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*“Anatomy, Physiology and Management of Patients
with Diffuse
Pulmonary Arteriovenous Malformations”*

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Tamara Lazic

2008

ANATOMY, PHYSIOLOGY AND MANAGEMENT OF PATIENTS WITH DIFFUSE PULMONARY ARTERIOVENOUS MALFORMATIONS

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Diffuse pulmonary vascular malformations (PAVMs) are a small and understudied, but nevertheless important subset of the PAVM population of patients, associated with significant mortality and morbidity.

A review of literature was undertaken to investigate the current understanding of diffuse PAVMs. This review demonstrated that no additional attempts to define diffuse PAVMs and describe their natural history was made before or after the in 2000 report by Faughnan et al [51]. Faughnan, M.E. 2000; [51].

To further expand the findings from 2000, we performed a retrospective review of 36 patients (21 female, 15 male) with diffuse PAVMs from a cohort of 821 consecutive patients with PAVMs. Diffuse PAVMs were classified angiographically as involving one or more segmental pulmonary arteries in one or both lungs. The following data were noted from the chart review: Hereditary Hemorrhagic Telangiectasia (HHT) status, gender, age at presentation, presence or absence of large focal PAVMs, oxygen saturations, morbidity and mortality.

Twenty nine out of 36 (81%) patients had HHT. Diffuse PAVMs were more commonly bilateral 26/36 (72%) than unilateral 10/36 (28%) ($p=0.02$). Initial O₂ saturations of patients with unilateral and bilateral diffuse PAVM were $87\% \pm 7\%$ and $79\% \pm 8\%$ ($p=0.02$), which the current values are $95\% \pm 3\%$ and $85\% \pm 7\%$ ($p < .0001$) respectively. Nine deaths occurred, but only in patients with bilateral involvement. Deaths were due to hemoptysis from bronchial artery hypertrophy (2), brain hemorrhage (1) and abscess (1), spontaneous liver necrosis (3), operative death during attempted lung transplantation (1), and hemorrhage from duodenal ulcer (1).

Yearly follow-up is recommended for this group of patients as they are at high risk for complications.

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INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome is a clinically and genetically diverse multisystemic vascular disorder (1). The manifestations of HHT are a result of abnormal vasculature, characterized by lack of capillary networks resulting in direct arteriovenous connections and fragile dilated vessels of various sizes. Telangiectases are small vascular lesions found on the face, lips, hands, as well as oral, nasal and GI mucosa(1). Arteriovenous malformations (AVMs) are larger vascular lesions found most commonly in the lung (2), brain(3), liver (4), or GI tract(5), and less commonly spinal cord(6).

HHT is a condition with an equal gender distribution, affecting all races and ethnic groups worldwide. The prevalence of HHT appears to be more common than previously thought. The reported incidence rates vary from country to country, and are found to be anywhere from 1 in 2351 in the French region of Ain (7), 1 in 3500 on the Danish island of Funen (8), 1 in 5155 in the Leeward Islands (9), 1 in 5,000-8,000 in the region of Akita in Japan (10), 1 in 16,500 in Vermont (11), and 1 in 39,216 in northern England (12). The general lack of public and physician awareness about HHT makes it a highly under-diagnosed condition.

HHT was first recognized toward the end of the 19th century as a genetic disorder causing nosebleeds, GI bleeding, and abnormal vascular structures. The first known report describing what is now known as hereditary hemorrhagic telangiectasia dates back to 1864 from Sutton's report of epistaxis as a result of degeneration of the vascular system (13). In 1896, Rendu distinguished the disease from hemophilia, and reported the association of epistaxis, cutaneous telangiectasia, and familial occurrence (14). A number

of case reports followed, including those by Osler (15) and Weber (16) further describing the disorder. These resulted in the eponym Osler-Weber-Rendu syndrome. However, the often preferred term “hereditary hemorrhagic telangiectasia” was coined in 1909 by Hanes (17), as an acknowledgement of the three features that defined the disorder at the time.

Currently, the clinical diagnosis of HHT is established according to the Curaçao criteria, as described by Shovlin *et al* (18), where fulfillment of three out of the four criteria is required for a definite clinical diagnosis of HHT:

1. spontaneous recurrent nosebleeds (epistaxis)
2. mucocutaneous telangiectases
3. visceral AVMs
4. positive family history

If only two criteria are present, the diagnosis of HHT is possible or suspected, and if less than two are present, the diagnosis is unlikely.

Genetics

HHT is a genetically heterogeneous autosomal dominant disorder with incomplete penetrance and age-related expressivity. Lethality of the homozygous condition is generally accepted, given the studies demonstrating lethality of homozygous ENG and ALK1 knockout mice, which die in the embryonic stage at mid-gestation, as well as the absence of conclusive reports on living homozygous individuals (19).

Five genotypes have been identified to date in HHT patients (Figure 1). The two main types of HHT, type 1 and type 2, are caused by mutations in the following genes, respectively:

1. *ENG* - localized on chromosome 9, encodes endoglin, a type III TGF- β receptor (20)
2. *ALK-1* - localized on chromosome 12, encodes the activin receptor-like kinase 1, a type I TGF- β receptor (21).

Recently, mutations were identified in several other genes: *SMAD 4* - a gene localized on chromosome 18, in families with both HHT and juvenile polyposis (22), as well as two unidentified genes- on chromosome 5 (HHT 3) (23) and chromosome 7 (HHT 4) (24).

Several studies investigating the prevalence of *ENG* and *ALK-1* mutations in HHT have shown conflicting results (25-28). The most recent study investigating this topic included the largest series of patients reported to date and has shown predominance of *ALK-1* over *ENG* mutations (29).

Currently, genetic testing for HHT is available on a clinical basis for mutations in endoglin and *ALK-1*. Genetic testing for *SMAD 4* is only available as a research test, and will be soon available clinically. A study by Cohen et al (30) has recently shown that genetic screening with targeted clinical protocol is more economically attractive than the conventional clinical screening, resulting in a reduction in the number of clinical tests for family members who do not have HHT. Therefore, once an individual with HHT is identified, screening and genetic counseling should be offered to the family.

Pathogenesis

The corresponding ENG and ALK-1 proteins are specific endothelial receptors of the TGF- β superfamily essential for maintaining vascular integrity (19). Generally, type II TGF- β receptors or accessory proteins (ENG) bind the ligand, subsequently forming a complex with type I receptors (ALK-1), which then activate downstream cytoplasmic signaling molecules including SMADs. SMADs translocate to the nucleus and modulate gene transcription(31). Therefore, it is expected that the abnormal vessels in HHT develop because of aberrant TGF- β signaling at some stage during vascular development and homeostasis.

It has been shown that endothelial cells derived from HHT1 or HHT2 patients express approximately one half of the normal endoglin or ALK-1 levels, respectively(32, 33), and that endothelial cells derived directly from AVMs also express half the normal levels of endoglin(34). Therefore, the current understanding is that HHT results from endoglin or ALK-1 haploinsufficiency (lack of sufficient protein for normal function), rather than from a “second hit” (additional local loss of endoglin expression). A complicated series of processes seems to be involved in the development and remodeling of blood vessels, and in addition to genetic factors, environmental factors might play an important role. Present knowledge about the function of endoglin and ALK1 in endothelial cells and the current haploinsufficiency model have suggested that the future therapeutic perspectives for HHT might include an increased expression of either endoglin or ALK1 (19). However, as the exact pathogenesis of HHT continues to be only speculative, it is still early to consider gene therapy as a treatment or prevention option.

Genotype-Phenotype Correlations

Significant clinical variability is observed in HHT, with both intra- and inter-familial variations in age-of-onset, localization of lesions, and severity of complications.

Genotype-phenotype correlations have been studied, but are still limited.

HHT type 1:

- earlier onset of epistaxis (35)
- higher number of PAVMs (35-37)
- higher number of CNS vascular malformations(35, 38)

HHT type 2:

- increased incidence of hepatic AVMs (35, 39, 40)
- reduced penetrance, lower expressivity, and a later age-of-onset (41)

All manifestations of HHT have been reported in both types, with the exception of rare reports of primary pulmonary hypertension (42, 43) and spinal AVMs (35), which have only been reported in HHT2.

The frequency of mucocutaneous telangiectases in different age groups appears to be similar in patients with either HHT1 or HHT2. By age 40, multiple telangiectases in one or more of the characteristic locations (hands, face, mouth) are found in 100% patients (35).

Furthermore, the predominance of HHT1 or HHT2 is thought to correlate with geographical location. While HHT1 is predominant in North America, Canada and Northern Europe, HHT2 is more abundant in the Mediterranean countries such as Italy, Spain and France (19).

Women and HHT

Women seem to be at an increased risk of developing PAVMs, as well as possibly hepatic involvement and cerebral hemorrhage (44). This may reflect a modification of the HHT vasculature by female hormones, as well as hemodynamic changes during pregnancy. These hormonal effects have been supported by the successful treatment of gastrointestinal bleeding in HHT patients using combined estrogen-progesterone therapy(45), a report of progesterone receptors in vessels of HHT patients (46), and variations in epistaxis during the menstrual cycle and menopause(47).

Clinical Manifestations of HHT

Manifestations of HHT are generally not present at birth, rather they develop with increasing age. An important exception are cerebral AVMs which have been described as early as during the neonatal period, representing a significant cause of mortality and morbidity in children with HHT (48, 49). Epistaxis is usually the earliest manifestation of disease, often occurring in childhood, pulmonary AVMs becoming apparent from puberty, with mucocutaneous and gastrointestinal telangiectases developing progressively with age.

Epistaxis

The most common manifestation of HHT is recurrent epistaxis, a result of the fragility and subsequent spontaneous bleeding from nasal mucosal telangiectases(1). While some patients only have occasional nosebleeds, others experience significant bleeding on a daily basis. Many patients require no treatment other than iron

supplementation, whereas others may require transfusions and emergency nasal packing. A number of topical, systemic, and surgical treatments are available for the treatment of epistaxis in HHT, but the principle of “doing as little as possible for as long as possible” seems to be the best, except in cases of HHT patients experiencing massive hemorrhage or daily nose bleeds (31).

Skin

Mucocutaneous telangiectases occur in about 75% of individuals occurring mostly on the face, lips, tongue and buccal mucosa, as well as fingertips (50). They typically present later in life than epistaxis, from about the second or third decade of life, increasing in size and number with age (50). They may bleed but this is rarely clinically important and the main concern is cosmetic, when short term benefits of laser or other ablation therapies may be obtained(31).

GI tract

Recurrent gastrointestinal tract hemorrhage occurs in about 25-33% of HHT patients, with a late onset, usually from the fifth or sixth decade (5, 50), and may result in severe anemia and blood transfusion requirements. Anemia out of proportion to epistaxis is often a presenting sign of GI hemorrhage (5). Distinguishing between epistaxis and GI bleeding can be challenging, given that many HHT patients are placed on iron supplementation that causes dark stools, making it difficult to detect a GI bleed. Epistaxis can also mimic GI bleeding upon swallowing of nasal blood (5). The extent of telangiectases, which are most commonly found in the stomach, duodenum and jejunum,

was found to correlate with the severity of a patient's anemia and transfusion requirement (5).

Treatment of HHT-related GI bleeding can be challenging. Most patients are managed conservatively with oral iron supplementation and, if necessary, blood transfusions. Other therapies include lasers and cautery, as well as various pharmacologic agents. The only pharmacologic therapy supported by randomized controlled trials is the use of female hormones in heavily transfusion-dependent patients.(45). Others include danazol (a weak androgen) and aminocaproic acid (inhibits fibrinolysis), both only supported by case reports (51-53). Risks and benefits should be carefully weighed in the decision to use drug therapy, taking into account the number of telangiectases and severity of bleeding versus potential side effects of treatment (5). If present, PAVMs should be repaired before initiation of hormonal therapy. Endoscopic treatment of asymptomatic telangiectases is not warranted, and surveillance endoscopy is unlikely to benefit patients if they show an improvement with treatment (5).

Liver

Although the majority of patients with HHT have hepatic vascular malformations, symptoms occur in only a minority, around the age of 30, and with clear female gender predominance (54). The symptoms of liver involvement in HHT are associated with blood shunting (arteriovenous, arterioportal, or portovenous), and fall into one of three categories: high output heart failure, portal hypertension, or biliary disease (4).

A clinical suspicion of hepatic involvement should be raised in an HHT patient with shortness of breath and/or edema without PAVMs or anemia, or those with ascites,

variceal hemorrhage, abdominal pain, encephalopathy or cholangitis. In either case, a physical examination finding of a bruit or thrill in the RUQ or epigastrium supports the diagnosis (54). Hepatomegaly and/or abnormal liver function tests may be present, as well.

A definite diagnosis of liver involvement is made with various imaging studies, including angiography (4), computed tomography (55), MRI (56), or Doppler sonography (57). According to consensus recommendations from the HHT Scientific Meeting in Lyon in April 2005(58), Doppler ultrasound is sufficiently accurate and should be the first-line imaging of the liver in the general HHT population, but only in those in whom liver involvement is suspected. Liver biopsy in any patient with HHT is considered unnecessary and should be avoided (58). According to the same consensus recommendations, liver transplantation should only be considered after failure of intensive medical therapy, and embolization of liver vascular malformations is a high-risk procedure and should only be used as a last resort in patients who are not candidates for liver transplantation.

Brain

Brain malformations in HHT include mainly telangiectases and cerebral AVMs (CAVMs). Most complications arise from CAVMs, which are thought to affect more than 10% of HHT patients(3, 31). They can lead to headache, seizures, ischemia of the surrounding tissue due to a steal effect, or hemorrhage. CAVMs can cause symptoms as early as during the neonatal period. In 2002, the first neonatal case of intracranial hemorrhage (ICH) secondary to a CAVM was reported in a patient who was

subsequently found to have HHT (48). In addition, the same group reported 8 more infants and children, ages 4 weeks to 16 years, who also presented with ICH secondary to CAVMs. Before these hemorrhages, none of the children were suspected of having HHT, despite a family history of the disease, demonstrating that infants and children with a family history of HHT are at risk for sudden and catastrophic ICH. Another study of arteriovenous fistulas (AVFs) in 41 children, demonstrated that even though cerebral AVFs are a rare disease, they are not infrequently seen in neonates and infants with AVMs, and that HHT is suspected to be present in about one fourth of these patients (49). Therefore, screening for CAVMs (Figure 2) with a single baseline MRI may potentially identify and prevent more serious sequelae (59). Neurovascular surgery, embolization and stereotactic radiosurgery may be used to treat CAVMs (1).

It is important to note that neurological symptoms occur not only due to cerebral or spinal AVMs, but also even more commonly with pulmonary AVMs. PAVMs can lead to cerebral abscess (9%) or TIA/stroke (24%) due to right-to-left shunting that facilitates the passage of paradoxical emboli into the cerebral circulation. But, the most common neurological manifestation of PAVMs is migraines (43%) (60). Several hypotheses have been formulated in explaining the increased prevalence of migraines in patients with PAVMs (61). A causal relationship between the presence of a right-to-left shunt and migraines has been suggested, and supported by a study which demonstrated a decreased prevalence of migraines in HHT patients that underwent embolization of PAVMs(62). Trigger substances, such as serotonin or micro emboli, instead of being trapped in the pulmonary capillaries might enter the systemic circulation via the shunt, resulting in cerebral vascular instability and causing migraine (63).

Lung

Together with the brain AVMs, pulmonary AVMs are the greatest cause of mortality and morbidity in HHT patients. It is not surprising then that the lung is the best studied organ involved in HHT to date. PAVMs are a marker for HHT, since about 85-90% of people with PAVMs have HHT (2). PAVMs are present in about 30% of patients with HHT, although the incidence varies depending on the specific genetic mutation present (64). PAVMs are more common in females, which may relate to effects of female hormones on HHT vasculature (44).

PAVMs are dilated, thin-walled vessels that replace normal capillaries between the pulmonary artery and vein (65). The presence of this high-flow low-resistance circuit gives rise to right-to-left shunting of deoxygenated blood, resulting in hypoxemia, and manifesting as clubbing, cyanosis and dyspnea. Orthodeoxia, a further decrease in oxygen saturation on assuming an upright posture, is common in HHT patients with PAVMs, and is attributed to increased flow of blood under the influence of gravity through shunts situated at the lung bases (44).

The loss of filtering capacity provided by pulmonary capillaries produces a conduit through which paradoxical emboli can pass into the systemic circulation, causing catastrophic neurological complications such as stroke and cerebral abscess. Neurological sequelae occur in about 40% of adults with untreated PAVMs, with approximately 30% of patients having a history of stroke, and 10% of brain abscess. Hemorrhagic complications include pulmonary or pleural hemorrhage and hemoptysis, and occur in about 10-15% of HHT patients with PAVMs(60, 66).

The angioarchitecture of PAVMs has been extensively studied in adults (2, 60, 67, 68). PAVMs are classified as focal (95%) or diffuse (5%) (67, 69). Focal PAVMs were further classified as simple (90%) or complex (10%)(2). A PAVM is considered *simple* when it is fed by one or more branches from the same pulmonary segmental artery. If more than one segmental artery is involved, the PAVM is considered *complex*. As originally characterized by Faughnan et al in 2000 (69), *diffuse* PAVMs are defined as involving all segmental arteries of at least one lobe of the lung. These patients are usually deeply cyanotic and have a greater predisposition to neurological complications.

The presence (but not size, location or number) of PAVMs is detected with high sensitivity and specificity using contrast echocardiography (CE), which is accompanied by injection of agitated saline solution. In normal individuals, all the microbubbles formed are filtered out by the pulmonary capillaries, and none should appear in the left side of the heart. In the presence of an intracardiac shunt (e.g. PFO, ASD or VSD), bubbles will appear in left cardiac chambers almost immediately after filling the right heart chambers. If there is a shunt at the pulmonary level (e.g. PAVM), bubbles will be seen in left cardiac chambers 2-3 cardiac cycles after filling the right heart chambers (64). A significant proportion of patients, presumably those with PAVMs that are too small, will have shunting identified on echocardiography, but not on CT or even pulmonary angiography (44). These patients are still advised to use antibiotic prophylaxis and follow-up CT scanning on the assumption that PAVMs are present (Figure 3).

Together with pulse oximetry (considered positive if oxygen saturation < 97%), CE has replaced shunt studies and non-contrast CT as initial screening methods. If either CE or pulse oximetry are positive, thin section non-contrast CT is used to determine the size

and type of PAVMs, which are included in the treatment criteria. In children, measurement of supine and upright oxygen saturation can be used for screening for PAVMs, with CE generally used after the age of 12, or earlier in cases when pulse oximetry is low, growth failure or difficulty with physical activity are present (70). In addition, exercise testing is currently being developed at Yale as an alternate screening method for PAVMs in children, in which a drop in oxygen saturation on exercise is indicative of the presence of significant PAVMs.

Before 1980, surgery was the only method of treatment; ligation, local excision, segmentectomy, lobectomy, or pneumonectomy was performed in most cases (2). Surgical resection may still have a role in patients in whom right-to-left shunting persists after embolization of all feasible vessels (44), or if a patient has severe contrast allergy, precluding angiography. Embolization therapy, first described by Porstmann in 1977 occludes the feeding arteries to a PAVM (71). Treatment using transcatheter embolotherapy (TCE) can prevent many of the debilitating and life-threatening complications of simple and complex type PAVMs, such as exercise intolerance due to hypoxemia, prevention of neurological complications and prevention of lung hemorrhage (2). TCE is a safe and efficient non-surgical procedure, which avoids major surgery, general anesthesia, and loss of pulmonary parenchyma. It is currently recommended for all pulmonary AVMs with a feeding artery ≥ 3 mm (60, 68, 72). The procedure is technically successful in over 98% of cases (71). Outcomes in children are as successful as in adults, with similar complication rates (70). Long-term follow-up is warranted after transcatheter vaso-occlusion of PAVMs due to frequent recanalization of treated PAVMs and development or growth of untreated PAVMs.

More difficult are the treatment considerations for patients with diffuse PAVMs. Lung transplantation has been tried unsuccessfully (unpublished), with no long-term outcome data available to date. Redistribution of pulmonary blood flow, by occluding the segmental arteries of an entire lobe has been used successfully and with improvement in oxygenation. Unfortunately, a late complication, such as hemoptysis due to bronchial artery hypertrophy has made this approach not ideal. One of the goals of this report is to propose a new treatment approach, which we hope will improve oxygenation and decrease the rate of hemoptysis in this subset of patients.

STATEMENT OF PURPOSE AND HYPOTHESIS

A small subset of patients with PAVMs has a more severe and diffuse pattern of disease. These patients have a greater predisposition to neurological complications compared to patients with focal PAVMs, and are more difficult to treat.

Before 2000, little was known about the clinical characteristics, course and management of this subset of patients. In 2000, Faughnan et al defined diffuse PAVMs and described the natural history of 16 patients with this subset of PAVMs (69). Since then, little investigation has been done in this field.

The purpose of our study was multi-faceted:

1. To further describe the natural history of patients with diffuse PAVMs
2. To perform a review of the English-language literature on diffuse PAVMs, focusing on how this subset has been defined to date
3. To develop a new anatomical classification of diffuse PAVMs and describe a new treatment approach.

We hypothesize that the lung of patients with diffuse PAVMs is focally diffuse, such that some areas of an affected lobe are more diffuse than others. For example, the right lower lobe has 5 bronchopulmonary artery segments. If 2 of 5 are diffusely involved, then perhaps occluding these 2 more severely affected segments from peripheral to central might show effective palliation (i.e. raise room air oxygenation of the patient). Developing a new classification of the lung in patients with diffuse PAVMs would aid in assessing whether occlusion of lung sub-segments with the most diffuse involvement improves their oxygenation.

SUBJECTS AND METHODS

Literature Review

Case reports and reviews of patients with diffuse PAVMs were searched using Medline and PubMed databases. Old reports that were not present in online databases were identified by examining article references. Only reports in which diffuse PAVMs were diagnosed by angiography or CT scan were considered to be properly classified as diffuse. We believe that the diagnosis of diffuse PAVMS cannot be made correctly by examining pathological specimens, so those reports were excluded.

Subject Selection, Demographics and Clinical Characteristics

36 patients with diffuse PAVMs were included in this study, from a cohort of 821 consecutive patients seen by Robert I. White, Jr. between May 1978 and December 2006. 15 of the 16 patients with diffuse PAVMs originally reported in the 2000 paper by Faughnan et al were followed in this study. The rest of our cohort consisted of the

additional 21 patients seen at the Yale Vascular Malformation Center or at the University of Bari HHT Center. A retrospective review of medical records and images was performed, after obtaining informed consents and an IRB approval. The following data were collected:

- HHT status - the diagnosis of HHT was made according to the Curaçao criteria, as presented by Shovlin *et al* (18)
- Gender
- Age at presentation
- Presence or absence of large focal PAVMs (≥ 3 mm diameter artery)
- Degree of diffuse involvement - all patients underwent diagnostic pulmonary angiography, including measurements of pulmonary artery pressures; patients were divided into 2 categories based on unilateral or bilateral lung involvement by diffuse PAVMs, as well as the extent of each lung involvement as $>$ or $<$ than 50%
- Oxygen saturations
- Complications
 - of the disease - brain abscess, TIA/stroke
 - of embolotherapy- pleurisy, angina, coil migration

It is still unclear whether hemoptysis is a part of the disease itself, or a complication of embolotherapy; regardless, it was included in this study as an important complication.

- Years of follow-up - calculated from the date of first visit to the date of last visit or death

- Survival

Definition of Diffuse PAVM

Faughnan et al defined diffuse PAVM as involving all segmental branches of one lobe (18). We believe that one lobe can be involved to different degrees, not necessarily involving all the branches. Therefore, we felt that a more precise classification of the diffuse subset of PAVMs was necessary. In our study, involvement was defined as diffuse is at least 1 out of the 18 lung segments was diffusely affected (Figures 4 and 5). Furthermore, if more than 5 out of 10 right lobe segments, or 4 out of 8 left lobe segments were affected, the extent of involvement was considered more than 50%.

Unlike the patients with multiple focal PAVMs (Figure 6), involving one or more segmental arteries, which are successfully treated with transcatheter embolotherapy (TCE), response to treatment in patients with diffuse PAVMs is less satisfactory, with a minimal rise in oxygen saturation after TCE. It is therefore important to distinguish between multifocal (i.e. multiple focal) and diffuse PAVMs, which is often uncertain until a post-occlusion angiogram is obtained.

Transcatheter Embolotherapy

The technique of embolotherapy performed at the Yale Vascular Malformation Center has evolved in the past decade, as the increased frequency of hemoptysis from bronchial arterial hypertrophy has been noted. The enlargement of bronchial arteries and collateral filling of distal pulmonary arteries are likely a consequence of occlusion of bronchial arteries by the central approach. Therefore, the technique was empirically

changed from central to peripheral, blocking only the most severely affected segments from distal to proximal with tightly packed fibered coils. This peripheral approach is expected to exclude the diffusely involved segmental arteries from the pulmonary circulation, thus redistributing the pulmonary blood flow to less involved or unaffected segments of the lung. All patients were heparinized during embolotherapy because of a thrombophlebitis in a previously reported patient (69).

Statistical Analysis

T-tests (continuous data) and chi-square (categorical data) analyses were used for comparing subjects with unilateral versus bilateral disease. Patient data were entered in an ACCESS database and imported in Statistical Analysis Software (SAS, Version 9.1; Cary NC, 2005). Means, standard deviations and percentages were used to describe the subjects.

RESULTS

Literature Review

About 5% of patients with HHT have a more severe and diffuse pattern of lung involvement, however, little is known about the clinical characteristics, course and management of these patients. A single attempt to assess the natural history and appropriate management of these patients has been made to date (69). The rest are case reports (73-95). From 1950 to 2007, over 50 patients have been reported as having diffuse PAVMs (also described as “multiple microscopic fistulae”, “dispersed telangiectasia”, “diffuse pulmonary telangiectasia”), excluding our cohort, and those with

hepatopulmonary syndrome. In addition, at least 10 more diffuse cases from foreign-language publications were identified through English-language reviews or author's translations in PubMed. Out of all these cases, only a minority used appropriate diagnostic tools (many inappropriately diagnosed diffuse PAVMs from pathology specimens; others were in fact multifocal rather than diffuse), and matched our definition of diffuse PAVMs.

Prior to the modern era, two papers defined diffuse PAVMs- Higgins and Currarino (76, 96), both in 1976 as “pulmonary telangiectasia, in which innumerable minute pulmonary arteriovenous fistulae between peripheral branches of the pulmonary arteries and veins are distributed diffusely throughout both lungs”. In 2000, Faughnan et al redefined the diffuse subset as “AVMs involving every subsegmental artery of at least one lobe” (69). Since 2000, very little has been published on patients with diffuse PAVMs.

The majority of patients with diffuse PAVMs have HHT, generally present with severe cyanosis and exercise intolerance, and appear to have a poor prognosis. Since occlusion or resection of all AVMs in these patients is not a realistic treatment approach, most of the reported patients have gone untreated. Prior to Faughnan's study, little was known about the risk of hemorrhagic and neurological complications in these patients. Faughnan demonstrated that neurological rather than pulmonary complications are the rule in this patient population. The incidence of neurological complications is higher in patients with diffuse than in those with discrete PAVMs, such that brain abscesses have a prevalence of 38% (69), as opposed to 9% in those with discrete PAVMs (60). This is not surprising, since diffuse involvement may include hundreds of AVMs. Embolization of

PAVMs in these patients does not improve the hypoxemia (as many untreated PAVMs remain), but may reduce the risk of neurological sequelae. Therefore, these patients have a fairly good prognosis with appropriate management, which should include embolotherapy of larger AVMs, and life-long antibiotic prophylaxis for bacteremic procedures.

In terms of pulmonary complications, these patients don't tend to develop spontaneous hemothorax, but can develop hemoptysis, often secondary to bronchial artery hypertrophy (69). It is not known whether this hypertrophy is part of the disease process or whether it develops subsequent to TCE. In terms of daily functioning, these patients lead fairly normal lives, adapting to chronic hypoxemia by mainly unknown mechanisms. Polycythemia, which likely helps compensate for hypoxemia, is present in the majority of these patients. Pulmonary artery pressures are normal or decreased, likely because of decreased pulmonary vascular resistance secondary to the diffuse AVMs. Some might expect development of pulmonary hypertension in these patients, secondary to chronic hypoxia. However, since hypoxic vasoconstriction occurs secondary to alveolar hypoxia (which is not present in these patients) rather than hypoxemia, these patients generally do not develop pulmonary hypertension.

When confronted with a patient with diffuse pulmonary AVMs, a clinician might incorrectly presume a poor prognosis and suggest referral for lung transplantation (74). However, the 2-year survival rate in the group presented by Faughnan et al that was treated with TCE (91%) was better than that seen after lung transplantation (70%) (97). Therefore, referral for lung transplantation has so far not been justified.

Multi-Center Diffuse PAVM Series

General Characteristics

Since 2000, when we reported 16 patients with diffuse PAVMs, we have now extended our database with additional 21 patients, and followed 15 out of the 16 previously reported ones. These 36 patients (21 female, 15 male) were chosen out of 821 consecutive patients (4.4%) because of their diffuse PAVM involvement, with one or more segmental pulmonary artery affected. Mean age at presentation was 35.4 ± 17.8 years, with a mean follow-up of 8.5 ± 6.1 years, and a range of 0.12 to 26 years. HHT was present in 29/36 (81%), and the morphology of PAVMs was consistent with HHT and different from the type seen in hepatopulmonary syndrome. (98). Nine out of 35 (25%) died during the follow-up period, all of which had bilateral involvement. No deaths occurred in patients with unilateral involvement, and this difference is statistically significant ($p=0.03$).

Unilateral Diffuse PAVM Patients (Tables 1 and 3)

Unilateral involvement was found in 10/36 patients (28%); 2 were female and 8 were male, 7 of them with HHT. Two of the 10 patients were seen prior to 1998 (69), and their mean age of first visit was 21 ± 11 years (range 4 to 37) with mean follow-up time of 5.7 ± 4.8 years (range 0.12 to 16). Three of the 10 patients (30%) had complications at the time of their initial presentation, including brain abscess (2) and hemoptysis (1). Since 1998, 3 patients have had significant complications, but have all recovered. All 10 patients have remained fully functional, working or attending school fulltime.

Bilateral Diffuse PAVM Patients (Tables 2 and 4)

Bilateral involvement was found in 26/36 patients (72%); 19 were female, 7 were male, and 22 of them had HHT. Thirteen of the 26 patients were seen prior to 1998 (69). The mean age at time of first visit was 24.8 ± 17.9 years (range 0.5 to 71) with the mean follow-up time of 9.6 ± 6.3 years (range 0.4 to 26 years). Nineteen of the 26 patients (73%) had complications at the time of their initial visit, including a single brain abscess (7), two brain abscesses (2), single TIA/stroke (9), two strokes (1). Of the 17 patients living, 14 are working or attending school fulltime, and 3 are considered disabled.

Transcatheter Embolotherapy

Two of the 10 (20%) patients with unilateral diffuse PAVM and 17/26 (65%) patients with bilateral diffuse PAVM involvement also had focal PAVM ($p=0.02$) (Tables 3 and 4). In these patients, only involved arteries with a diameter $\geq 3\text{mm}$ were occluded as close to the fistula (peripherally) as possible (72).

In the severely symptomatic patients, peripheral to central occlusion of diffusely involved segments was performed using standard coil techniques (Figure 7) (99). Oxygen saturation values for patients with unilateral and bilateral diffuse PAVMs were initially $87\% \pm 7\%$ and $79\% \pm 8\%$ ($p=0.02$), and most recently $95\% \pm 3\%$ and $85\% \pm 7\%$ ($p < 0.0001$), respectively (Tables 3 and 4).

Six of the 36 patients underwent angiography and measurements of pulmonary pressures, but without TCE. Three of those had no rise of 10mm or more of PaO_2 upon temporary occlusion of lower lobe pulmonary arteries, and were therefore not considered

to be candidates for embolization. The other three patients did not require TCE because they were relatively asymptomatic.

Complications

None of the patients had pulmonary hypertension, although some had elevated pulmonary artery and left atrial pressures secondary to liver disease.

Thirteen of the 30 patients that underwent TCE had early complications post-embolization with full recovery, including self-limited pleurisy in 11/12 and transient angina in 1/12 (most likely due to introduction of air embolus during TCE). Coil migration did not occur in any of our patients.

Hemoptysis

Six of the 36 patients developed hemoptysis sometime during their course: one with unilateral and one with bilateral before treatment, and four late after treatment (Tables 1 and 2).

A. Hemoptysis in Patients with Unilateral Diffuse PAVM

Two patients with unilateral involvement developed hemoptysis- one before and one after embolization. The first one (Patient 5) had a viral URI causing severe hemoptysis, and was treated successfully by bronchial artery embolization. She continues to be aggressively treated with antitussives to prevent recurrence secondary to hard coughing. The second patient (Patient 8) has developed recurrent hemoptysis, either

spontaneous or with URIs, after initial TCE treatment of 3 segments of the right lower lobe.

B. Hemoptysis in Patients with Bilateral Diffuse PAVM

Hemoptysis was present in 4/26 patients. The first patient (Patient 12) developed massive hemoptysis and was treated by bronchial artery embolization, but in 2003 and 2005 developed hemoptysis again and died (69, 100). The second one (Patient 14) had not been treated (69). The third patient (Patient 18) had massive hemoptysis, was evaluated at another institution, and underwent a successful partial right lower lobe lobectomy without recurrence of hemoptysis in 8 years. The fourth patient (Patient 20) had recurrent spontaneous as well as URI-induced hemoptysis related to hard coughing. Diffuse telangiectases were demonstrated in this patient with bronchoscopy. His hemoptysis spontaneously resolved after 1996, with no recurrence.

Mortality

None of the patients with unilateral diffuse involvement died during 27 years of follow-up. Nine deaths occurred in the group of 26 patients with bilateral diffuse involvement. Six of these deaths occurred during the interval follow-up, and were secondary to brain abscess (Patient 13), brain hemorrhage (Patient 25), hemoptysis (Patient 12), and three from liver complications (Patient 17, 19 and 27)- subacute liver hemorrhage and biliary necrosis (2) and ammonia intoxication (1).

The mean age at first visit of patients who died was not significantly different from those still living- 25 ± 16 years versus 24 ± 23 years ($p=0.22$). Neither were the oxygen saturations- $78\% \pm 7\%$ versus $82\% \pm 9\%$ ($p=0.18$).

DISCUSSION

Pulmonary arteriovenous malformations can cause hypoxemia, pulmonary hemorrhage, and serious neurological complications, such as stroke or brain abscess. About 5% of patients with PAVMs have a more severe and diffuse pattern of disease. Little was known about the clinical characteristics, course and management of these patients prior to the study by Faughnan et al in 2000 (69). Before that only case reports appeared in the literature (73-95). Faughnan et al studied the natural history of 16 patients with diffuse PAVMs, and concluded that these patients are at increased risk of neurological complications, and that transcatheter embolotherapy does not significantly improve their profound hypoxia, but may reduce the risk of neurological complications.

Since then, very little has been published about these patients. Because patients with diffuse PAVMs are associated with significant morbidity and mortality, more frequent monitoring is required(69). In addition, we observed that hemoptysis, which is rarely seen in patients with focal PAVMs, is a frequent finding in patients with diffuse PAVMs. This is consistent with the finding that diffuse involvement is associated with more complications, but we also began to question our treatment approach as a possible cause of hemoptysis. Since Faughnan's paper, the Yale technique has empirically changed from proximal to distal occlusion, treating only the most severely affected segmental arteries, as opposed to occluding the entire lobe proximally, in hopes of preventing bronchial artery hypertrophy and, hence, hemoptysis. The need to re-classify

the anatomy of diffuse PAVMs was recognized in light of this necessity for a better treatment approach.

We extended the observations from the 2000 paper to additional 21 patients with diffuse PAVMs, and followed up on 15 out of the 16 previously reported patients (69). Furthermore, we performed an extensive literature review of diffuse PAVMs, searching for other attempts to re-define the anatomy of diffuse PAVMs.

Definition of Diffuse PAVMs

Prior to the 2000 report, diffuse PAVMs were often called pulmonary telangiectases or microscopic arteriovenous fistulae, and were vaguely described as innumerable fistulae or “spidery” small vessels, distributed diffusely throughout both lungs.

Classification of PAVMs into focal, multiple and diffuse has been around for decades (67, 96), but there have been no prior attempts to distinguish between various degrees of involvement of the lung with diffuse PAVMs. In the 2000 report, diffuse PAVMs were defined as affecting all segmental branches of one lobe (69). We observed that many patients with diffusely involved segmental arteries did not necessarily have all arteries of a single lobe affected- some were spared or much less involved. Therefore, we feel that it is more accurate to report diffuse involvement with respect to segments rather than lobes. We consider involvement as diffuse if at least 1 of the 18 lung segments is diffusely affected. Patients with only a small number of segments diffusely involved (2 or 3) have a sustained rise in oxygen saturation after peripheral to central occlusion.

It is important to note that multifocal PAVMs may be difficult to distinguish from diffuse ones, in fact, many of the PAVMs that were reported in previous studies as

diffuse were actually multifocal. The difference is that multifocal PAVMs respond well to TCE, such that their post-embolization pulmonary angiogram generally appears almost normal, and their oxygen saturation rises significantly. This does not happen with diffuse PAVMs, making them much more difficult to treat.

Natural history of Diffuse PAVMs

Patients with diffuse PAVMs have been found to present earlier in life, usually with exercise intolerance and profound cyanosis and appear to have a poor prognosis.

Neurological Complications

In patients with HHT, neurological complications are more frequently related to PAVM than to hemorrhagic cerebral AVM (101).

Traditionally, neurological events occur in about 30% of patients with focal PAVMs (66). Stroke/TIA occur in 10-20% of these patients(102), whereas cerebral abscesses have been found in about 10% (60, 102). It has been pretty well shown that follow-up every 5 years is all that is necessary in these patients with focal PAVMs (72).

In the small subset of HHT patients with diffuse PAVMs, these events are more common. Faughnan and colleagues reported the rates of 50% for stroke/TIA and 38% for cerebral abscesses (69). In our study, in which we followed for additional 8 years fifteen out of the sixteen patients from Faughnan's cohort (69), 5 patients (30%) had a stroke or TIA during the follow-up period, while brain abscess occurred in 2 patients (13%). In the 21 new patients that we followed from 1998-1996, strokes/TIAs occurred in 3 of them (14%), and two abscesses occurred in each of the 2 patients. Because of the higher risk of

neurological complications, among others, yearly follow-up is recommended in patients with diffuse PAVMs.

Neurological manifestations generally result from: secondary polycythemia and hyperviscosity due to chronic hypoxia from right to left shunting, communication between the airways and pulmonary circulation during cough produces gas embolism and hemoptysis, and paradoxical emboli that pass through PAVMs (74). In patients with diffuse PAVMs, hypoxemia is more severe, leading to greater degree of polycythemia and hyperviscosity. In addition, since more PAVMs are present, there is a greater loss of capillary filter function. Therefore, an increased risk of neurological complications in patients with diffuse PAVMs is not surprising.

Cerebral abscesses in HHT are frequently due to multiple anaerobic organisms and predominate in supratentorial areas of the brain (103). They were found to follow dental procedures in more than half the cases (69). In HHT, brain abscesses occur at a younger age than in the general population and may relapse (102). One of the deaths that occurred in our cohort was due to a brain abscess in a patient that did not seek medical attention in time. Any patient with PAVMs should seek medical attention for headache lasting more than 24 hours. In addition, due to the risk of infections, antibiotic prophylaxis prior to potentially bacteremic procedures is recommended in all HHT patients with a positive bubble study, including those without a visible PAVM on imaging.

Hemoptysis

Hemoptysis in patients with diffuse PAVMs has emerged as an important symptom that requires further understanding. In our cohort, hemoptysis was associated with a URI

in most cases. If treated appropriately with antitussives, it rarely becomes massive (>100ml/day). As part of the hemoptysis work-up, bronchoscopy is performed to rule out telangiectasia of the tracheal bronchial mucosa.

In a recent report by Brillet et al, about 40% of patients with previously treated focal PAVMs were found to have enlarged bronchial arteries (104). In this group of patients, the frequency of clinical events suggestive of lung infarction in the days or months after embolotherapy and the frequency of CT features suggestive of sequelae of lung infarction on CT angiograms were significantly higher than those observed in the group of patients without abnormal enlargement of systemic arteries. This supports the already suggested hypothesis that the treatment of focal PAVMs may induce ischemia, which could trigger enlargement of bronchial arteries supplying the PAVMs. Another hypothesis is that bronchial artery hypertrophy is a part of the HHT syndrome. We have empirically changed our treatment from central to peripheral occlusion, in hopes of avoiding bronchial artery enlargement and collateral filling of distal pulmonary arteries, and thus hemoptysis. In those patients that do not respond well to antitussives and progress to massive hemoptysis, the Yale center has been successful at controlling this symptom by performing bronchial embolotherapy (69, 100).

Improved knowledge of the frequency of congenital and acquired systemic arterial supply of PAVMs, as well as predictive factors for the latter situation, requires precise mapping of systemic arteries before embolotherapy, which was not done in the above mentioned study by Brillet et al. Future studies investigating the role of bronchial embolotherapy are needed.

Mortality

Patients with bilateral involvement have greater mortality than those with unilateral involvement. Six deaths occurred in our series, and neither age nor oxygen saturations were predictors of death. Three of the deaths were potentially preventable. One was due to massive hemoptysis and delay in seeking medical attention. The second one was in a patient with a history of brain abscess, who did not seek prompt medical attention for headache, which turned out to be a second abscess 21 years after the first one. Any patient with a PAVM should seek medical attention for headache lasting over 24 hours. Finally an infant with diffuse bilateral involvement died of cerebral hemorrhage, most likely secondary to an undiagnosed CAVM, further emphasizing the importance of screening all HHT patients for CAVMs during initial work-up.

The remaining 3 patients died of liver complications, which likely occur due to shunting of poorly oxygenated blood through multiple liver AVMs. Up to 80% of HHT patients have liver shunts(4), which rarely cause symptoms due to high output failure (54). In our patients, 2 developed “liver disintegration”, a syndrome of liver hemorrhage, pain and elevated alkaline phosphatase (105). The last patient developed progressive ammonia intoxication without acute symptoms. Presently, in the United States, the United Network for Organ Sharing (UNOS) does not recognize HHT as an indication for liver transplant.

Treatment of Diffuse PAVMs

Before 1980, surgical resection was the only method of treatment of PAVMs (106, 107), and it rarely still has a role in patients in whom right-to-left shunting persists after

embolization of all feasible vessels (44), or if a patient has severe contrast allergy, precluding angiography.

Transcatheter embolization therapy has been the preferred method of treatment since the 1980's as it avoids major surgery, general anesthesia, and loss of pulmonary parenchyma and is technically-successful in over 98% of cases (71).

In 2006, Pollak et al published their results regarding outcomes of TCE in 154 patients with focal PAVMs (72). They had about a 3% reperfusion rate for focal PAVMs, which may occur due to recanalization of an embolized vessel, or growth of missed or previously small accessory artery.

More difficult are the treatment considerations for patients with diffuse PAVMs.

Lung transplantation has been reported in only a small number of patients. One of the patients from the 2000 cohort died in the lung transplant peri-operative period. There have been 2 case reports to date of lung transplantation as a therapeutic option for PAVMs unresponsive to other forms of treatment (108, 109). The first case reported was a double lung transplant in a patient with diffuse PAVMs, severe hypoxemia and multiple previous failed attempts of TCE (109). This patient had a satisfactory short-term outcome, but no follow-up has been published. The second case was a patient with bilateral multifocal PAVMs with a previous lobectomy and one AV fistula occlusion, who at 3 years post-transplantation of the right lung was performing normal daily activities with oxygen saturations of 99%, even during exercise. The potential for recurrence of the disease in the donor organ is still unknown. Given the very small number of lung transplant cases in patients with PAVMs who are unresponsive to other forms of treatment, more long-term outcome data is needed. Because of this lack of data

and because survival with disease is difficult to predict, we currently do not recommend lung transplantation as a therapeutic approach to diffuse PAVMs.

Redistribution of pulmonary blood flow, by occluding the segmental arteries of an entire lobe has been used successfully and with improvement in oxygenation. Unfortunately, a late complication, such as hemoptysis due to bronchial artery hypertrophy has made this approach not ideal. Consequently, the Yale technique has changed empirically based on follow-up of patients since 2000, such that only those segmental arteries with diffuse involvement are occluded peripherally, from distal to proximal, with pushable fiberoptic coils (99). Our primary indication for embolotherapy at initial evaluation of patients with diffuse PAVMs remains the same- occluding all focal PAVMs with arteries 3mm or larger (72). In our series, large focal PAVMs were more commonly found in the bilateral group. Embolization of these arteries protects against paradoxical embolization, but not necessarily against bacterial embolization. Therefore, antibiotic prophylaxis remains necessary to cover potentially bacteremic procedures (72).

The new Yale treatment approach to diffuse PAVMs is performed only in very symptomatic patients, such as those experiencing dyspnea and fatigue, in the absence of anemia as the underlying cause. Interestingly, many of our patients are relatively asymptomatic despite very low oxygen saturations, likely reflecting the absence of pulmonary hypertension or airway issues.

Complications of embolization therapy include pleuritic chest pain, air embolism, with angina and bradycardia caused by air in the coronary arteries, and device migration (2, 68, 110). In experienced hands, complication rates as a result of embolotherapy are low, except for hemoptysis, which may or may not be due to TCE.

Pleuritic chest pain may develop in 10% of patients after embolization, usually developing 2 to 4 days after the procedure, often self-limited, and usually resolving within 1 to 2 days with simple analgesia or anti-inflammatories (2).

Device migration has a previously reported incidence of 1.2% (66), but its incidence in experienced hands is lower (2, 68, 110), and did not occur in any of our patients. Migration of balloons or coils to the hepatic artery, the internal iliac artery, the femoral artery, the carotid artery and the left ventricle has been reported (68, 111-113). None of the reported migrations has resulted in permanent disability, although about half required some intervention, usually with an intravascular retrieval device or, rarely, emergency surgery (71, 112, 113). Device migration may be due to misjudgment of balloon location, use of a balloon or coil that is too small for the artery to be occluded, suboptimal fluoroscopic visualization, or complex anatomy with difficult access (68). Various techniques for fixing the coil position to prevent distal migration can be used in PAVMs with large feeding arteries (111).

In our cohort, complications were overall less in the unilateral group and their response to TCE was superior to that in patients with bilateral involvement.

As a result of a low, but significant risk of reperfusion after embolization, which results in recurrent risk of paradoxical embolization, monitoring for PAVM growth after treatment is necessary. With all the concern from radiation (114), we should be able to assess growth and monitor by less invasive means. Exercise testing measuring oxygen saturation might be a solution to this problem, and is currently being developed at Yale. Assessment of bronchial artery hypertrophy as a result of embolization and as a possible

cause for hemoptysis, is another important issue which will be studied in the near future at the Yale HHT Center.

Recommendations

Because of the small number of patients reported with diffuse PAVMs, it is still difficult to make concrete recommendations about their management. However, we firmly recommend yearly follow-up, given the increased morbidity and mortality associated with these patients.

Embolization of PAVMs in patients with diffuse PAVMs does not improve their hypoxemia (as many untreated PAVMs remain), but may reduce the risk of neurological sequelae. Therefore, these patients have a fairly good prognosis with appropriate management, which should include embolotherapy of larger AVMs, and life-long antibiotic prophylaxis for bacteremic procedures (Figure 8).

FIGURES

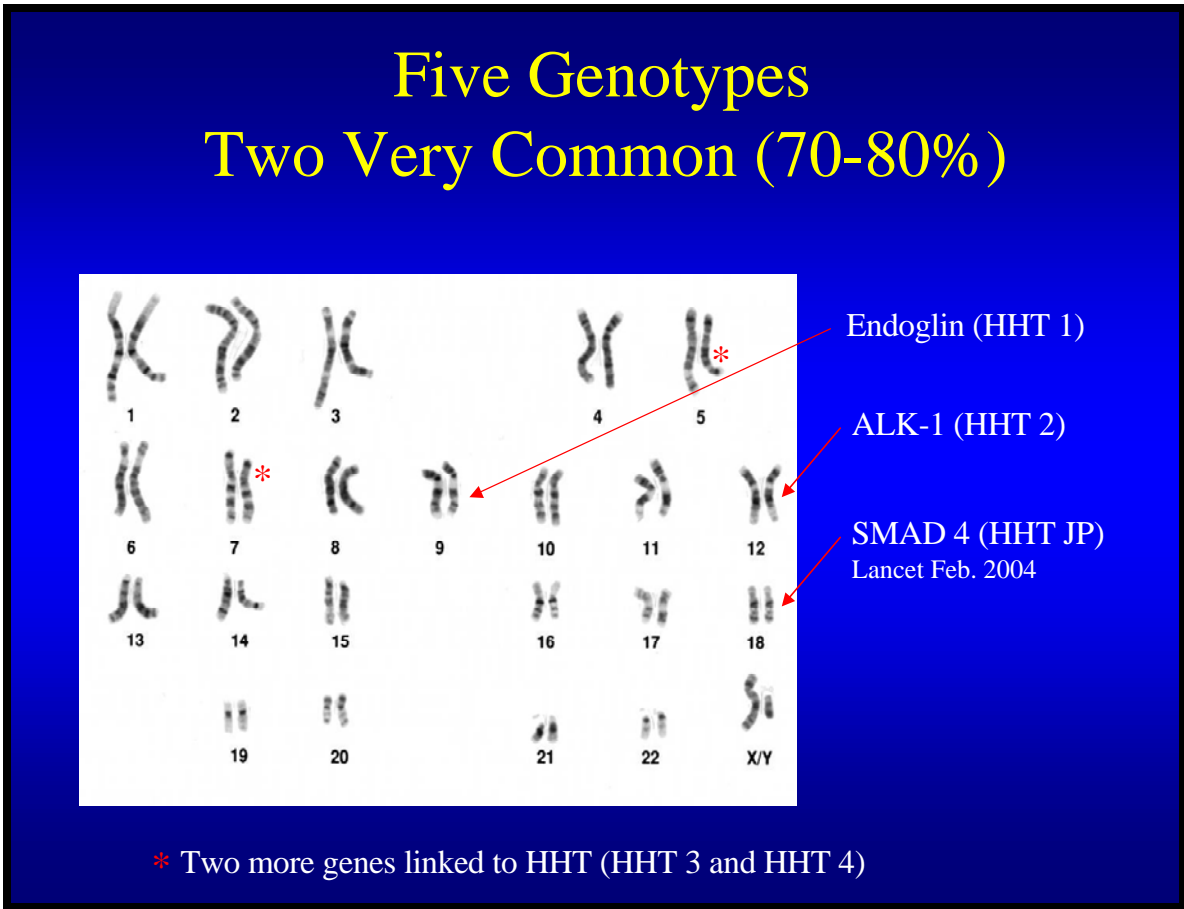


Figure 1. HHT Genotypes.

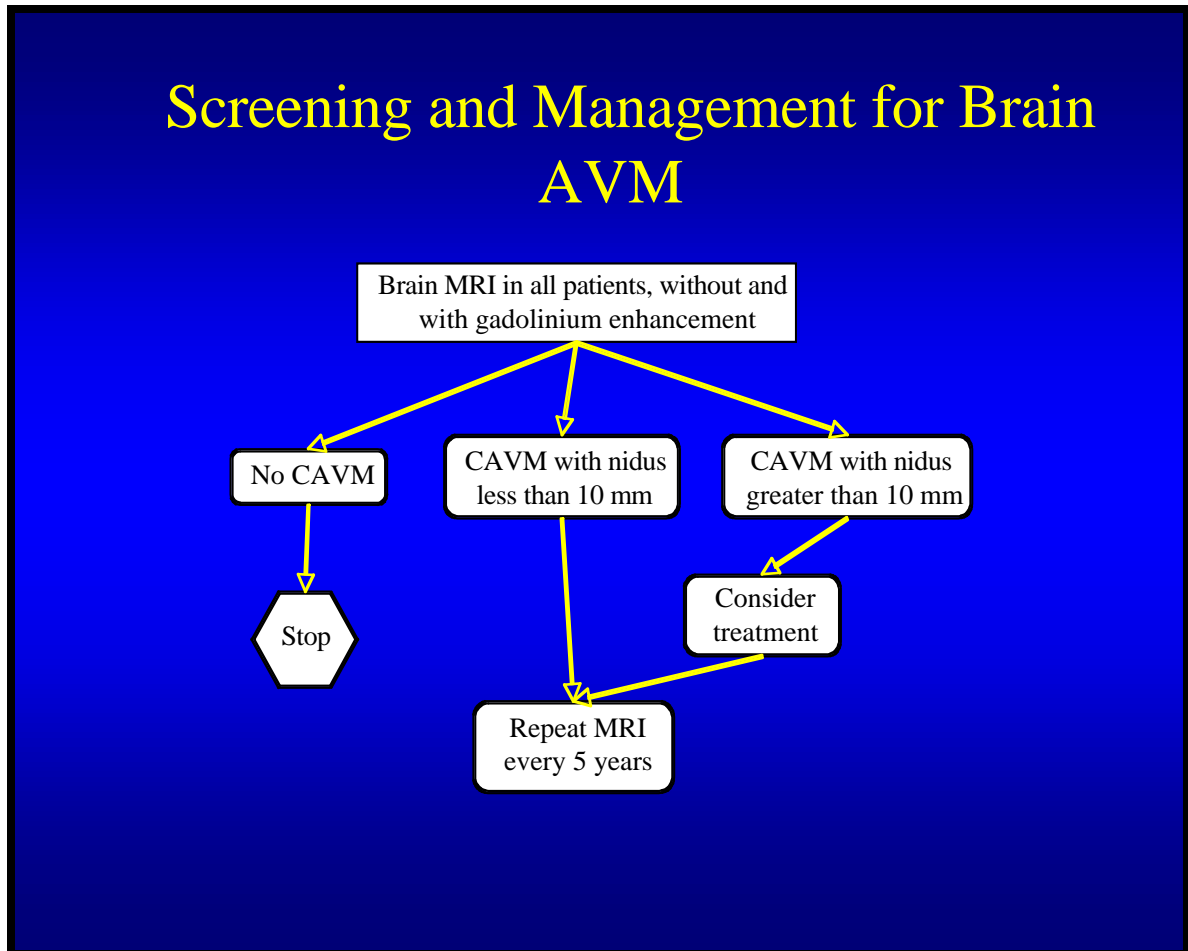


Figure 2. Yale HHT Center Recommendations: Screening and Management of Cerebral Arteriovenous Malformations.

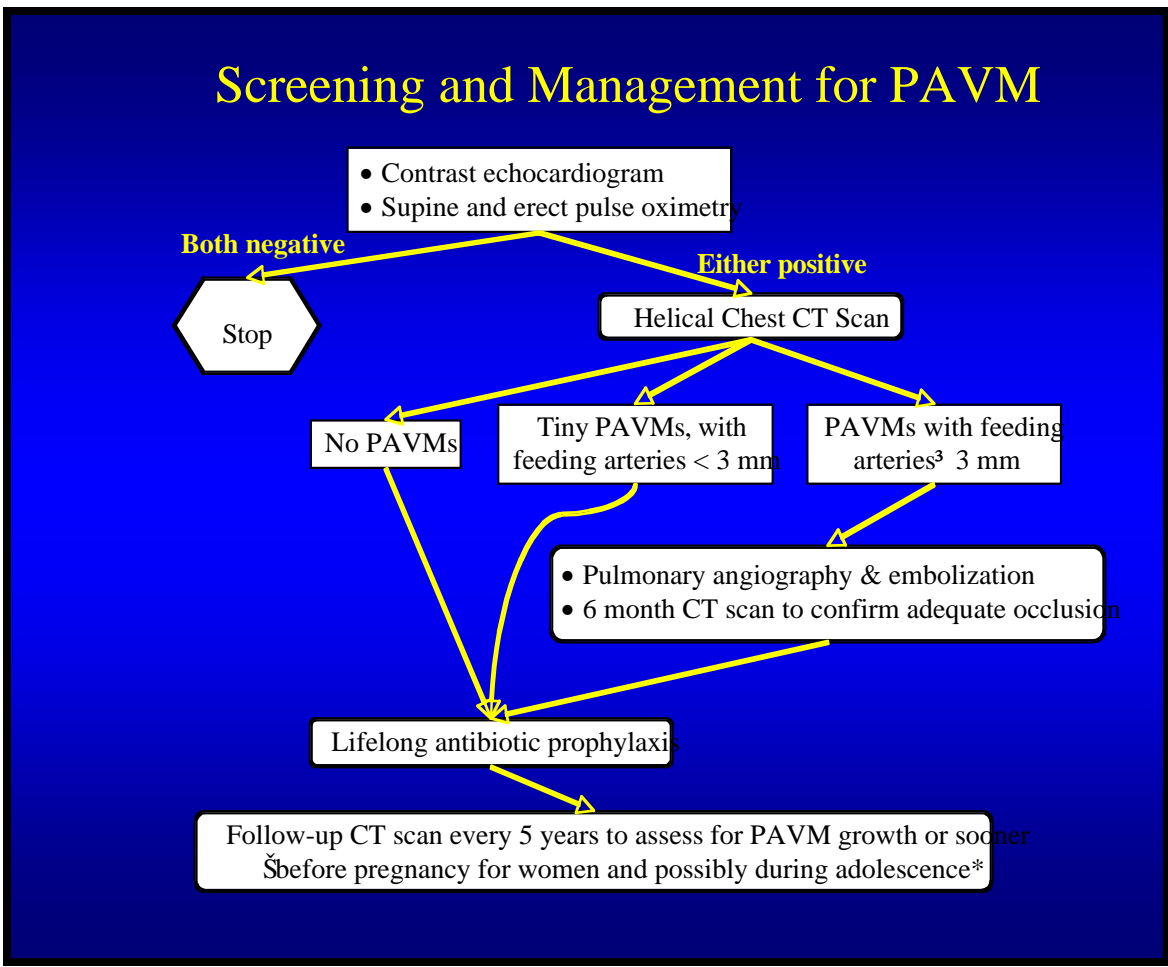


Figure 3. Yale HHT Center Recommendations: Screening and Management of Pulmonary Arteriovenous Malformations.

4A.



4B.

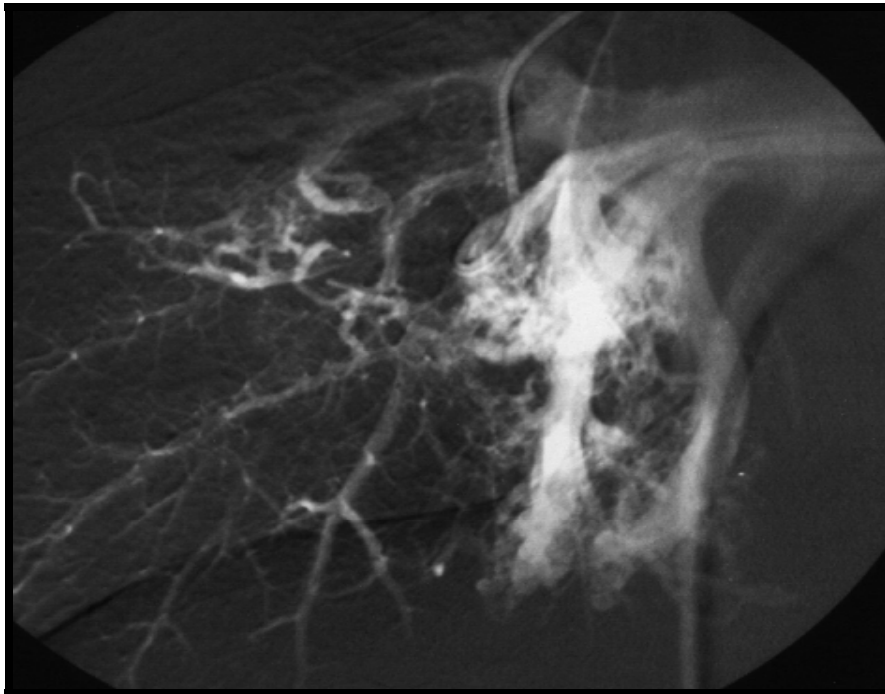
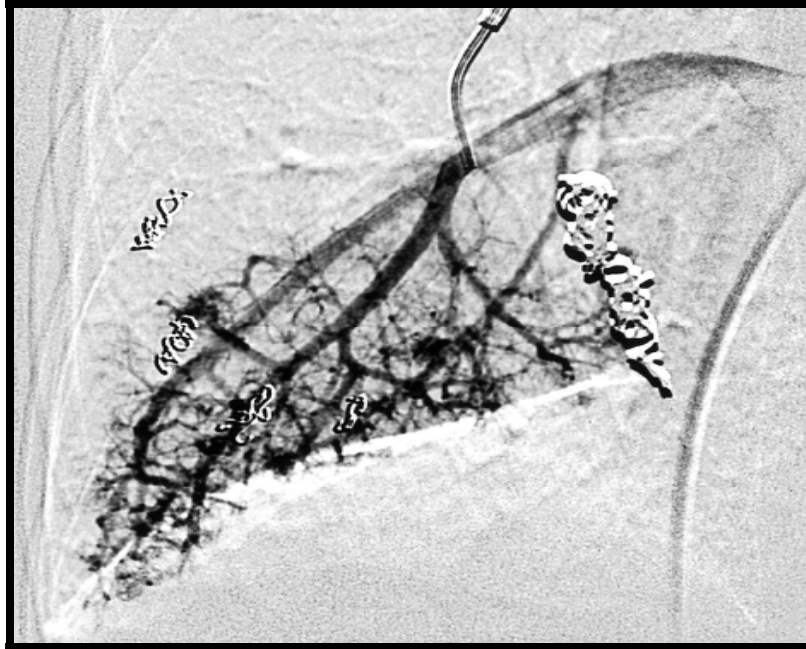


Figure 4A-B. Left anterior oblique selective right pulmonary angiogram early and late arterial images. A. Diffuse involvement of the posterior and medial segment arteries, while the anterior and lateral segments are uninvolved. B. In the late arterial phase, early venous drainage into the left atrium is seen from the diffusely involved posterior medial segments.

5A.



5B.

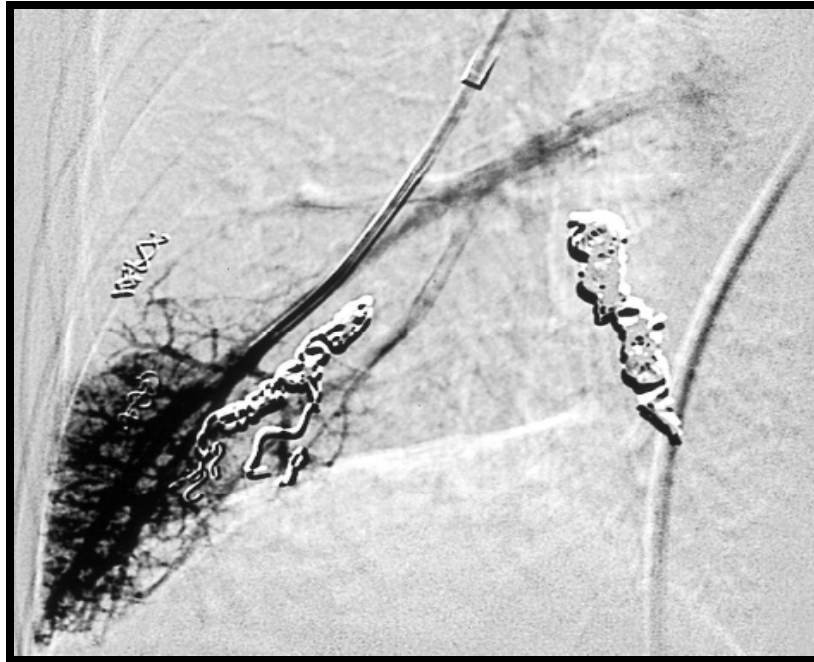
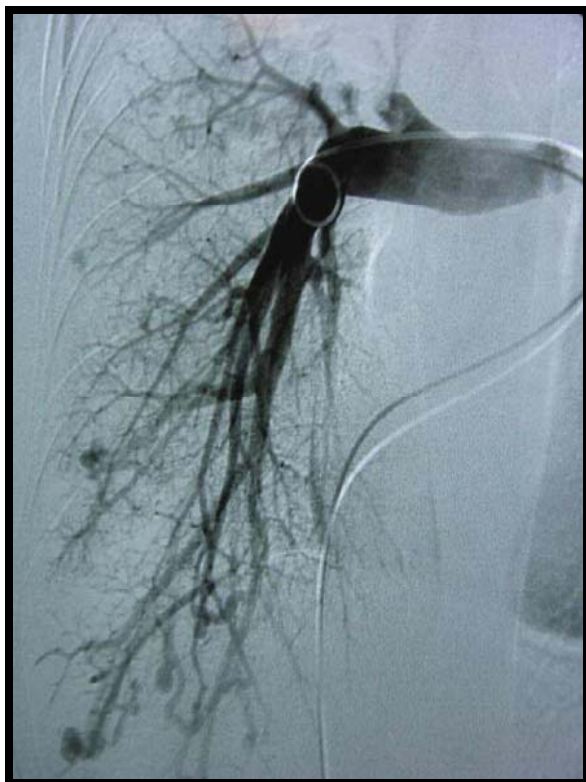
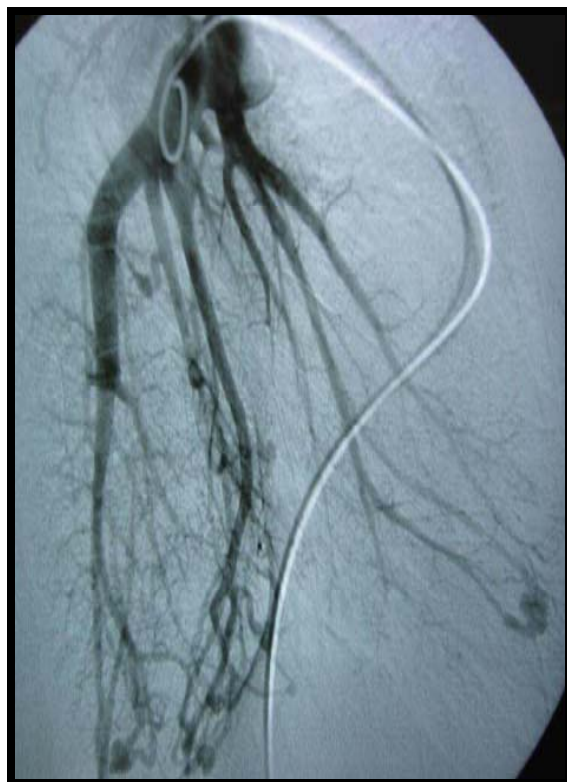


Figure 5A-B. Shallow anterior oblique views of super selective right pulmonary angiograms in late arterial phase. In both A (anterior segment) and B (lateral segment), diffuse involvement from each subsegmental branch is noted. At the end of each subsegmental branch are tiny, almost “telangiectasia type” abnormalities. The pulmonary veins from each of these segments are already opacified.

6A.



6B.



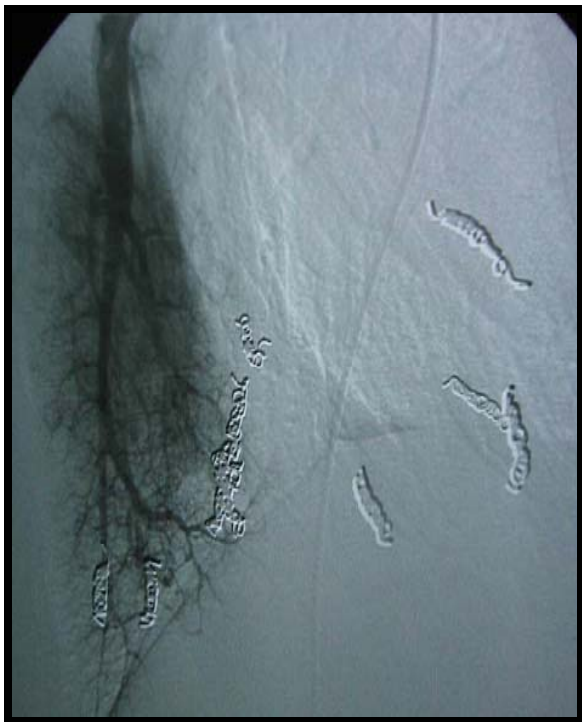
6C.



6D.



6E.



6F.

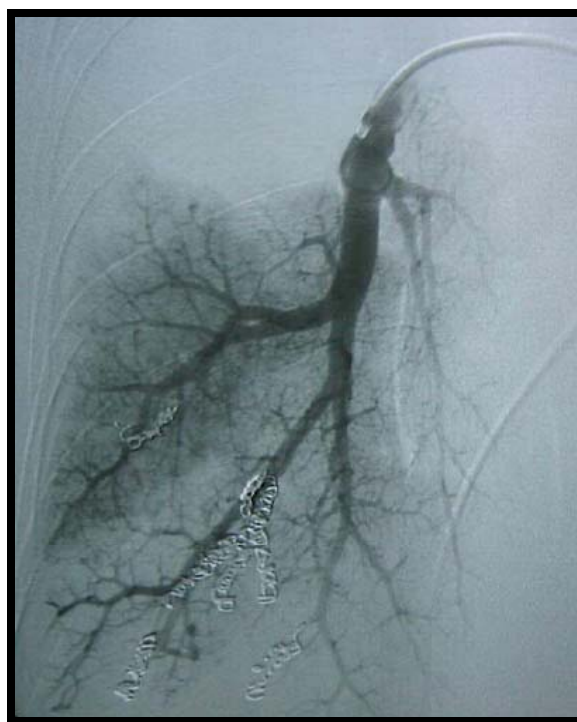
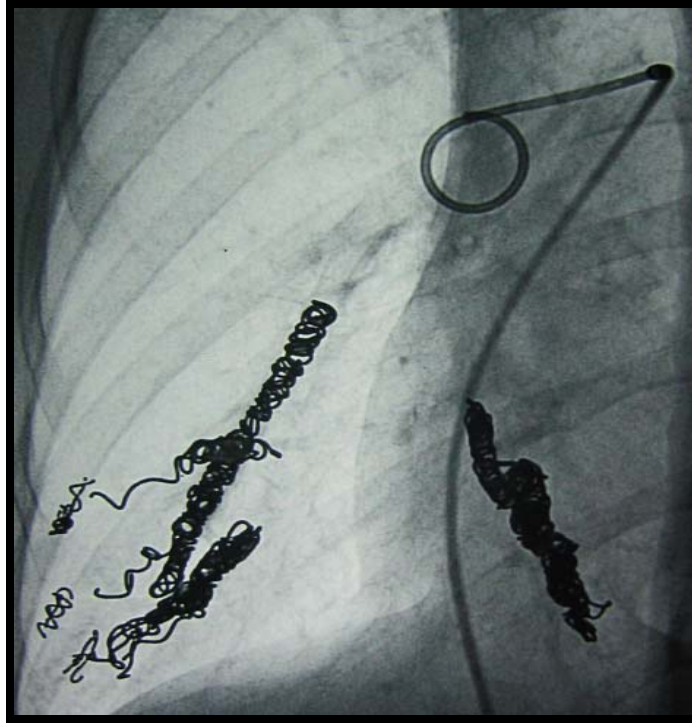


Figure 6A-F. Young patient with multifocal PAVM in right lung. Earlier in life surgical resection of her right superior segment had been performed. A (anterior) and B (lateral) right pulmonary angiograms are demonstrating small PAVMs distally in right lower lobe and right middle lobe. In C and D, super selective pulmonary angiogram in anterior segment of right lower lobe demonstrates multiple focal PAVMs with early venous drainage. In E and F, super selective pulmonary angiogram with catheter beyond right middle lobe and anterior segment of lower lobe demonstrates “normal” pulmonary artery anatomy following distal occlusion of each small focal PAVM. No early veins are seen and angiogram is almost normal in the post-occlusion angiogram.

7A.



7B.

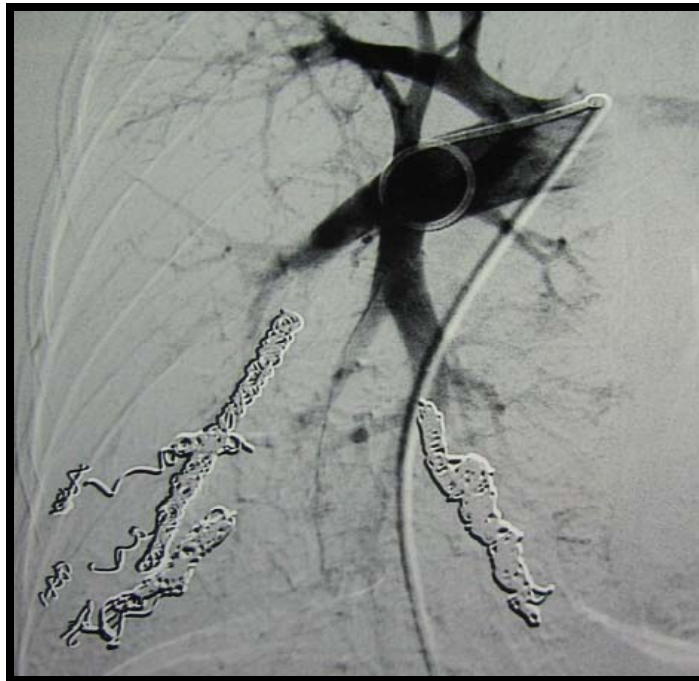


Figure 7A-B. Post-occlusion angiograms from patient in Figure 1 after peripheral occlusion of most involved segments in right lower lobe (posterior, anterior and lateral), demonstrating the new approach of occluding from distal to proximal, using “tightly” packed coils

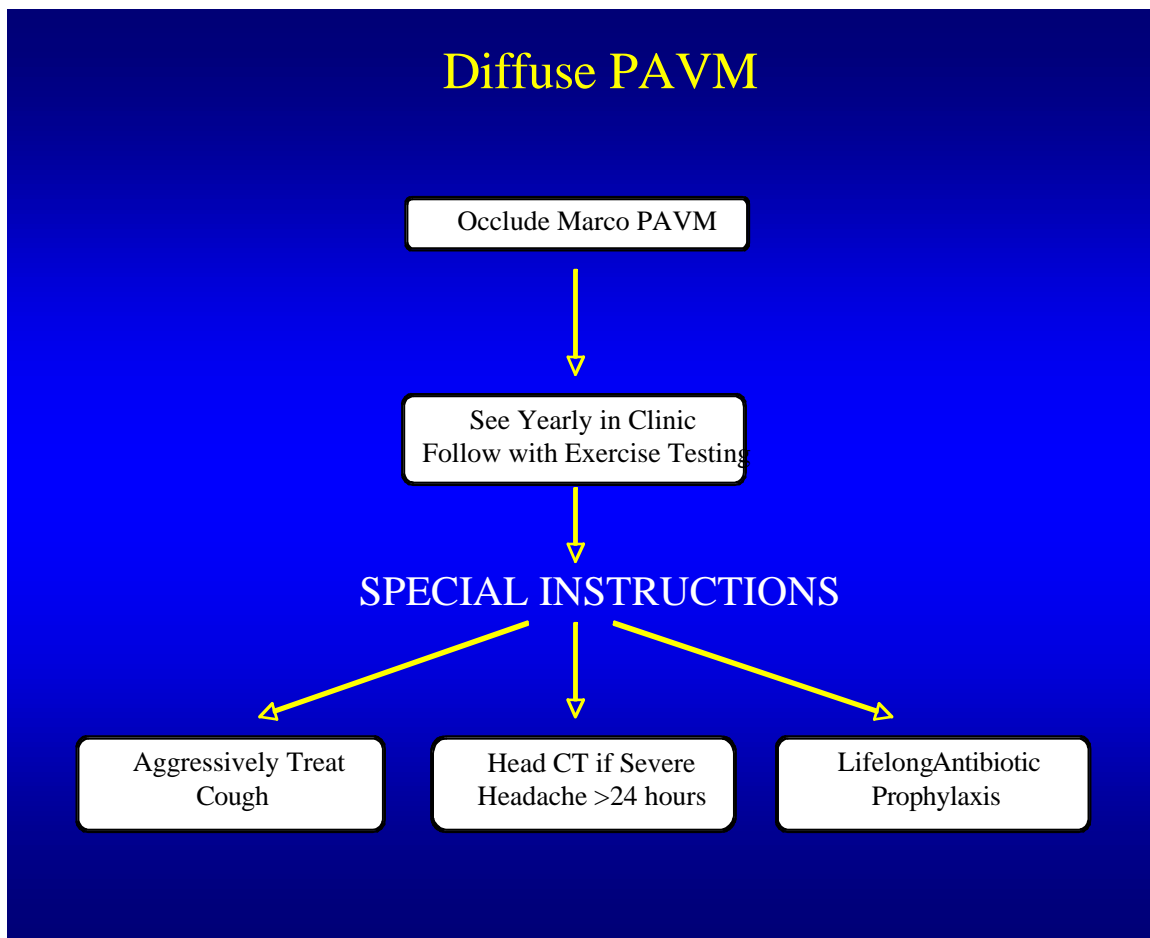


Figure 8. Yale HHT Center Recommendations: Diffuse PAVM Management Algorithm.

TABLES

Table 1. PATIENTS WITH UNILATERAL DIFFUSE PAVM										
1980-1998						1998-2006				
PT	HHT	Sex	Age	Stroke/TIA	BA	HEMO	Stroke/TIA	BA	HEMO	Y/F
1	N	M	33		Y					16
2	Y	F	31				Y			10
3	Y	M	22					Y		4
4	Y	M	37							6
5	Y	F	10						Y	6
6	N	M	23				Y			1
7	N	M	25							1
8	Y	M	7						Y	6
9	Y	M	4							4
10	Y	M	7							<1

PT=patient, N=no, Y=yes, Sex, F=female, M=male, Age= age in years at presentation, BA=brain abscess, HEMO= hemoptysis, Y/F=years of continuous follow-up. Patients 1-2 reported in previous paper. Patients 3-10 seen after 1998.

Table 2. PATIENTS WITH BILATERAL DIFFUSE PAVM										
1980-1998							1998-2006			
PT	HHT	Sex	Age	Stroke/TIA	BA	HEMO	Stroke/TIA	BA	HEMO	Y/F
11	N	F	29							17
12	Y	F	24		Y	Y			2	15*
13	Y	M	15	Y	Y			Y		17*
14	Y	F	14		Y	Y				5*
15	Y	F	39	Y			Y			14
16	Y	M	6	Y						5*
17	Y	F	42	Y	Y					6*
18	Y	F	20	Y			Y	Y	2	9
19	Y	F	17	Y			Y			22*
20	Y	M	20	Y					Y	26
21	Y	F	50	Y	Y		Y			9
22	N	M	23							13
23	N	F	0.8							1.5*
24	Y	F	12							3
25	N	F	0.5							0.4*
26	Y	F	43							5
27	Y	F	71				Y			3*
28	Y	F	6							4
29	Y	F	4							8
30	Y	F	49					2		9
31	Y	F	28							7
32	Y	F	5							5
33	Y	M	9							1
34	Y	M	15							16
35	Y	M	9							4
36	Y	F	31				Y	1+1 spinal abscess		10

N=no, Y=yes, Sex, F=female, M=male, Age= age in years at presentation, BA=brain abscess, HEMO= hemoptysis, Y/F=years of continuous follow-up. Patients 11-23 reported in previous paper. Patients 24-36 seen after 1998.

Table 3. PATIENTS WITH UNILATERAL DIFFUSE PAVM: DISTRIBUTION AND OXIMETRY

PT	HHT	Sex	Right		Left		Focal PAVM		O ₂ saturation		
			>50%	<50%	>50%	<50%	Unil	Bilat	Initial	Current	
1	N	M	Y					Y		85%	95%
2	Y	F	Y							82%	90%
3	Y	M				Y				91%	99%
4	Y	M				Y				88%	96%
5	Y	F	Y							73%	82%
6	N	M				Y				92%	92%
7	N	M		Y						N/A	N/A
8	Y	M		Y				Y		90%	93%
9	Y	M	Y							92%	89%
10	Y	M		Y						71%	71%*

PT=patient, Sex F=female, M=male, >50%=5 or more segments of right lung or 4 or more segments of left lung diffusely involved, <50% less than 5 segments of right lung or 4 or more segments of left lung diffusely involved, Unil=unilatera, Bilat=bilateral, N/A=not available. Inital and current O₂ saturations are values in room air, usually standing when first seen by us, and current values up to December 2006. Patients 3-10 seen after 1998. *Patient 10 was subsequently treated at another institution, with O₂ saturation of 98% in May 2007.

Table 4. PATIENTS WITH BILATERAL DIFFUSE PAVM: DISTRIBUTION AND OXIMETRY

PT	HHT	Sex	Right		Left		Focal PAVM		O2 saturation	
			>50%	<50%	>50%	<50%	Unil	Bilat	Initial	Current
11	N	F	Y		Y			Y	87%	93%
12	Y	F	Y		Y			Y	71%	94%
13	Y	M	Y		Y			Y	71%	86%
14	Y	F	Y			Y			67%	N/A
15	Y	F	Y		Y			Y	85%	87%
16	Y	M	Y		Y			Y	82%	81%
17	Y	F	Y		Y			Y	84%	70%
18	Y	F	Y		Y			Y	82%	92%
19	Y	F	Y		Y		Y		86%	87%
20	Y	M	Y		Y			Y	79%	74%
21	Y	F	Y		Y			Y	84%	96%
22	N	M	Y		Y				91%	87%
23	N	F	Y		Y			Y	75%	N/A
24	Y	F	Y		Y			Y	82%	76%
25	N	F	Y		Y				77%	77%
26	Y	F	Y		Y			Y	78%	89%
27	Y	F	Y		Y			Y	86%	90%
28	Y	F	Y			Y			74%	65%
29	Y	F	Y		Y				67%	73%
30	Y	F	Y		Y			Y	87%	76%
31	Y	F		Y	Y				88%	82%
32	Y	F	Y		Y				60%	68%
33	Y	M		Y		Y			83%	70%
34	Y	M	Y			Y			86%	94%
35	Y	M	Y		Y			Y	65%	73%
36	Y	F	Y		Y			Y	83%	89%

PT=patient, Sex F=female, M=male, >50%=5 or more segments of right lung or 4 or more segments of left lung diffusely involved, <50% less than 5 segments of right lung or 4 or more segments of left lung diffusely involved, Unil=unilatera, Bilat=bilateral, N/A=not available. Inital and current O2 saturations are values in room air, usually standing when first seen by us, and current values up to December 2006. Patients 11-23 reported in previous paper. Patients 24-36 seen after 1998.

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