in the gastrointestinal tract is seen in patients with PAVM and HHT. The incidence of gastrointestinal hemorrhage in patients with HHT is 15 to 30% (17, 21), but the specific incidence in patients with PAVM and HHT has not been reported. Gastrointestinal bleeding develops later in life: half between the ages of 30 and 58, and half after age 58 (21). Occasionally, the severity of extrapulmonary bleeding may be sufficient to cause anemia (9, 18). Less common complaints include chest pain, cough, migraine headaches, tinnitus, dizziness, dysarthria, syncope, vertigo, and diplopia. Many of these symptoms are vague and may be related to hypoxemia, polycythemia, or cerebrovascular complications such as stroke.

Signs

Superficial telangiectases attributable to HHT are the most common—and frequently the only—physical finding in patients with PAVM. These lesions are papular, slightly rounded, 1 to 3 mm in diameter, and are sharply demarcated from surrounding skin with few dendritic projections (Figure 1). They are ruby-colored, blanch partially with pressure, and are widely distributed over the body. They are most commonly located on the face, mouth, chest, and upper extremities. In one large series of patients with HHT, about one-third of patients had telangiectases in each of the following areas: lower lip, nose, tongue, and cheek skin (21). These characteristics differentiate PAVM from the flat spider nevi in advanced liver disease, which are mainly found on the face and anterior chest, and blanch readily (56).

Murmurs or bruits over the site of the PAVM are heard in about 46% of patients (Table 1). The murmurs are most audible during inspiration (14), and usually increase on assuming positions which put the PAVM in a gravitationally dependent position. However, a case of right lower lobe PAVM was reported in which the murmur was softest in the right lateral decubitus position, and this was proven angiographically to be caused by kinking of the communicating artery and vein (57). Although digital clubbing and cyanosis were seen in 62 to 82% of patients reported in older literature reviews (2, 44, 46), they were seen in only 39 and 34% of patients, respectively, in consecutive series (Table 1). Despite being reported in textbooks as classic for PAVM, the triad of dyspnea, cyanosis, and clubbing was unequivocally present in only 10% of patients with PAVM in one study (47).

Pulmonary Function Tests

Oxygenation is commonly affected in patients with PAVM. The largest group of patients with data on oxygenation comes from a literature review of 349 cases of PAVM, 101 of which had information on oxygen saturation: 32% of cases had a Sa_{O_2} of $< 76\%$; 23% had a Sa_{O_2} of 76 to 85%; 26% had a Sa_{O_2} of 86 to 90%; 14% had a Sa_{O_2} of 91 to 95%; and 6% had a Sa_{O_2} of 96 to 100% (38). Data from recent case-series of consecutive patients show that 81 to 100% of patients with PAVM have either a $Pa_{O_2} < 80$ mm Hg or a $Sa_{O_2} <$ 97-98% on room air (14, 15, 46). A study of 32 patients treated with embolization—10 of whom were asymptomatic—found all patients to have hypoxemia (defined as a $Pa_{O_2} < [104 - (0.24 \cdot \text{age})]$) (51). The true incidence of hypoxemia is difficult to estimate because all these studies suffer from selection bias of patients who had oxygenation assessed in the first place. Two cases of unsuspected PAVM were reported in which the patients demonstrated increased alveolar–arterial gradients for oxygen while receiving positive pressure ventilation, which improved upon resumption of spontaneous ventilation (58, 59).

Orthodeoxia is the laboratory correlate of platypnea and represents a decrease in Pa_{O_2} or Sa_{O_2} when going from the recumbent to the seated or upright position; it is probably present in most patients with PAVM (60, 61). Dutton and coworkers (60) studied 53 patients referred for embolotherapy and found that all had hypoxemia when supine with a mean Sa_{O_2} of 89%, which decreased an average of 6% on standing. Terry and coworkers (61) studied 10 patients with PAVM before and after embolotherapy. All but one patient had orthodeoxia with a mean supine Pa_{O_2} of 53 mm Hg, which decreased to 43 mm Hg when seated. Other pre-embolotherapy studies have found orthodeoxia in the majority of patients (40, 49). Whyte and coworkers (59) reported that 21 of 26 patients with PAVM had a decrease of $\geq 1\%$ in Sa_{O_2} between supine and erect positions, but patient selection was not mentioned. Although orthodeoxia appears quite common in patients with PAVM based on these data—and is likely even more common than supine hypoxemia—it is important to remember that all

but one of these studies evaluated patients referred for embolotherapy (40, 49, 60, 61). Thus these patients may reflect a more symptomatic and selected group.

There are no reports of pulmonary function testing in a series of unselected consecutive cases of PAVM. However, Terry and coworkers (61) reported 10 patients with PAVM who underwent extensive pulmonary function testing before embolotherapy. All ten patients had exercise intolerance. Their spirometric indices were within normal limits, but the pulmonary diffusing capacity for carbon monoxide ($D_{L_{CO}}$) was mildly reduced in six of 10 patients. Resting minute ventilation was increased in all patients with a mean value of 12 L/min, and seven of 10 patients had a resting dead space-to-tidal volume ratio within the upper limits of normal. Several other studies have similarly found normal spirometry and mildly reduced $D_{L_{CO}}$ in patients with PAVM (60, 62).

Chest Radiography

The chest radiograph shows some abnormality in about 98% of patients from consecutive series of patients with PAVM (14, 15, 48). The classic roentgenographic appearance of a PAVM is that of a round or oval mass of uniform density, frequently lobulated but sharply defined, more commonly in the lower lobes, and ranging from 1 to 5 cm in diameter (Figure 2) (2, 14, 34, 38, 46, 63). Roentgenographic shadows of PAVM are single in about two-thirds of cases (38, 63, 64). Patients with multiple PAVM usually have 2 to 8 lesions (17, 38, 51), though occasional patients have dozens (38) or even hundreds of lesions (36). Figure 3 shows the chest radiograph from a patient with at least 22 PAVM who later had embolization of 20 lesions. PAVM on plain chest radiographs may be obscured by hemorrhage into contiguous parenchyma, or by atelectasis resulting from bronchial compression (46). Patients with microvascular telangiectases may have normal chest radiographs, or only a vague increase in pulmonary vascular markings at the bases (65–67), and roentgenographic shadows of PAVM may come and go (17).

Individual PAVM will often show feeding vessels on chest radiography, with the artery radiating from the hilus, and the vein deviating toward the left atrium (14, 15). Feeding vessels are typically 4 to 7 mm in diameter but may rarely exceed 20 mm; occasionally they are undetectable on plain chest radiographs (17). Plain tomography of the chest may be more accurate than plain chest radiography at demonstrating the connection between such linear shadows and the putative PAVM (14). In a review of 27 patients with proven PAVM, the plain chest radiograph was strongly suggestive of PAVM in six patients, somewhat suggestive in five, and not suggestive in 16 (48). Plain chest tomography was performed in 26 of the 27 patients, and was strongly suggestive of PAVM in 21 and somewhat suggestive in three (48). Angiography confirmed PAVM in 20 of 21 patients with strongly suggestive plain tomography. Evaluation of a lesion under fluoroscopy during Valsalva and Mueller maneuvers may show pulsations and changes in size which are highly suggestive of a PAVM (68). Therefore, while a completely normal chest radiograph makes the diagnosis of PAVM unlikely, a lack of typical features on a chest radiograph should not preclude further evaluation in a patient with other features suggestive of PAVM.

Pulmonary Hemodynamics

The pulmonary artery pressure is normal or low in nearly all patients with PAVM. This makes sense intuitively because a PAVM would be expected to act as a low resistance circuit. In fact, Whyte and coworkers (69) found pulmonary vascular resistance to be moderately low in seven patients with PAVM who were referred for embolotherapy, with a mean value of 32 $dyn \cdot s \cdot cm^{-5}$ (normal, 60 to 150 $dyn \cdot s \cdot cm^{-5}$). There are no systematic studies of pulmonary hemodynamics in consecutive cases of PAVM, but there are several reports that present hemodynamic data on a total of 88 selected patients with PAVM (14, 15, 46, 48, 62, 69–76). Despite the presence of severe oxy-

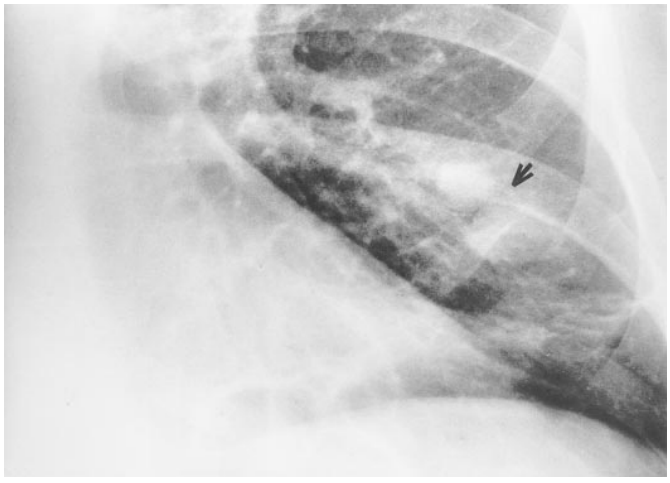

Figure 2. Magnified view of the left lower lung field from a plain chest radiograph showing a single, bilobed PAVM with smooth borders (*arrow*). There is an area of infiltrate from a recent episode of adult respiratory distress syndrome that lies inferior and lateral to the PAVM.

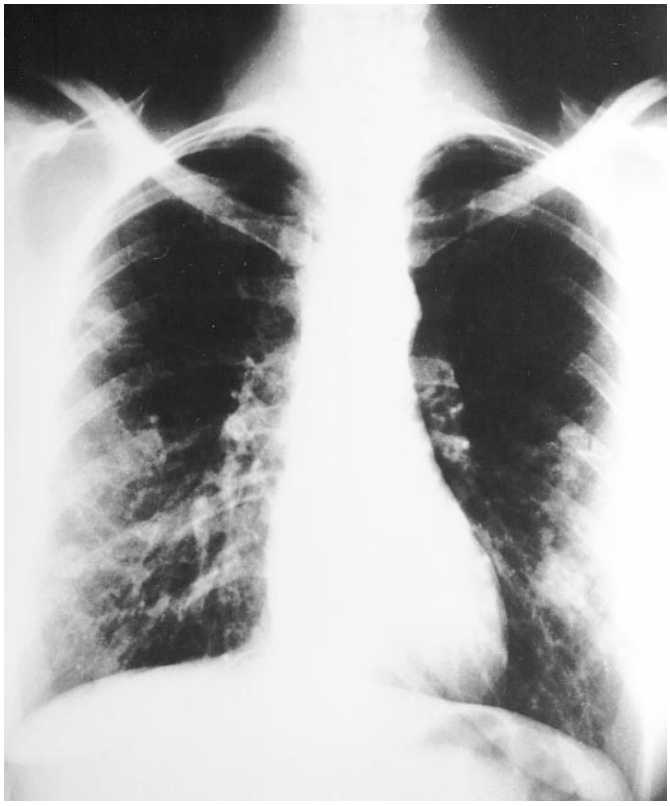

Figure 3. Plain chest radiograph showing multiple PAVM in the lower and middle zones of both lungs from a 22-yr-old woman with severe dyspnea and hypoxemia.

gen desaturation in many patients, the mean pulmonary artery pressure was normal or low in 80 of 88 (91%) patients and elevated ($\geq$ 25 mm Hg at rest) in only eight patients. However, several of these reports were isolated case reports of PAVM associated with pulmonary hypertension (72–74). If one excludes such case reports, only four of 84 (4.8%) patients had pulmonary hypertension (14, 15, 46, 48, 62, 69–71, 75, 76). The eight patients with pulmonary hypertension had mean pulmonary artery pressures ranging from 36 to 50 mm Hg and pulmonary vascular resistance indices of 730 to 1,160 dyn · s · cm^{-5} · m^2 while breathing room air (62, 70, 72–74). The pulmonary hypertension was likely related to underlying chronic lung disease in one patient (72) and bilharzia in another patient (74). There was not enough information in the other reports to fully determine the cause of the pulmonary hypertension, although it may have been partly related to chronic hypoxemia which was seen in four of the six patients.

In two of the above patients with pulmonary hypertension (73), and in a patient with rheumatic mitral stenosis (77), there was evidence that the underlying pulmonary hypertension may have contributed to enlargement of the PAVM. Presumably, the elevated pulmonary vascular resistance in these cases resulted in preferential flow of blood through the PAVM, leading to rapid enlargement. Furthermore, several patients have developed new pulmonary hypertension or experienced an increase in baseline pulmonary hypertension following embolization or resection of a large PAVM, as detailed in later sections (62, 70, 72, 74, 78).

Cardiac index (CI) has been variable when measured, but in general is normal to moderately elevated in most patients with PAVM (14, 46, 61). Moyer and coworkers (46) found a moderate elevation in CI, with a mean value of 6.3 L/min/m^2 in nine patients (range, 3.35 to 9.2 L/min/m^2). Terry and coworkers (61) found a mean value of 5 L/min/m^2 (range, 2.1 to 7.9 L/min/m^2). However, Dines and coworkers (14) found that CI was normal in 11 of 12 patients with PAVM (range, 2.4 to 5.9 L/min/m^2). The reasons for these differences are unclear, but may relate to measurement techniques or patient selection.

Exercise Physiology

Although patients with PAVM have reduced exercise tolerance, it is often remarkably well maintained relative to the size of the shunt fraction (52, 69). Patients with similar degrees of hypoxemia from other causes (e.g., cyanotic congenital heart disease or severe interstitial lung disease) have considerably less tolerance to exercise owing to a baseline increase in pulmonary vascular resistance, which prevents the appropriate increase in cardiac output and maintenance of tissue oxygen delivery. Chilvers and coworkers (52) reported exercise physiology in 15 patients with PAVM who were referred for balloon embolotherapy. Symptom-limited incremental exercise resulted in a decrease in Sa_{O_2} from 86% at rest to 73% with peak exercise. Despite this impressive degree of desaturation, exercise capacity was generally well preserved with 11 of 15 patients achieving $>$ 70% of predicted maximal workload. In a study of eight patients with PAVM, incremental exercise resulted in an increase in dead space but no change in alveolar–arterial oxygen tension difference (AaP_{O_2}) (62). For the group as a whole, maximum oxygen consumption was 61% of predicted (62).

More recently, Whyte and coworkers (69) reported on detailed noninvasive exercise physiology in seven patients with PAVM whose mean maximal power output was 80% of predicted. Steady-state exercise at a workload equal to 33% of their predetermined maximal power output resulted in a decrease in Sa_{O_2} from 80% at rest to 74% during exercise, and an increase in shunt fraction from 31 to 34%. Despite such high shunt fractions, patients were able to maintain normal pulmonary blood flow and tissue oxygen delivery during exercise. The authors postulated that exercise tolerance was relatively well-maintained due to a lower than normal pulmonary vascular resistance (mean, 32 dyn · s · cm^{-5}), which allowed them to appropriately augment pulmonary blood flow and cardiac output during exercise (69).

Complications

Table 2 lists the various complications that can occur in patients with PAVM. The most frequently reported complications relate to the central nervous system and are seen in about 30% of patients. The incidence of these complications was best documented by White and coworkers (40), who evaluated 76 consecutive patients prior to embolotherapy. They reported strokes in 18% of patients, transient ischemic attacks in 37%, brain abscesses in 9%, migraine headaches in 43%, and seizures in 8%. The last 59 consecutive patients had CT scanning of the brain which showed unequivocal evidence of stroke in 36% and cerebral AVM in 5% (40). The incidence of stroke in other studies has varied from 2.6 to 25%, with an average of 8.5% (14, 15, 17, 47, 48); however, investigation for stroke was not done systematically. Paradoxic embolism across a PAVM is the most likely mechanism for major noninfectious cerebrovascular accidents, which are rarely caused by *in situ* thrombosis related to polycythemia, or by coexisting cerebral AVM (18, 79). Embolism of infected material is also presumed to account for solitary as well as recurrent brain abscesses (80). In a review of the neurologic complications of HHT, Roman and coworkers (81) reported 28 cases of brain abscess. All but three of the abscesses were associated with concomitant PAVM, reinforcing the role of paradoxical embolism. There is even a case report of a patient who presented with brain abscesses 20 and 32 yr prior to diagnosis of multiple PAVM (82). Although the majority of serious central nervous system events have occurred in symptomatic or cyanotic patients, there are several reports of previously asymptomatic patients presenting with strokes or brain abscesses (15, 80, 82–88). Furthermore, these complications occur almost exclusively in patients with feeding arteries $>$ 3 mm in diameter (41).

Less common but potentially life-threatening complications include hemothorax and hemoptysis. Hemothorax may result from rupture of a subpleural PAVM, while hemoptysis may be due either to a ruptured PAVM or to a ruptured endobronchial telangiectasia. In a series of 143 patients with

TABLE 2

COMPLICATIONS OF PAVM

Seizure
Migraine headache
Transient ischemic attack
Cerebrovascular accident
Brain abscess
Hypoxemia/orthodeoxia
Hemothorax
Life-threatening hemoptysis
Catamenial hemoptysis
Pulmonary hypertension
Congestive heart failure
Polycythemia
Anemia
Infectious endocarditis

PAVM and HHT who were referred for embolotherapy, 11 (8%) had a history of massive hemoptysis or hemothorax that required hospitalization; five had hemoptysis, five had hemothorax, and one had both (89). Pulmonary hemorrhage was the initial symptom in nine of 11 patients and one of them died with recurrent hemoptysis 7 d after the initial hemorrhage (89). Seven of the 11 patients were women, three of whom experienced hemorrhage during pregnancy (89). There are reports of at least 30 patients in the literature with PAVM complicated by hemothorax, 33% of which occurred during pregnancy and always in the last half of pregnancy (89–91). Mechanisms by which pregnancy may exacerbate PAVM include increased blood volume, increased cardiac output, and increased vascular distensibility—all of which promote increased blood flow through PAVM (91). Catamenial hemoptysis is the term used to describe hemoptysis which occurs during the menses. Although usually assumed to be due to pulmonary endometriosis, it was pathologically demonstrated to be caused by a PAVM in at least one case (92).

Polycythemia and anemia are seen in 25% and 17% of patients with PAVM, respectively (14, 15, 46, 48). Complete blood count and blood volume studies typically reveal increased red blood cell mass with normal or near normal plasma volume (46). The incidence of polycythemia was 60% in older literature reviews, likely reflecting reporting bias of more severe cases (44, 46). As discussed previously in the section on PULMONARY HEMODYNAMICS, PAVM are rarely complicated by pulmonary hypertension.

DIAGNOSIS

Shunt Fraction Measurement

The fraction of cardiac output that shunts from right-to-left (shunt fraction, normal $\leq 5\%$) is elevated in 88 to 100% of selected patients with PAVM (15, 19, 48, 49, 51, 52, 61, 62, 93). Dines and coworkers (15) reported that 21 patients with PAVM who had shunt determination from arterial blood gas measurement had shunts between 9.5 and 42% with a mean value of 20%. Sluiter-Eringa and coworkers (48) reported that 13 of 14 patients had a shunt fraction of $> 5\%$ by arterial blood gas determination. However, neither of these studies reported whether shunt fraction was calculated while breathing 100% oxygen. A shunt fraction of $> 5\%$ using the 100% oxygen method showed a sensitivity of 87.5% and specificity of 71.4% in 12 patients with PAVM and HHT who were discovered by formal screening of 98 relatives of HHT patients (19). Haitjema and coworkers (51) reported a series of 32 patients who underwent embolotherapy and found that 30 of 31 patients had a shunt fraction of $> 5\%$ (mean 16.6%, range 3.5 to 35%) by the 100% oxygen method [assuming an arteriovenous oxygen content difference, $C(a\text{-}v)O_2$, of 5 ml%]. Other smaller studies of patients prior to embolotherapy have found shunt fraction by the 100% oxygen method to be uniformly increased at between 14 to 55% (49, 52, 61, 62, 93). Combined, these studies found that 119 of 122 (97.5%) patients with PAVM had a shunt fraction $> 5\%$ (15, 19, 48, 49, 51, 52, 61, 62, 93). Although the true sensitivity of a shunt fraction $> 5\%$ in detecting all PAVM is likely lower than 97.5%, this is a reasonable estimate of its sensitivity in detecting clinically important PAVM.

Shunt fraction is most accurately assessed by the 100% oxygen method, which involves measurement of Pa_{O_2} and Sa_{O_2} after breathing 100% oxygen for 15 to 20 min (52). The details of shunt fraction measurement by the 100% oxygen method and some of its pitfalls are discussed in the APPENDIX. A shunt fraction of $> 5\%$ by this method is considered abnormal and warrants additional workup as noted in the section on DIAGNOSTIC APPROACH TO SUSPECTED PAVM.

In instances where the 100% oxygen method cannot be reliably performed, an alternative approach is to measure Sa_{O_2} and Pa_{O_2} while breathing room air. A $Pa_{O_2} > 90$ mm Hg and a $Sa_{O_2} > 96.5\%$ effectively rule out significant shunt, while a $Pa_{O_2} < 85$ mm Hg or a $Sa_{O_2} < 96\%$ indicate a potential shunt fraction of $> 5\%$. This method is less specific than the 100% oxygen method because it does not differentiate shunt from hypoxemia due to ventilation–perfusion mismatch. Estimation of oxygen saturation by pulse oximetry has been shown to be insensitive as a screening tool for PAVM in patients with HHT (94), most likely because of inaccuracy compared with measurement of arterial Sa_{O_2}.

Contrast Echocardiography

Contrast echocardiography is an excellent tool for evaluation of cardiac and intrapulmonary shunts, and is able to identify small right-to-left shunts even when they are not suggested by gas exchange data (95–97). This technique involves injection of 5 to 10 ml of indocyanine green or saline (agitated with a small amount of air) into a peripheral vein while simultaneously imaging the right and left atria with 2-D echocardiography. Both liquids contain microbubbles which are easily visualized during echocardiography as contrast compared with the normally echolucent blood. In patients without right-to-left shunting, the contrast is rapidly visualized in the right atrium as a cloud of echoes and then gradually dissipates as the bubbles become trapped in the pulmonary circulation (98). In the case of intracardiac shunts, the contrast is visualized in the left heart chambers within one cardiac cycle following its appearance in the right atrium (98). In the case of PAVM, there is nearly always a delay of 3 to 8 cardiac cycles (2 to 5 s) before contrast is visualized in the left atrium, due to the time required for the contrast to traverse the pulmonary vasculature (65, 95, 99, 100).

Barzilai and coworkers (95) performed contrast echocardiography in 19 patients with HHT (four with suspected PAVM) and 10 patients with known atrial right-to-left shunts. Fourteen of the patients with HHT had a positive contrast echocardiogram, all with a significant delay in the appearance of microcavitations in the left atrium of > 1 s, compared with < 1 s in the patients with interatrial shunt (95). Eleven of the 14 patients with positive contrast echocardiography underwent pulmonary angiography and all had visible PAVM; only six of the 11 had abnormal chest radiographs and eight had an abnormally high $aaPO_2$. Although not clearly delineated in this study, contrast echocardiography probably has a sensitivity close to 100% for detecting clinically important PAVM because it continued to demonstrate some amount of shunt in all patients following embolotherapy of angiographically visible PAVM (95). Furthermore, contrast echocardiography has been shown to be more sensitive than radionuclide perfusion lung scanning (101), and transesophageal echocardiography has been shown to be more sensitive than transthoracic echocardiography (102) in the detection of intrapulmonary shunts in patients with hepatopulmonary syndrome—although neither comparison has been made in patients with congenital PAVM. Imaging of the pulmonary veins with pulsed doppler transesophageal echocardiography during contrast injection may allow localization of a PAVM to a specific lobe of one lung (99). The finding of intrapulmonary shunt by contrast echocardiography warrants additional evaluation for PAVM, usually with standard pulmonary angiography (Figure 4). However, contrast echocardiography is somewhat limited as a first-line

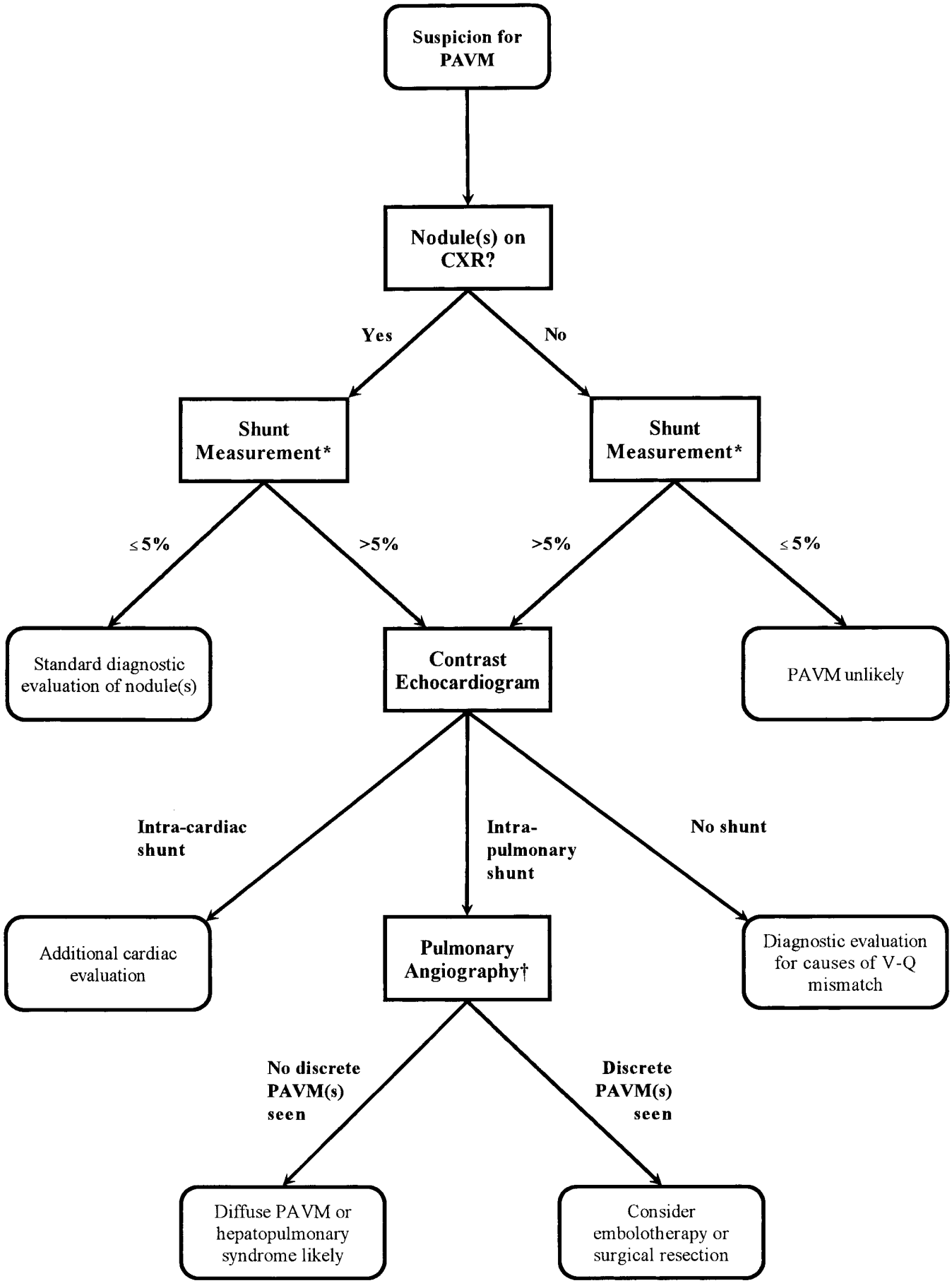

Figure 4. Algorithm for the evaluation of patients with suspected PAVM. *Abbreviations*: CXR = chest radiograph; V-Q = ventilation-perfusion. *Shunt fraction measurement is made by the 100% oxygen method (*see* APPENDIX *for details*); if the suspicion for PAVM is especially high, contrast echocardiography or radionuclide scanning could be used as first-line tests rather than shunt fraction measurement. †Three-dimensional CT imaging of the chest is a reasonable alternative to pulmonary angiography.

screening test for PAVM owing to cost, availability, and overdetection of clinically unimportant PAVM.

Radionuclide Perfusion Lung Scanning

Radionuclide perfusion lung scanning is also useful in the diagnosis of PAVM. It may be used as an adjunct to the above tests, or may be used alone when neither contrast echocardiography nor shunt measurement by the 100% oxygen method is feasible. In subjects without intrapulmonary shunt, peripheral intravenous injection of ^{99m}Tc pertechnetate–labeled macroaggregated albumin (particle diameter of 10 to 60 μm) or albumin microspheres (particle diameter of 7 to 25 μm) results in filtering of these particles by the capillaries of the lung. However, anatomic shunts with dilated pulmonary vascular channels will allow passage of these particles through the lungs, and subsequent filtering by capillary beds in other organs such as brain and kidneys. By performing differential radionuclide scanning over the lungs and right kidney, Whyte and coworkers (59) found that six normal subjects had a mean shunt fraction of 2.7%, whereas 19 patients with PAVM had a mean shunt fraction of 23% at rest. There was excellent agreement between the microsphere method and the 100% oxygen method, which showed a mean shunt fraction of 23% at rest in patients with PAVM (59).

The radionuclide method of shunt calculation has several advantages over the 100% oxygen method: arterial blood sampling is not needed; the 100% oxygen method may overestimate intrapulmonary shunt; and the radionuclide method is more suitable for shunt measurement during exercise (59, 103). However, the radionuclide method is expensive and is not routinely available at most hospitals.

Radionuclide scanning can occasionally result in direct imaging of a PAVM, rather than providing only indirect evidence. A PAVM was visualized by rapid injection of ^{99m}Tc pertechnetate intravenously with rapid accumulation of the radionuclide in the PAVM during the arterial phase, and rapid washout in the venous phase (104). In another patient, radionuclide angiography using labeled red blood cells demonstrated increased activity with rapid resolution in the basal lung segments bilaterally; multiple bilateral PAVM predominantly located in the lower lobes were later confirmed by pulmonary angiography (105).

Computed Tomography

The presence of a PAVM and its vascular anatomy can also be evaluated by contrast-enhanced ultrafast CT (85, 106, 107). Remy and coworkers (107) compared the usefulness of contrast-enhanced CT and selective pulmonary angiography in the follow-up of patients who received treatment for PAVM, as an isolated diagnostic procedure in elderly patients, and for screening family members of patients with HHT. They developed criteria for the diagnosis of PAVM by CT scanning which included size, angioarchitecture, location by lobe, segmental anatomy, and timing of enhancement of the lesion (107). Using these criteria, CT detected 107 of 109 (98%) PAVM in 20 patients, while conventional angiography detected only 65 (60%) PAVM (107). The superior sensitivity of CT was attributed to the absence of superimposition of lesions in transaxial CT views. However, angiography was better able to determine angioarchitecture of individual PAVM than was CT (107).

Three-dimensional (3-D) helical CT is a technique in which CT data are collected continuously by a helical CT scanner; the CT window setting can be adjusted to preferentially visualize the vascular structures, which can be viewed from any angle as a 3-D shaded-surface display. In a study of 33 consecutive patients with 37 PAVM, noncontrasted 3-D helical CT scanning allowed full analysis of 76% of PAVM, compared with only 32% with unilateral pulmonary angiography (42). Unilateral angiography was often limited because of superimposed vessels. Concomitant analysis of 3-D helical images with cross-sectional images improved accuracy to 95%. Hyperselective pulmonary angiography allowed analysis of 100% of PAVM but required additional contrast material and radiation (42).

The obvious advantages of 3-D helical CT scanning over angiography are the noninvasiveness and avoidance of contrast injection with CT. The main disadvantages of CT are that prolonged breath holding is required (24 s in this study) and that large PAVM may be difficult to visualize with optimal spatial resolution (42). Additionally, several false-positive diagnoses of PAVM by CT have been reported with vascular tumors (108–110).

Magnetic Resonance Imaging

Magnetic resonance (MR) imaging of PAVM has been studied less than CT. Conventional spin-echo MR imaging of most pulmonary nodules shows lesions with increased signal intensity on T-2 weighted images (111). Rapidly flowing blood results in absent or minimal MR signal—a so-called "flow void"—although regions of slow blood flow (especially in large lesions with peripheral stagnation) may result in intermediate signal intensity (108, 112, 113). Therefore, a PAVM may be rendered indistinguishable from adjacent air-filled lung on spin-echo MR imaging, which is a significant limitation when screening for small lesions (108, 113). Other lesions that may produce low signal intensity include calcified lesions, air cysts, and scar tissue (111). For these reasons, spin-echo MR imaging results in reduced sensitivity and specificity for detection of PAVM.

Several techniques have been used to improve MR sensitivity to flow in order to differentiate the various causes of low signal intensity. Brown and coworkers (111) used a rotating gated MR technique with reconstructed phase images to differentiate a PAVM from a pulmonary hematoma in two patients with lung nodules. Dinsmore and coworkers (108) used gradient-refocused echo (GRE) MR imaging techniques to evaluate six lesions in four patients with suspected PAVM. The five lesions that ultimately proved to be PAVM showed high signal intensity on GRE sequences, consistent with the presence of high flow (108). These lesions also showed pulsatile changes in size and signal intensity over the cardiac cycle when GRE MR images were reviewed in cine mode (108). In the sixth lesion, a diagnosis of carcinoid tumor was correctly suggested based on combined CT and MR imaging; the CT scan showed a hypervascular structure suggestive of PAVM, while GRE sequences revealed a hypointense signal suggestive of a solid mass (108).

Silverman and coworkers (112) recently reported their experience with three MR imaging criteria in 11 patients who were referred for possible PAVM. Four of the six patients who satisfied all three criteria for PAVM underwent conventional angiography and were found to have PAVM; the two patients not undergoing angiography were presumed to have PAVM. Three patients had conflicting results with the three MR techniques and all were proven to have diagnoses other than PAVM. The remaining two patients had MR images "consistent" with PAVM but did not undergo angiography. The authors concluded that phase contrast cine sequences were the most accurate of the three MR techniques; however, their reported data were inadequate to allow confirmation of their conclusion (112). More recently, MR angiography with

venous or arterial signal elimination and multiplanar reconstruction was able to define the vascular anatomy of a PAVM, which was confirmed at surgery (114).

These data suggest that a combination of MR techniques may be useful in differentiating PAVM from various types of pulmonary nodules, but the number of patients studied with MR imaging thus far is too small to allow firm conclusions. When all three MR techniques show images consistent with a PAVM (112), a diagnosis of PAVM seems very likely. If the MR techniques show conflicting images, however, additional methods of diagnosis should be sought. The main limitations of MR imaging to routine evaluation of PAVM include expense, limited availability, and the highly specialized techniques required for accurate interpretation.

Pulmonary Angiography

Despite advances in the techniques mentioned thus far, contrast pulmonary angiography remains the gold standard in the diagnosis of PAVM, and is usually necessary if resectional or obliterative therapy is being considered (9, 37, 41, 68). Angiography is sensitive for the detection of PAVM that are amenable to embolotherapy, and when supplemented with hyperselective angiograms can accurately define the angioarchitecture of individual lesions (42, 107). Angiography should be performed on all portions of the lungs looking for unsuspected PAVM, and intra- and extrathoracic vascular communications should be searched for at the same time. During the past 10 yr, digital subtraction angiography appears to be replacing conventional angiography in the diagnosis and treatment of PAVM, although there has been no systematic comparison of the two techniques (40, 42, 49, 115). Figure 5A shows the typical appearance of a simple bilobed PAVM on digital subtraction angiography. Whether CT or MR imaging will replace standard pulmonary angiography in the diagnosis of PAVM will require additional comparative studies of the techniques. In the meantime, CT and MR imaging may be best suited for follow-up of patients with proven PAVM, and for diagnosis in patients unable to undergo conventional angiography.

Diagnostic Approach to Suspected PAVM

The diagnosis of PAVM should be suspected in patients with any of the following presentations: (*1*) one or more pulmonary nodules associated with typical roentgenographic findings (*see section* on CHEST RADIOGRAPHY), (*2*) mucocutaneous telangiectases, and (*3*) unexplained findings such as dyspnea, hemoptysis, hypoxemia, polycythemia, clubbing, cyanosis, cerebral embolism, or brain abscess. Furthermore, all family members of patients with HHT should undergo routine screening for HHT and PAVM (*see next section*) (19). Indirect methods of diagnosis include techniques that suggest the presence of an intrapulmonary right-to-left shunt. Definitive diagnosis, however, requires direct imaging of the PAVM with some type of contrast study, such as pulmonary angiography or CT scanning.

Figure 4 shows a simple algorithm for the evaluation of patients with suspected PAVM. There are no studies, to our knowledge, that have prospectively compared any of the main diagnostic modalities in a large group of patients with actual or suspected PAVM. As outlined in the previous sections, the 100% oxygen method, contrast echocardiography, and radionuclide scanning are nearly 100% sensitive for the detection of clinically significant PAVM (i.e., those for which treatment would be recommended). We have suggested measurement of shunt fraction by the 100% oxygen method as the initial screening test in most patients with suspected PAVM because it is inexpensive, can be performed relatively easily in almost any hospital, and is fairly accurate as long as the operator attends to certain details (*see* APPENDIX). Although comparative data are not available, it would be expected that contrast echocardiography and radionuclide scanning are more specific for a diagnosis of PAVM than the 100% oxygen method (since the former methods indicate intrapulmonary shunting through larger communications). However, because contrast echocardiography and radionuclide scanning are much more expensive than the 100% oxygen method and are not as readily available, we believe that they are better utilized as confirmatory tests.

Because 90 to 98% of patients with PAVM will have an abnormal chest radiograph, this is usually the initial test in the evaluation of a patient with suspected PAVM. Additionally, a PAVM is often first suspected when a pulmonary nodule is unexpectedly found on a routine chest radiograph in an asymptomatic patient. Patients with suspected PAVM should

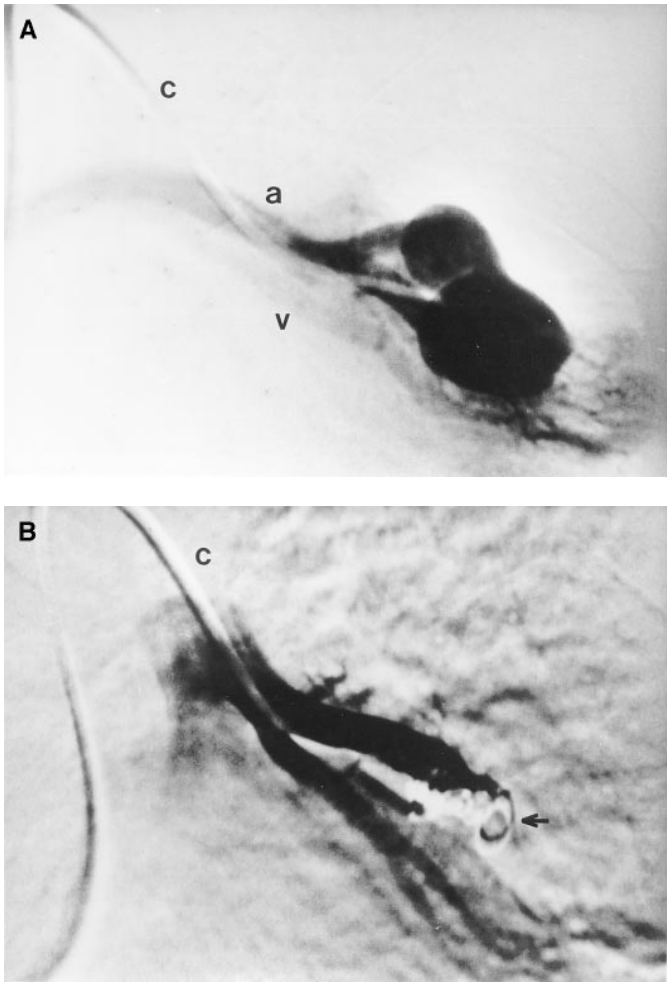

Figure 5. (*A*) Magnified view of the left lower lung field from a digital subtraction angiogram in the patient from Figure 2. The angiography catheter (c) is seen entering the feeding artery at the *upper left corner*. The angiogram shows a single feeding artery (a) which bifurcates to supply the two sacs of the bilobed PAVM. The draining vein (v) is seen as a faint vessel inferior to the feeding artery. (*B*) Magnified view of the left lower lung field from a conventional angiogram in the patient from Figures 2 and 5A following embolotherapy with a coil. The angiography catheter (c) is seen entering the feeding artery at the *upper left corner*. The feeding vessels are visualized but not the PAVM sac. The bright refractile structure at the end of the feeding artery is the coil (*arrow*).

next have measurement of the shunt fraction by the 100% oxygen method. Evaluation of shunt fraction is especially important in the few patients who have suspected PAVM despite a chest radiograph that is normal or shows abnormalities that are atypical for PAVM. In circumstances where the clinical suspicion for PAVM is especially high (e.g., patients with pulmonary nodules associated with significant hypoxemia and patients with a personal or family history of HHT), or when the 100% oxygen method is not available, contrast echocardiography and radionuclide scanning could be used as first-line tests. If the shunt fraction is $\leq$ 5% by the 100% oxygen method, clinically significant PAVM is unlikely and the evaluation can be redirected as outlined in Figure 4. If the shunt fraction is $>$ 5%, additional evaluation for PAVM is warranted. Using Equation 3 in the APPENDIX, a measured Pa_{O_2} of $<$ 575 mm Hg is consistent with a shunt fraction of $>$ 5%.

An occasional patient will have $>$ 5% shunt fraction by the 100% oxygen method and a negative contrast echocardiogram, suggesting either spurious overestimation of shunt fraction (*see* APPENDIX) or a false-negative echocardiogram. If the suspicion for PAVM is high, additional evaluation should be performed. Also, documentation of an intracardiac shunt by echocardiography should not preclude further evaluation for PAVM if the suspicion for PAVM is high (since the presence of intracardiac shunt on contrast echocardiography would prevent concomitant detection of intrapulmonary shunt).

Screening of Families with HHT

Family members of patients with HHT should routinely be screened for possible PAVM, as several reports have noted a high incidence of unsuspected pulmonary and cerebral AVM in family members of patients with HHT (17, 19, 48). The incidence of PAVM is about 15 to 20% in unselected patients with HHT (17, 18). However, in HHT families in which at least one member has PAVM, the incidence of PAVM in other family members with HHT is approximately 35% (20, 89). Thus, it is especially important to screen families with HHT in which at least one member has already been diagnosed with PAVM. Additionally, it is recommended that all women with HHT undergo screening before becoming pregnant because PAVM are associated with a high incidence of hemothorax and hemoptysis during the last half of pregnancy (89–91).

A comprehensive screening approach was recently reported by Haitjema and coworkers (19). Ninety-eight members from 17 families with HHT were screened with a stepped approach (19). All participants underwent a standardized history, general physical examination, examination by an otolaryngologist, chest radiography, and seated arterial blood gas analysis. Additional tests were done in selected participants: shunt fraction measurement by the 100% oxygen method in those with arterial hypoxemia ($Pa_{O_2} <$ 98 mm Hg for ages $<$ 26; $Pa_{O_2} <$ 90 for ages 26 to 55; $Pa_{O_2} <$ 83 for ages $>$ 56); digital subtraction angiography of the lungs in those with shunt fraction greater than 5% or probable PAVM on chest radiography; and cerebral digital subtraction angiography in those with skin or mucosal telangiectases. Thirty-six of the 98 participants were diagnosed to have HHT, including 12 patients with PAVM and four patients with cerebral AVM. Symptoms were noted in 86% of patients with HHT and telangiectases were seen in 100%, with the most common sites for telangiectases being nasal mucosa (83%) and oral mucosa or lips (67%). Of the 12 patients with PAVM, three had previously unrecognized cyanosis, 10 had abnormal chest radiographs, eight had a decreased Pa_{O_2}, and seven of eight with hypoxemia had an increased shunt fraction. Although chest radiography had a sensitivity of only 83%, it was positive in all patients with PAVM large enough for intervention. Since no single test had a sensitivity of $>$ 90%, the stepped approach that they outlined seems appropriate. The approach of Haitjema and coworkers (19) is similar to the approach outlined in Figure 4, except that they bypassed contrast echocardiography in HHT patients. This seems reasonable because this group is typically minimally symptomatic and has a high preevaluation prevalence of PAVM. Furthermore, laboratory evaluation could be potentially confined to those with documented telangiectases because all 36 patients with HHT had telangiectases (19).

Some investigators have recommended screening of all patients with HHT for PAVM by chest CT scanning (13, 47). Although screening with CT is fairly sensitive, it has the disadvantages of radiation exposure and cost. Others have recommended screening with pulse oximetry during childhood, after puberty, before pregnancy, and then at 10-yr intervals (116). Pulse oximetry, however, has been shown to be insensitive as a screening tool (94). While contrast echocardiography appears to be very sensitive in detecting intrapulmonary shunts, it is probably too sensitive for this disorder in that it will pick up microvascular shunts in asymptomatic patients who do not require treatment (19, 95).

Routine genetic screening of HHT family members will likely play an increasingly important role. Using three different methods of genetic screening, Shovlin and coworkers (30) demonstrated endoglin mutations in eight of 32 HHT families, with complementary DNA (cDNA) analysis yielding the best results. Interestingly, endoglin mutations were found in only two of the four families showing linkage to endoglin, suggesting that current genetic screening methods may miss as much as half of endoglin mutations (30). Berg and coworkers (27) used genomic DNA sequencing to screen 12 families for mutations in the activin receptor-like kinase 1 gene. Mutations were found in all six families with linkage to locus 12q13 or in which linkage to endoglin had been excluded, and in three of six families with insufficient linkage data (27). Taken together, these studies suggest that current screening methods are able to detect responsible mutations in 75 to 100% of families with HHT (27, 30). However, these studies are small and regional differences in mutational frequency have not been studied. Routine genetic screening for HHT is currently limited by the absence of a predominant mutation at either major locus and the lack of commercially available screening tests. Once the genetic defect is identified for a given HHT family, however, genetic screening has shown 100% sensitivity and specificity for determining the presence or absence of clinical HHT in individual family members (27, 30).

Therefore, in families with a known genetic defect, we recommend genetic screening (if available) of all family members by analysis of peripheral blood. Family members with the HHT genotype should be further screened for PAVM with chest radiography and/or measurement of shunt fraction (19). In circumstances where genetic screening is not readily available or when genetic screening has been unable to identify a responsible mutation in a given HHT family, we recommend screening for PAVM in all family members using a protocol similar to the one described by Haitjema and coworkers (19), as this is the only protocol that has been adequately reported in the literature to date.

TREATMENT

It is important to understand the natural history of an illness in order to approach its treatment. Unfortunately, the natural history of untreated PAVM is not well delineated as there are no

prospective reports of patients who were randomized to treatment versus observation only. When followed over time, PAVM typically remain unchanged in size, although about 25% enlarge gradually (14, 17). Serial chest radiographs over a median observation time of 18.9 yr in 16 patients with PAVM and HHT showed enlargement in four patients and near total regression in one patient (10 mm decrease over 14 yr) (17). The growth rate tended to be slow—about 5 to 10 mm every 5 to 15 yr; one of the four patients whose PAVM enlarged showed a subsequent decrease of 10 mm over 6 yr (17). Dines and coworkers (14) followed 27 patients who were not treated and found PAVM enlargement in seven patients over a mean of 6 yr. They also found that the incidence of PAVM enlargement was greater in the patients with HHT versus those without HHT (14).

Table 3 lists all reports from the English medical literature that provide information concerning the natural history of untreated PAVM. Mortality was considered to be secondary to PAVM if death was due to brain abscess, stroke, hemoptysis, or hemothorax. Deaths from HHT that were unrelated to PAVM were not counted. PAVM-related mortality ranged from 0 to 55%. The highest mortalities were recorded from the first three studies, which were all literature reviews of reported cases, and likely reflect the tendency to report the most severe cases (39, 44, 45). Furthermore, all three series had tremendous overlap of cases (both treated and untreated) and should not be considered as separate reports. Interestingly, although the reports of both Muri (45) and Stringer (44) reviewed the literature for all PAVM (treated and untreated) from 1897 to 1953, Muri reported 22 cases not reported by Stringer, and Stringer reported 45 cases not included by Muri! More recent studies have reported mortalities ranging from 0 to 15.8% (14, 47, 48, 117), but the duration of follow-up was short or not specified, which might have underestimated the long-term incidence of complications.

The morbidity of untreated PAVM is also significant (Table 3). Dines and coworkers (14) followed 27 patients with untreated PAVM for a mean of 8 yr and noted the development of stroke in 11%. Combining the three contemporary studies of consecutive patients with untreated PAVM, the incidence of stroke was 11.4%, the incidence of brain abscess was 6.8%, and total morbidity and mortality was 23% (14, 47, 48). The high incidence of neurologic complications outlined earlier in the section on CLINICAL MANIFESTATIONS, and reported most carefully by White and coworkers (40), is further evidence of additional morbidity that would likely be seen if the duration of untreated follow-up were extended further.

Although the natural history of untreated PAVM has not been optimally delineated, it is clear from these data that there is considerable morbidity and mortality in some patients. Traditional indications for treatment have been progressive PAVM enlargement, paradoxic embolization, and symptomatic hypoxemia (15). Recently, PAVM < 2 cm in diameter with afferent arteries ≥ 3 mm in diameter have been documented to cause transient ischemic attacks, strokes, and brain abscesses (41, 83, 118, 119). Other reports have documented stroke or brain abscess as the initial presentation in otherwise asymptomatic patients with PAVM (15, 80, 82–87). Based on such findings, White and coworkers (40, 41, 119) have recommended treatment of all PAVM with feeding vessels 3 mm or larger.

Surgery

The first report of a PAVM diagnosed during life was published in 1939 (120). Between 1942 and 1977, surgery was the only method of treatment; ligation, local excision, segmentectomy, lobectomy, or pneumonectomy was performed in most cases. Conservative management and observation were the choice in some asymptomatic cases. Staged bilateral thoracotomies were performed in some cases (121), and transection of the pulmonary artery was suggested as a possible alternative to pulmonary resection in patients with multiple unilateral lesions who were unfit for major surgery (122). Watanabe and coworkers (83) recently reported resection of a small PAVM (< 2 cm) by video-assisted thoracoscopy.

Surgery as a mode of treatment for PAVM carries at least the same risks as any other thoracic surgery, but when properly performed in well-selected patients has been associated with minimal morbidity and mortality, and rare postoperative recurrences (14, 38, 48, 117). Table 4 shows that reported perioperative mortality has varied from 0 to 9.1%. Contemporary studies reporting on consecutive patients show no perioperative mortality in a total of 99 patients undergoing resection of PAVM (14, 15, 47, 48, 117). The higher mortality values, however, represent data from literature reviews published before 1960 (38, 39, 44, 45). Thus, these figures are likely to be overestimates due to reporting of more severe cases and use of noncontemporary surgical techniques and management. There are reports of two patients who died of acute right heart failure within 12 h of PAVM resection (70, 74). One patient definitely had (74), and the other patient probably had pulmonary hypertension at baseline. Presumably, removal of the low-resistance PAVM (along with some normal lung parenchyma) resulted in an acute increase in pulmonary vascular resistance

TABLE 3

CLINICAL COURSE OF PATIENTS WITH UNTREATED PAVM*

Author (Reference)	Year	Patients	PAVM-related Mortality†	Stroke	Brain Abscess	Total Mortality and Morbidity‡	Follow-up
Yater (39)§	1949	11	6 (55)	0	NR	6 (55)	NR
Muri (45)§	1955	48	12 (25)	NR	7 (14.6)	14 (29.2)	NR
Stringer (44)§	1955	49	11 (22.4)	1 (2.0)	5 (10.2)	13 (26.5)	NR
Gomes (117)‖¶	1969	19	3 (15.8)	3 (15.8)	NR	3 (15.8)	1–12 yr, mean 6 yr
Sluiter-Eringa (48)‖	1969	13	1 (7.7)	NR	1 (7.7)	1 (7.7)	1–11 yr, mean about 4.5 yr
Dines (14)‖	1974	27	3 (11.1)	3 (11.1)	NR	6 (22.2)	1–12 yr, mean 6 yr
Puskas (47)‖	1993	4	0	2 (50)	2 (50)	3 (75)	1–22 yr, median 10 yr

Definition of abbreviation: NR = not reported (NR was recorded when a report made no mention of a particular complication for any of its patients).

* The numbers in parentheses reflect the percentage of affected patients from a given series.

† PAVM-related mortality includes death due to stroke, brain abscess, hemothorax, or hemoptysis.

‡ The number of patients who were reported with stroke, brain abscess, or mortality in follow-up.

§ Studies from a review of the literature.

‖ Studies of consecutive patients from a single institution.

¶ All patients included in this study were also reported in the study by Dines (14).

TABLE 4

CLINICAL COURSE OF PATIENTS WITH SURGICALLY RESECTED PAVM*

Author (Reference)	Year	Patients	Operative Mortality	PAVM-related Mortality†	Stroke	Brain Abscess	Total Mortality and Morbidity‡	Follow-up
Yater (39)§	1949	22	2 (9.1)	0	NR	NR	NR	NR
Muri (45)§	1955	67	5 (7.5)	NR	NR	NR	NR	NR
Stringer (44)§	1955	82	7 (8.5)	0	1 (1.2)	0	8 (9.8)	NR
Bosher (38)§	1959	239	13 (5.4)	NR	NR	NR	NR	NR
Gomes (117)‖	1969	27	0	1 (3.7)	1 (3.7)	NR	1 (3.7)	1–12 yr, mean 8 yr
Sluiter-Eringa (48)‖	1969	13	0	0	NR	0	0	1–15 yr, mean about 5 yr
Dines (14)‖¶	1974	33	0	1 (3.0)	1 (3.0)	NR	1 (3.0)	1–12 yr, mean 8 yr
Dines (15)‖	1983	18	0	NR	NR	NR	NR	NR
Puskas (47)‖	1993	8	0	0	0	0	0	1–25 yr, median 12 yr

Definition of abbreviation: NR = not reported (NR was recorded when a report made no mention of a particular complication for any of its patients).
* The numbers in parentheses reflect the percentage of affected patients from a given series.
† PAVM-related mortality includes death due to stroke, brain abscess, hemothorax, or hemoptysis.
‡ The number of patients who were reported with stroke, brain abscess, or mortality in follow-up.
§ Studies from a review of the literature.
‖ Studies of consecutive patients from a single institution.
¶ The patients in this study included all patients reported by Gomes (117), but did not overlap with Dines (15).

and subsequent right heart failure (70). This possibility is supported by data from Moyer and coworkers (46) showing a small increase in pulmonary artery pressure postoperatively even in patients with normal pressures at baseline.

Postoperative follow-up shows recurrence or enlargement of PAVM in 0–12% of patients (14, 38, 47, 48, 117). In addition, there is at least one report of a stroke and one report of PAVM-related mortality during a mean of 8 yr of follow-up after surgery (14). One report has documented marked worsening of pulmonary hypertension following resection of a PAVM (72). This effect may also result in enlargement of previously undetected PAVM during postoperative follow-up (38). In summary, contemporary surgical resection of PAVM is associated with negligible mortality and few postoperative complications related to the PAVM, but still carries the morbidity accompanying a thoracotomy, and requires a 4- to 7-d hospital stay and its associated expenses.

Embolization Therapy

Embolization therapy, or "embolotherapy," is a form of treatment based on occlusion of the feeding arteries to a PAVM. The first successful case of embolotherapy of PAVM was reported by Porstmann (123) in 1977 using hand-made steel coils. Since that time embolotherapy with coils and/or detachable balloons has been reported in numerous series numbering over 250 patients (Table 5) (40, 49, 51, 60, 61, 93, 124, 125). Other embolic materials have included polyvinyl alcohol (Ivalon), wool coils, and stainless steel coils. It is thought that the arterial occlusion of simple PAVM is technically easier and less time-consuming than that of complex PAVM, but involves a greater risk for paradoxical embolization (37, 126, 127).

The technique of coil embolotherapy involves localization of the PAVM by angiography followed by selective catheterization of the feeding artery (60). The catheter tip is advanced past the point of any proximal vessels that supply normal lung parenchyma and positioned as close to the neck of the PAVM as possible. A steel coil is advanced through the catheter and released at this point, angiography is repeated, and additional coils are positioned if needed until blood flow to the PAVM has ceased. Up to 10 coils have been used on a single PAVM (49). Pulmonary arteriovenous malformations with short feeding arteries may be embolized by placement of large coils in the venous sac (41, 118). Depending on patient tolerance and the amount of contrast material used, multiple PAVM may be embolized during a single session. Additional sessions may be performed after a hiatus of 1 to 2 wk if additional PAVM remain open. Figure 5B

TABLE 5

CLINICAL COURSE OF PATIENTS UNDERGOING EMBOLOTHERAPY OF PAVM*

Author (Reference)	Year	Patients	Type	PAVM Attempts†	PAVM Occluded‡	CNS Complications§	Device Migration	PAVM Recanalization	Follow-up
Terry (61)	1983	10	B	NR	58	NR	1	NR	NR to > 4 yr
White (40)	1988	76	B > C	276	276	1	2	NR	NR
Hartnell (93)‖	1990	11	C	NR	44	1	0	0	10–48 mo (mean 26 mo)
Jackson (49)	1990	16	C	NR	79	0	NR	0	NR
Remy-Jardin (124)	1991	19	C	61	58	NR	1	1	1–10 yr
Pollak (125)	1994	35	B,C	96	94	0	2	1	3–19 mo
Dutton (60)	1995	53	C	NR	102	2	2	NR	3 mo to > 4 yr
Haitjema (51)	1995	32	C	92	90	NR	2	2	2–71 mo (mean 25 mo)
Total		252		525	801	4 (1.6%)	10 (1.2)	4 (0.5)	

Definition of abbreviations: CNS = central nervous system; B = balloon embolization; NR = not reported; C = coil embolization.
* The number in parentheses reflects the percentage seen in all patients (CNS complications) or in all PAVM occluded (device migration and PAVM recanalization).
† The number of PAVM for which embolization was attempted.
‡ The number of PAVM that were successfully occluded.
§ The number of patients who experienced either stroke or brain abscess in follow-up.
‖ There is probably some overlap between this series and the one by Jackson (49).

shows a selective angiogram following successful coil embolotherapy of the PAVM seen originally in Figures 2 and 5A.

The second major embolotherapy technique makes use of detachable balloons (40). Following localization of the PAVM by angiography, a balloon catheter is exchanged over a guidewire and positioned at the neck of the PAVM. The balloon is inflated with radiopaque contrast material, angiography is repeated to ensure vessel occlusion, and the balloon is detached. An advantage of the balloon technique is that the balloon can be deflated and repositioned if necessary. For PAVM with feeding vessels greater than 7 to 10 mm in diameter, a combination of coils and balloons is commonly used to achieve total occlusion (40, 41, 119, 125). Autodeflation of balloons, with or without recanalization, and recurrence of symptoms in the recanalized cases have been reported (125). Balloon deflation may be minimized by use of iohexol 140, which is isotonic to blood, to fill the balloons (125). Additional technical details of coil and balloon embolotherapy have been exhaustively reviewed by White and coworkers (41).

The general results of embolotherapy are shown in Table 5. This table includes all series of embolotherapy for PAVM reporting on 10 or more unselected, consecutive patients from the English literature (40, 49, 51, 60, 61, 93, 124, 125). A total of 801 PAVM were successfully occluded in 252 patients. Slightly more than half of the patients were embolized with coils, with or without balloons. Those series that documented both attempted and successful occlusions reported an average success rate of 98.7% (518 of 525 PAVM) (40, 51, 124, 125).

No periprocedural mortality has been reported to date with embolization of PAVM and complications have in general been infrequent and self-limited. Pleuritic chest pain is the most common complication and has been seen in 12.7% of patients (40, 49, 51, 60, 61, 93, 124, 125). The incidence seems to be higher in large PAVM, as it was seen in 31% of patients who had occlusion of PAVM with feeding vessels $\geqslant$ 8 mm (119). It usually occurs in the first 24 to 48 h following embolization and responds well to analgesics (40, 125). Radiographic evidence of pulmonary infarction was seen in 3.2% of patients and most likely was secondary to occlusion of pulmonary arterial branches that were proximal to the targeted PAVM and supplied normal lung (40, 61, 93, 124). Air embolism during embolotherapy was suspected in 4.8% of patients who developed various transient symptoms such as angina, bradycardia, and perioral paresthesias (19, 40, 49, 61, 125). Careful flushing of the catheters and observation of back bleeding make this complication completely avoidable (40, 125). Deep venous thrombosis of the lower extremity used for catheterization was reported in 1.6% of patients (40, 49, 61, 93). Device migration has been reported in 1.2% of embolization attempts (40, 51, 60, 61, 124, 125). Although device migration was reported in 4% of patients undergoing occlusion of large PAVM, these migrations occurred early in the authors' experience (40). None of the reported migrations has resulted in permanent disability, although about half required some intervention, usually with an intravascular retrieval device. There have also been isolated reports of a balloon migration to a noninvolved portion of the lung (which necessitated deflation with a transthoracic needle) (125), a transient episode of aphasia during embolization (47), a seizure during embolization (49), a self-limited hemopericardium due to myocardial puncture (51), and a stroke which fully resolved over 5 d (60). The above frequencies of these complications were calculated based on a total of 252 patients, and may represent minimum frequencies since not all studies noted the rigor with which these complications were monitored.

Terry and coworkers (61) reported arterial blood gases and pulmonary function tests in 10 patients pre– and post–balloon embolotherapy (Table 6). Embolotherapy resulted in improvement of dyspnea, oxygenation, and shunt fraction, but there was no major improvement in resting ventilation. The investigators concluded that ventilatory responses in patients with embolized PAVM are similar to those of people from sea level who are acclimated to high altitudes. Other postembolotherapy studies have shown similar improvements in gas exchange and shunt fraction (52, 62). Although these studies showed marked improvement in shunt fraction after embolotherapy, the postembolotherapy shunt fraction typically remained elevated with mean values ranging from 13 to 24% (52, 61, 62). The residual shunt was believed to represent the shunt through microvascular PAVM and PAVM too small to embolize (i.e., those with feeding arteries $<$ 3 mm) (52). Contrast echocardiography is probably too sensitive for monitoring the response to embolotherapy since Barzilai and coworkers (95) found the test to be positive in 11 of 11 patients after embolotherapy, despite successful occlusion of all angiographically visible vessels. However, patients with markedly positive studies postembolotherapy may have previously unrecognized PAVM (95). Embolotherapy has not had an effect on either D_{LCO} (61) or vital capacity (52).

Long-term follow-up of patients treated with embolotherapy has been variable in the individual series (Table 5). Potentially serious complications have been seen in 2.0% of patients, including two cerebral abscesses and two strokes (40, 60, 93). These were presumably caused by paradoxical embolization either from treated PAVM or new PAVM. Symptomatic recanalization was seen with 0.5% of devices and was typically heralded by the recurrence of dyspnea (51, 124, 125). White and coworkers (41) have recently reported on the delayed occurrence of pleurisy 4 to 6 wk after embolotherapy. It may be severe, associated with high fever, and seems to be most common following coil embolotherapy. Several patients have been reported to develop new (78) or increased (62) pulmonary hypertension after embolization—presumably secondary to a reduction in low resistance vascular circuits. Several investigators have therefore recommended estimation of post-treatment pulmonary hemodynamics, which can be accomplished by transient occlusion of the blood supply to a PAVM by a balloon-tipped catheter (51, 62, 128). This would seem most appropriate in patients with clinical evidence of baseline pulmonary hypertension or elevated cardiac output, and in patients with large or multiple PAVM. An elevated cardiac output may occasionally result from concomitant systemic AVM in patients with HHT, and should be suspected in patients with shunt fractions that seem inappropriately low (due to underestimation by the 100% oxygen method) relative to the radiographic appearance of the PAVM (78).

In one study, follow-up with CT scan one or more years after embolotherapy showed that 96% of PAVM were either

TABLE 6

PHYSIOLOGIC EFFECTS OF EMBOLOTHERAPY*

	Pre-embolotherapy	Postembolotherapy
Pa_{O_2} seated, mm Hg	43	64
Pa_{O_2} supine, mm Hg	53	66
Sa_{O_2}, %	79	92
Shunt fraction, %†	44	24
Minute ventilation, L/min	12.0	9.3

* Results of various physiologic parameters in 10 patients with PAVM before and after embolotherapy (61).

† Measured by the 100% oxygen method (*see* APPENDIX).

undetectable or reduced in size (107). This phenomenon was believed to be the result of thrombosis and retraction of the aneurysmal sac following successful vascular obstruction (107). Three-dimensional helical CT scanning 3 yr after embolotherapy suggested perfusion of a PAVM by a systemic feeding artery in one patient, and development of a new feeding pulmonary artery in another patient 1 yr postembolotherapy. Both findings were documented by angiography, showing the potential utility of 3-D helical CT for follow-up (42). In another study, 40 of 44 (91%) large PAVM disappeared on plain chest radiography at a mean follow-up of over 4 yr (119). White and coworkers (41, 119) have recommended routine follow-up of patients with arterial blood gases at 1 mo and 1 yr after embolotherapy, and spiral CT every 3 to 5 yr to assess growth of small PAVM. Significant hypoxemia or no change in the size of the PAVM would warrant further evaluation for continued perfusion of the PAVM or development of new PAVM.

Lee and coworkers (119) recently reported on the follow-up of 45 patients who underwent embolotherapy of 52 large PAVM with a feeding artery $\geqslant$ 8 mm, and who were culled from a larger group of 221 consecutive patients referred for embolotherapy. This report was not included in Table 5 as this was a selected group of patients. Ninety-eight percent of PAVM were occluded on the initial attempt. One hundred percent follow-up at a mean duration of 4.7 yr showed that 84% of patients remained successfully treated, while 16% of patients showed persistence of PAVM. Eight persistent PAVM were seen in seven patients; five were due to recanalization of initially successful occlusions, while three were due to interval growth of new feeding vessels. All eight PAVM were successfully occluded during a second procedure, although one PAVM required a third procedure for permanent occlusion. Only two patients (4.4%) suffered a stroke during long-term follow-up, and in both, the strokes were associated with recurrence of the PAVM. These are important data in that they show that embolotherapy of even large PAVM is technically successful and relatively safe even during long-term follow-up.

Although the natural history of untreated PAVM has not been fully delineated, the data from Table 3 indicate considerable morbidity and mortality during follow-up. Contemporary treatment of PAVM with either surgery (Table 4) or embolotherapy (Table 5) is associated with minimal morbidity and virtually no mortality. Therefore, it is recommended that all symptomatic PAVM and PAVM $>$ 2 cm in diameter be treated with either surgery or embolotherapy. Embolotherapy seems preferable in most cases because it avoids major surgery, general anesthesia, and loss of pulmonary parenchyma. Embolotherapy is also the clear choice in patients with multiple or bilateral PAVM, and in patients who are poor operative risks. Surgery is the best choice for patients with untreatable allergy to contrast material. Although surgery has been previously recommended in patients with large PAVM, the report by Lee and coworkers (119) suggests that even large PAVM are amenable to embolotherapy. The appropriate management of asymptomatic patients with PAVM $<$ 2 cm in diameter is less clear, though White and coworkers (40, 41) have recommended that all PAVM with feeding arteries $\geqslant$ 3 mm in diameter should be occluded in order to minimize the risk of paradoxical embolization during long-term follow-up. This seems prudent because several cases of serious neurologic sequelae have occurred in patients with small or asymptomatic PAVM (15, 41, 80, 82–88).

Other Treatment Modalities

One area worth mentioning at least briefly is that of hormonal and pharmacologic interventions in the prevention of bleeding from AVM. Menefee and coworkers (129) have reported electron microscopic data from nasal mucosal biopsies in patients with HHT suggesting that treatment with estrogen resulted in improvement in vessel integrity. Marshall and coworkers (130) recently reviewed the role of hormonal therapy in patients with recurrent bleeding secondary to gastrointestinal and nasopharyngeal AVM. Although the majority of studies reviewed were small and nonrandomized, most suggested benefit. One randomized placebo-controlled trial in 14 patients with bleeding gastrointestinal AVM (nine with HHT) showed a significant reduction in transfusion requirements over a 6-mo period of treatment with ethinyl estradiol and norethisterone (131). Marshall and coworkers (130) concluded that though unproven, hormonal therapy may offer benefit in patients with significant bleeding that is unresponsive to other modalities such as ablative therapy. There are also anecdotal reports suggesting successful treatment of epistaxis and gastrointestinal hemorrhage using other pharmacologic agents including danazol, octreotide, desmopressin, and aminocaproic acid (132). The role of pharmacologic therapy in patients with PAVM is much less clear as there are no published reports of even single cases that we are aware of. If used in PAVM, pharmacologic therapy would seem most likely to benefit patients with diffuse microscopic PAVM and recurrent bleeding or severe hypoxemia. However, the potential benefits would need to be weighed against the known complications of such agents, especially estrogen.

Finally, it is recommended that patients with PAVM be given antibiotic prophylaxis before dental and surgical procedures to avoid seeding of PAVM and subsequent development of cerebral abscess. Patients with PAVM and patients with HHT (with or without PAVM) should be fully educated about their diagnosis, its clinical implications and complications, and its hereditary nature. Educational materials for patients with HHT, and the location of specialized centers for managing HHT and PAVM patients are available from the HHT Foundation International (P.O. Box 8087, New Haven, CT 06530; 800-448-6389; 1-604-596-3418 in Canada, 1-313-561-2537 for other countries; http://www.hht.org via the Internet).

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APPENDIX

Shunt Fraction Measurement by the 100% Oxygen Method

In order for this test to be accurate, it is important that the patient truly receives 100% oxygen. For most patients, the optimal apparatus interface is a mouthpiece used in conjunction with a noseclip. For patients who have difficulty using this interface, an airtight mask with an inflatable cushion and head strap can be used (King Systems Corp., Noblesville, IN). Venturi masks and nonrebreather bag systems are not acceptable because of leaks and potential entrainment of room air. A one-way valve between the mouthpiece and the oxygen source prevents rebreathing, while a second one-way valve allows for exhalation, continuous flow-by of oxygen, and prevents entrainment of room air (133). One hundred percent oxygen should be breathed for at least 15 to 20 min to allow full washout of nitrogen from alveoli; taking a deep inspiration every minute may help prevent the microatelectasis that may occasionally result from nitrogen washout (52).

The exact shunt fraction can be calculated from Equation 1 where Cc_{O_2}, Ca_{O_2}, and Cv_{O2} represent oxygen content of capillary, arterial, and mixed venous blood, respectively (52). This is the most accurate way to calculate shunt fraction but is not routinely practical as it requires sampling of mixed venous blood from the pulmonary artery. A more practical estimate of shunt fraction can be rendered from Equation 2 which assumes a $Ca_{O_2} - Cv_{O_2}$ difference of 5 ml O_2/dl blood, and does not require measurement of mixed venous P_{O_2} (52). Actual calculation of the shunt fraction can be further simplified by using Equation 3 (where Sa_{O_2} represents the measured saturation of arterial oxygen between 0 and 100%), which further assumes a hemoglobin value of 14 g/dl blood and a Pa_{CO_2} of 40 mm Hg. If the Sa_{O_2} = 100%, then Equation 3 simplifies to Equation 4 (134). If the measured hemoglobin is < 12 or > 16 g/dl blood, Equation 2 should be used to maintain accuracy. It is critical to account for dissolved oxygen (reflected by the Pa_{O_2}) when doing these calculations, especially when the Sa_{O_2} is near to 100%. For example, a patient with a Sa_{O_2} of 100% and a Pa_{O_2} of 150 mm Hg would have a calculated shunt fraction of 23.5% if dissolved oxygen were included, and zero percent if dissolved oxygen were neglected!

$$\text{Shunt fraction} = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - Cv_{O_2}) \quad (1)$$

$$\text{Shunt fraction} = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - Ca_{O_2} + 5) \quad (2)$$

$$\text{Shunt fraction} = [21 - (Sa_{O_2} \cdot 0.19) - (Pa_{O_2} - 0.003)]/[26 - (Sa_{O_2} \cdot 0.19) - (Pa_{O_2} \cdot 0.003)] \quad (3)$$

$$\text{Shunt fraction} = (Pa_{O_2} - Pa_{O_2})/(Pa_{O_2} - Pa_{O_2} + 1{,}670) \quad (4)$$

There are, however, several potential sources of error in calculating shunt fraction with the 100% oxygen method. A small leak in the oxygen delivery system will overestimate the degree of shunt fraction by lowering the true alveolar P_{O_2}. For example, a patient breathing 100% oxygen with an AaP_{O_2} of 63 mm Hg will have a Pa_{O_2} of 600 mm Hg and a true shunt fraction of 3.6%; a small leak in the system that results in an actual fraction of inspired oxygen ($F_{I_{O_2}}$) of 0.7, however, will result in a Pa_{O_2} of 386 mm Hg and a calculated shunt fraction of 14.3%. Similarly, breathing 100% oxygen for an inadequate

period of time may result in an overestimation of shunt fraction owing to inadequate denitrogenation of poorly ventilated alveoli. Conversely, it has been shown that breathing 100% oxygen can occasionally cause the development of a small amount of shunt (up to 11%) in normal subjects owing to complete denitrogenation and collapse of perfused but poorly ventilated alveoli (135).