

# **Pulmonary Vascular Manifestations of Hereditary Hemorrhagic Telangiectasia**



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**Purpose and Overview:** The purpose of this presentation is to familiarize the audience with the clinical manifestations of hereditary hemorrhagic telangiectasia, with a focus on the diagnosis and treatment of the pulmonary vascular manifestations of HHT and their treatment.

**Educational Objectives:** At the conclusion of this, the listener will be able to:

1. Discuss the criteria used in the diagnosis of hereditary hemorrhagic telangiectasia.
2. Describe the clinical features of HHT.
3. Oversee the diagnosis and management of the common pulmonary vascular manifestations of HHT.

## **Introduction and Background**

### Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), originally known eponymously as Osler-Weber-Rendu, is an inherited disorder of blood vessel formation characterized by the presence of mucocutaneous telangiectasias and visceral vascular malformations<sup>1</sup> resulting in direct communication between arterioles and venules without intervening capillary beds. These abnormal vascular communications lead to variable clinical manifestations, depending largely on which tissues are affected and to what extent. Vascular malformations can arise in virtually any tissue in HHT. Recurrent epistaxis from nasal telangiectasias is the most frequent symptom<sup>2</sup>, but potentially life-threatening complications can arise from arteriovenous malformations (AVMs) and telangiectasias in other organs, most commonly involving the brain, liver, GI tract, and lung. This presentation will begin with brief general overview of HHT then focus in more depth on the pulmonary vascular manifestations of the disease.

### Historical Perspective

A familial syndrome of recurrent epistaxis was first described by the English physician, Henry Gawen Sutton, in 1864<sup>3</sup>; however, neither he nor others who soon after provided similar descriptions went on to receive eponymous credit for the disease. Instead, that recognition went to three other physicians – Henri Rendu, who differentiated HHT from hemophilia<sup>4</sup> in 1896; William Osler, who described the disease as an inherited disorder in 1901; and Frederick Weber who in 1907 published a case series of patient with HHT<sup>5</sup>. That same year one of Osler's trainees proposed the term hereditary hemorrhagic telangiectasia, but the condition continued to be called Osler-Weber-Rendu for many years hence.

### Genetics and Pathogenesis

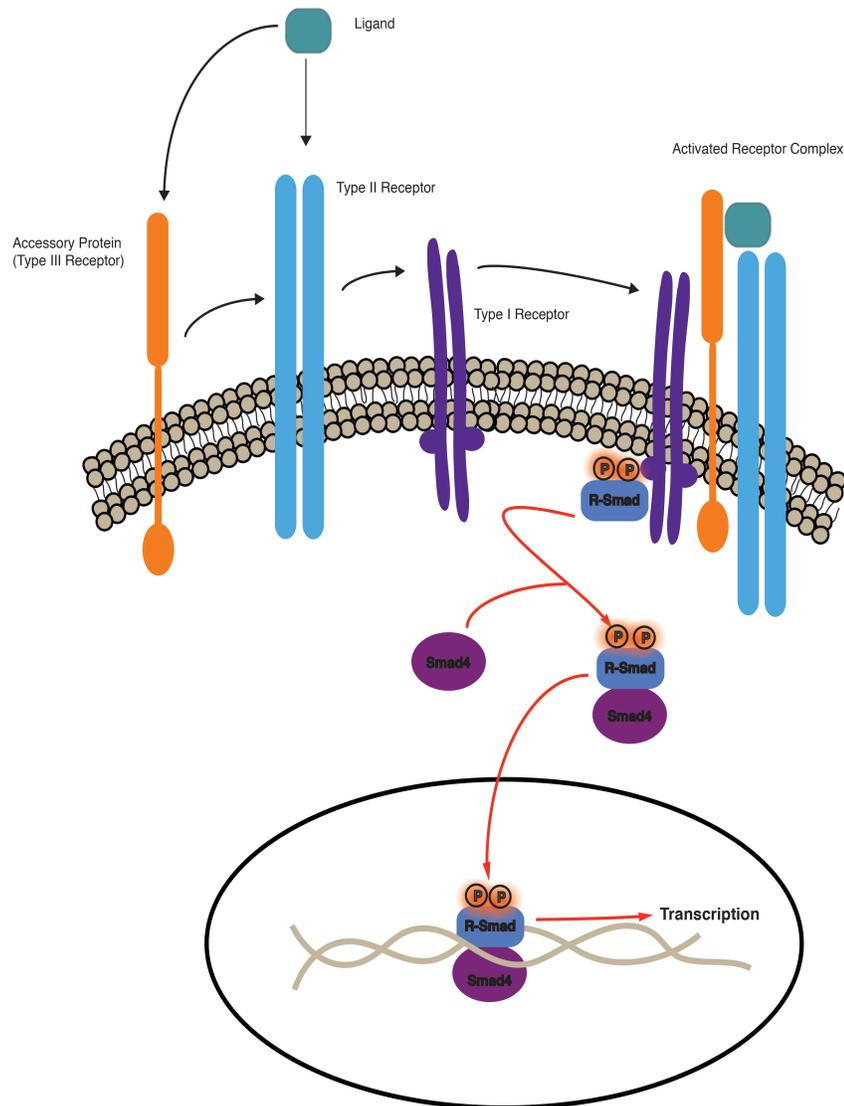
HHT is a genetic disorder with an autosomal dominant pattern of inheritance, affecting 1 in 5000 individuals worldwide<sup>6</sup> and as many as 1:1300 individuals in certain populations, suggesting that HHT is not nearly as rare as many clinicians believe. The past two decades have seen major advances in our understanding of the genetic mechanisms underlying HHT<sup>2,7-9</sup>. Over 85% of HHT is caused by mutations in one of two genes, endoglin and ACVRL1. Endoglin (ENG, chromosome 9q34.11) is an accessory protein involved in transforming growth factor beta (TGF- $\beta$ ) signaling, pathogenic mutations of which lead to HHT type 1 (HHT1) characterized by relatively early clinical manifestations and an increased likelihood of AVMs in the brain<sup>6</sup> and lungs<sup>9</sup>. ACVRL1 (also known as ALK1, chromosome 12q.13.13) encodes activin-like kinase 1, a type I TGF- $\beta$  superfamily receptor. Pathogenic mutations in ACVRL1 lead to HHT type 2

(HHT2) in which liver AVMs are more prevalent while pulmonary and brain AVMs are seen less frequently<sup>8</sup>. Another ~2% of HHT is associated with mutations in Smad4, which is linked to the juvenile polyposis-HHT syndrome. Additional genes involved in TGF- $\beta$  signaling<sup>10</sup> have recently been implicated in HHT-overlap syndromes. Fewer than 8% of HHT patients will not have mutations in any of these genes but instead are believed to have mutations in other TGF- $\beta$  pathway genes that have not yet been identified (Table 1).

Gene	Name	Phenotype	Frequency	
Endoglin	HHT-1	Epistaxis, lung, brain AVMs	47%	<b>Classic HHT</b>
ACVRL1	HHT-2	Epistaxis, liver and GI AVMs	43%	
Smad4	HHT-Juvenile polyposis syndrome	HHT plus juvenile polyposis	2%	
Unknown gene, chromosome 5	HHT-3	Same as HHT-1	< 8%	
Unknown gene, chromosome 7	HHT-4	Epistaxis, CVMs, PAVMs		
RASA1	Capillary malformation-AVM syndrome; Parkes Weber	Cutaneous capillary malformations; visceral AVMs (muscle, bone, spine, brain)	NA	<b>HHT Overlap Syndromes</b>
GDF2	HHT-5	Similar to HHT-2	NA	

**Table 1. Genes associated with classic HHT and HHT-overlap syndromes.** Listed frequencies refer only to classic HHT phenotypes. HHT-5 has not been completely characterized and its frequency is not established, but most reports are phenotypically consistent with HHT-2, suggesting that HHT-5 may be another classic HHT phenotype rather than an overlap syndrome.

The precise mechanisms by which alterations in TGF- $\beta$  signaling lead to the vascular manifestations of HHT are not known. TGF- $\beta$  signaling is critical to various essential cellular functions including differentiation, homeostasis, proliferation, and morphogenesis. Signaling is initiated by ligand binding to a type II TGF- $\beta$  receptor – for example TGF $\beta$ R2 or BMPR2 - either directly or via an accessory protein, such as endoglin (Figure 1). Many TGF- $\beta$  ligands have been identified including the archetypal TGF- $\beta$  as well as bone morphogenetic proteins



**Figure 1. TGF-beta signaling.** Upon ligand binding, type II receptors join with a type I receptor forming a heteromeric receptor complex. Formation of this complex activates the type I receptor's serine/threonine kinase domain leading to phosphorylation and activation of receptor-associated cytoplasmic signaling molecules, or receptor Smads (R-Smads). R-Smads complex with Smad4 to translocate to the nucleus and modify gene expression in a cell- and context-specific fashion, in the case of the pulmonary vasculature affecting genes involved in endothelial proliferation, vascular regeneration, and angiogenesis.

(BMPs), growth and differentiation factors (GDFs), and activin/inhibins, each with varying affinity for different TGF-β receptors. BMP signaling, in particular, is fundamental to cardiovascular and lymphatic development with mutations in this signaling pathway leading to a range of vascular dysfunctions and defects in angiogenesis<sup>10</sup>. Not surprisingly, defective TGF-β signaling initiated by binding of

BMPs, in particular, and, to a lesser extent GDFs, has also been implicated in HHT pathogenesis and related conditions.

## Diagnosis

Although the genes responsible for most cases of HHT have been identified, the diagnosis is still made on clinical grounds. An individual with at least three of the following four criteria is considered to have definite HHT: recurrent epistaxis, multiple characteristic telangiectasias, visceral vascular malformations, and a first-degree relative that meets diagnostic criteria for HHT<sup>11</sup> (Table 2).

Level of Diagnostic Certainty	Number of Criteria Present
Unlikely	$\leq 1$
Possible	2
Definite	$\geq 3$

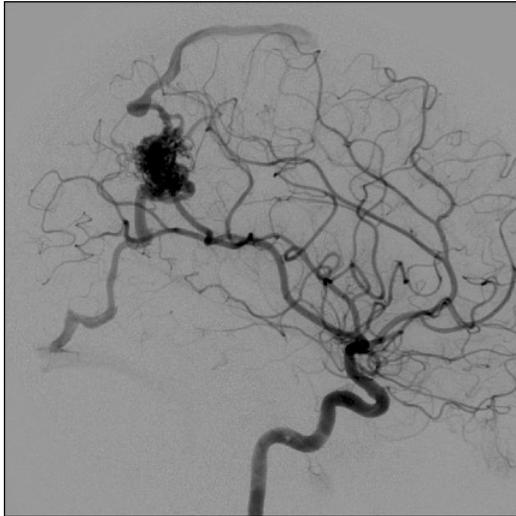
**Table 2. Clinical Diagnostic Criteria for HHT.** The level of diagnostic certainty of HHT is determined by the presence or absence of four clinical features known as the Curacao criteria: recurrent spontaneous nose bleeding, multiple characteristic mucocutaneous telangiectasia, visceral vascular anomalies, and any first degree relative meeting these criteria.

Genetic testing alone is not sufficient to establish a diagnosis of HHT because individuals with mutations in causative genes that have not yet been identified will have negative genetic testing. In addition, polymorphisms in endoglin or ACVRL1 may not represent causative mutations, limiting genetic testing as a definitive diagnostic tool. Instead genetic testing is best used to screen family members of HHT patients who carry known causative mutations. In that setting, a negative genetic test allows an individual to avoid extensive clinical screening, which is costly and often anxiety provoking.

## Clinical Manifestations

The clinical manifestations of HHT can vary significantly from one patient to another even in the same family, depending on which and to what extent various tissues are affected. **Recurrent epistaxis** is the most commonly observed symptom and can range from occasional nosebleeds to frequent epistaxis resulting in symptomatic anemia and, rarely, life-threatening hemorrhage. The average age of epistaxis onset is around age 12 but can present much earlier. It

is estimated that nearly 100% of HHT patients will have experienced abnormal recurrent epistaxis by age 40.



Various **cerebral vascular malformations** (CVMs) can occur in patients with HHT. Overall, CVMs are identified in up to 25% of patients with HHT and are classified based on morphology, but many of these will have a benign course. Large cerebral AVMs and high flow pial fistulae are at the highest risk of hemorrhage but are fortunately not seen as commonly as lower risk malformations with less bleeding risk, including micro-AVMs (less than 1 cm) and cerebral capillary telangiectasias. Screening for CVMs is recommended for all patients with HHT so that amenable lesions can be

treated before producing life-threatening or debilitating complications. Large series of sporadic CVMs suggest the risk of spontaneous bleeding approaches 2-4% per year. HHT-related CVMs might be less prone to bleeding than the sporadic variety, around 0.5% per year.

**Gastrointestinal telangiectasias** are present in most patients with HHT, but clinically significant bleeding occurs in less than 10%. GI hemorrhage is more common in past the 5<sup>th</sup> decade of life and can present unique treatment challenges since the GI tract can be diffusely affected, rendering endoscopic intervention less effective. GI blood loss occurs in most instances on top of years of recurrent epistaxis, rapidly depleting iron stores and leading to anemia, if not already present. Telangiectasias affect the entire GI tract but are most commonly observed in the stomach and small bowel.



**Hepatic vascular malformations** are present in most patients with HHT<sup>12</sup>, but they cause symptoms in fewer than 10%. Symptoms typically arise when intra-hepatic shunting exceeds 20% of cardiac output. Three distinct types in intra-hepatic shunting have been described. Specific clinical manifestations depend on which type of shunt predominates. Hepatic artery to hepatic veins shunting leading to high output heart failure is most common, although shunting between portal and hepatic veins has

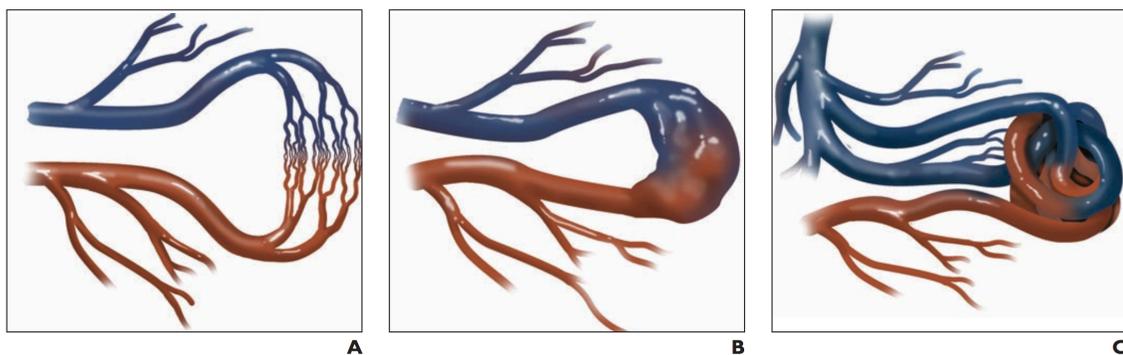
less frequently been implicated. Portal hypertension, biliary necrosis, hepatic encephalopathy, and intestinal ischemia from mesenteric steal have also been reported.

Pulmonary involvement is reported in at least half of patients with HHT and is a source of significant morbidity in this population. Because of their relative frequency and unique complications, the rest of this presentation will focus on the pulmonary vascular manifestations of HHT.

## **Pulmonary Vascular Manifestations of HHT**

### Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) are the most frequently observed pulmonary vascular manifestation of HHT, present in up to 50% of patients with HHT overall and up to 70% of those with causative mutations in the endoglin gene. Less than 20% of PAVMs occur sporadically in patients without HHT, so the presence of PAVMs should prompt an evaluation for HHT. Multiple discrete PAVMs are seen almost exclusively in patients with HHT. Most PAVMs in HHT are composed of a feeding pulmonary artery, a single aneurysmal nidus or sac, and a draining pulmonary vein. Complex AVMs can also occur and include AVMs with multiple feeding arteries and/or draining veins, those with more than one nidus, as well as those whose feeding vessels arise from a systemic rather than pulmonary artery (Figure 2).



**Figure 2.** Diffuse (A), simple (B), and complex (C) pulmonary AVM morphologies, from Trerotola et al., *AJR* 2010; 195:383.<sup>13</sup>

### Screening for PAVMs

Consensus guidelines for the care of patients with HHT recommend screening anyone with possible or confirmed HHT for the presence of PAVMs, both to assist in establishing the diagnostic certainty of HHT and to identify AVMs

amenable to closure. There are several ways to screen for PAVMs. Large AVMs may appear as discreet nodules or masses on routine chest radiograph, but this approach lacks specificity, misses smaller AVMs, and has largely been abandoned as a screening tool for PAVMs.

An elevated shunt fraction (greater than 5%) is present in essentially all patients with PAVMs and can be as high as 60%. An elevated shunt fraction can be used to screen for PAVMs, and it often still is used in pediatric patients because it is relatively non-invasive. To assess shunt fraction patients breathe 100% O<sub>2</sub> for 15-20 minutes through an occlusive mask or a mouthpiece with a nose clip. The most precise measure of shunt fraction requires sampling blood the oxygen content in mixed venous blood and for that reason it is not routinely done. Instead, shunt fraction can be estimated by the following formula:

$$\text{Estimated Shunt Fraction} = \frac{\text{PAO}_2 - \text{PaO}_2}{[(\text{PAO}_2 - \text{PaO}_2) + 1670]}$$

PAO<sub>2</sub> is calculated from the alveolar gas equation:

$$\text{PAO}_2 = \text{FiO}_2 (\text{P}_{\text{atmos}} - \text{P}_{\text{H}_2\text{O}}) - \text{PaCO}_2 / \text{R}$$

There are several sources of error in measuring shunt fraction beyond the inherent limitations of the non-invasive estimation. In particular, even small air leaks in the system can result in a marked reduction in PaO<sub>2</sub> giving the false appearance of an elevated shunt fraction. These limitations notwithstanding, in a patient with otherwise normal gas exchange at sea level, a PaO<sub>2</sub> lower than 575 mmHg would equate to a shunt fraction of greater than 5%. A less specific approach uses cutoffs of room air PaO<sub>2</sub> > 90 mmHg and SaO<sub>2</sub> > 96.5% to exclude significant right-to-left shunting; however, it is not possible to know if lower values are due to problems with V/Q mismatch or shunt since the room air approach cannot differentiate shunting from other sources of hypoxemia.

Shunt Grade	Number of micro-bubbles	PPV
0	0	NA
1	< 30	0 – 0.02
2	30 - 99	0 – 0.25
3	≥ 100	0.8 – 1.0
4	≥ 100 with endocardial definition	1.0

**Table 3.** Intrapulmonary shunt grade and positive predictive value for PAVM on CT angiogram.

Contrast echocardiography has largely replaced assessments of shunt fraction as the initial screening modality in adult patients suspected of having PAVMs. The most frequently employed contrast agent when screening for intrapulmonary

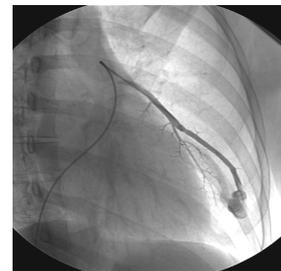
shunting is agitated saline. The appearance of bubbles in the left ventricle indicates right-to-left shunting but cannot by itself distinguish intra-cardiac from intr-pulmonary shunts. A delay of 3-4 cardiac cycles before visualization of bubbles in the LV is suggestive of extra-cardiac shunting. Intra-pulmonary shunting is further suggested by the appearance of bubbles in the pulmonary veins prior to entering the LV. Numerous schemes have been proposed to grade the extent of intrapulmonary shunting, but the most commonly used system grades shunts from 0 to 4 based on the maximum number of bubbles visualized in the LV on a single still frame<sup>14</sup> (Table 3). In most series, grade 0 and grade 1 intrapulmonary shunts were not associated with detectable PAVMs on CT chest angiogram. The data regarding grade 2 shunts is more variable, with positive predictive values ranging from 0 to 0.25 depending on the study. Higher-grade shunts are nearly always associated with PAVMs on subsequent CT chest. On the basis of these data, grade 3 or 4 shunts are investigated further with CTA or pulmonary angiogram to identify PAVMs amenable to embolization, whereas grade 0 - 1 shunts can generally be followed with another contrast echo in 3 – 5 years. What to do with a grade 2 shunt is less certain. Our practice is to image the chest to better assess grade 2 or larger shunts seen on echo because of the seriousness of the potential complications related to untreated PAVMs.



CT chest angiogram is currently the gold standard for diagnosing PAVMs following positive screening contrast echocardiogram. However, the absence of a PAVM on CT does not definitively exclude the presence of PAVMs since some proportion of HHT patients will have diffuse micro-AVMs or multiple small discrete AVMs that may not be detected on CT yet could produce significant intrapulmonary shunting. Furthermore, AVMs with systemic artery to pulmonary vein communications may not be clearly seen if

contrast administration is timed to assess the pulmonary artery circulation, and since these AVMs result in left-to-left shunting, they will also not be detected by contrast echocardiography.

Pulmonary angiography does not have superior resolution compared to CT angiography for detecting PAVMs, and for that reason and because angiography is more invasive than contrast CT, it is not used routinely for diagnosing PAVMs in HHT. Instead, pulmonary angiography is performed in the process of therapeutic embolization of amenable AVMs, or when unusual AVM anatomy confounds evaluation by CT.



## Clinical Manifestations of PAVMs

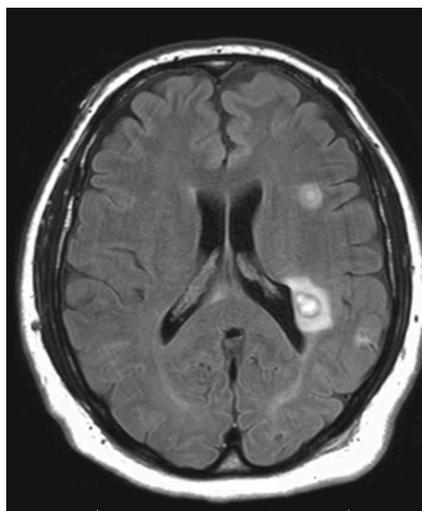
### Hypoxemia

Even in the presence of significant shunting, hypoxemia is relatively uncommon with HHT-associated PAVMs, affecting around 15% of patients. Dyspnea in this setting is also uncommon even in the face of severe hypoxemia (resting SpO<sub>2</sub> < 85%). Orthodeoxia is present in many of these patients, but despite the commonly held belief, platypnea is extremely rare. In one series of 250 patients with PAVMs, none of the 75 patients who exhibited orthodeoxia reported platypnea<sup>15</sup>. Diffuse PAVMs may be associated with more pronounced hypoxemia compared to multiple discreet PAVMs, posing a therapeutic challenge since diffuse PAVMs cannot be readily embolized. Fortunately, most of these patients remain asymptomatic for years and are highly functional despite the hypoxemia. Cyanosis and clubbing have been described in hypoxemic HHT patients but are not commonly seen.

### Paradoxical Embolic Complications

In addition to its role in gas exchange, a major role of the pulmonary artery circulation is to filter the blood that passes through it of thrombi and microbes. PAVMs allow these particles to bypass pulmonary capillary filtration and place patients at risk of paradoxical embolic complications, most commonly migraine headaches, embolic stroke, or cerebral abscess. The majority of embolic strokes and cerebral abscesses occur in patients prior to receiving a diagnosis of HHT, and in many cases the diagnosis is delayed even after the embolic event.

**Brain abscess** can result when transient bacteremia results in transit of microorganisms across PAVMs and into the systemic circulation. The risk is significant - patients with HHT and PAVMs are 400-fold more likely to develop a brain abscess compared to the general population, affecting an estimated 10% of such patients. Periodontal microbes cause most brain abscesses. The most commonly identified risk factor is preceding dental procedure, including routine dental cleaning. Poor dental hygiene also increases risk, and in some cases a precipitating event cannot be identified. The significant morbidity and mortality associated with brain abscess justify preventive measures. All patients with PAVMs and any HHT patients who have not been screened for PAVMs should receive prophylactic



antibiotics prior to non-sterile procedures. Once identified, amenable PAVMs should be closed to reduce embolic risk.

**Embolic stroke** is also common in HHT patients with PAVMs. As many as 25% of patients with PAVMs will experience clinical stroke by age 65, and over half of patients with PAVMs will have cortical or subcortical infarcts on brain imaging. Transient ischemic attacks (TIA) occur even more commonly. And emboli to other organs have been reported, including cases of paradoxical emboli to coronary arteries resulting in acute myocardial infarction<sup>16</sup>. The risk of paradoxical thromboembolic complications can be significantly reduced by closure of PAVMs<sup>17</sup>.

Many patients with HHT also suffer from **migraine headaches**<sup>18</sup>. Several lines of evidence support an association between migraines, especially those with aura, and shunting through PAVMs including the observation that migraines often abate after AVM closure<sup>19</sup>. Transit of micro-thrombi through PAVMs has been implicated in the pathogenesis of these migraines, supported by the observations that patients are more likely to manifest evidence of TIA or subclinical infarct on imaging<sup>20</sup>, symptoms often improve after PAVMs are closed, and, in other types of right-to-left shunt, migraine frequency can be reduced with the administration of anti-platelet agents<sup>21</sup>.

### Hemorrhagic Complications

Spontaneous rupture of pulmonary arteriovenous malformations can result in massive hemoptysis or, in the case of subpleural AVMs, hemothorax. The frequency of spontaneous PAVM rupture has not been definitively established. In one large series, 8% of patients with PAVMs experienced massive hemoptysis or hemothorax<sup>22</sup>. All of the patients in that series had been referred for PAVM embolotherapy suggesting that they had larger AVMs amenable to transcatheter embolization, so it is reasonable to infer that far less than 8% of all PAVMs will experience spontaneous AVM rupture when smaller AVMs are taken into consideration. Anecdotally, among the more than 300 patients followed in the UT Southwestern HHT Center, only one has experienced an AVM-related hemothorax and none have experienced massive hemoptysis. Instead, it seems that clinically silent, contained hemorrhage around smaller PAVMs may be relatively common, while massive hemoptysis occurs less commonly. Risk of spontaneous rupture increases with larger AVMs and those with systemic arterial supply, usually from the bronchial artery, rather than relatively low-pressure pulmonary artery circulation.

Pregnancy represents a special circumstance in which pulmonary hemorrhage with massive hemoptysis is well described and has been associated with increased maternal mortality. In the series referenced above, nearly half of the

patients who experienced massive hemoptysis from spontaneous rupture of PAVMs were pregnant<sup>22</sup>. In a more recent series of pregnant patients with HHT, between 1 and 2% experienced PAVM rupture<sup>23</sup>. Current recommendations advise screening patients of childbearing potential for treatable PAVMs prior to becoming pregnant. Treatment of asymptomatic PAVMs is not recommended during pregnancy due to concern of fetal radiation and contrast exposure. When hemoptysis occurs during pregnancy, PAVMs should be closed without delay to prevent catastrophic complications. Fortunately, in most reported cases of PAVM rupture during pregnancy sentinel symptoms are present prior to the development of life-threatening hemorrhage, allowing the opportunity for definitive treatment.

### **Pulmonary Hypertension in HHT**

Patients with HHT are at increased risk of pulmonary hypertension (PH). Most cases of PH in HHT result from high output heart failure due to shunting through liver AVMs, although systemic shunting outside the liver has also been rarely implicated. High output heart failure typically presents in the seventh decade with nonspecific symptoms such as exertional dyspnea and lower extremity edema<sup>24</sup> and tends to affect females more than males. However, in the presence of extensive intra-hepatic shunting, high output heart failure can present much earlier. Hepatic artery to hepatic vein shunts behave similarly to other extra-cardiac left-to-right shunts. Increased cardiac preload and decreased systemic vascular resistance are met with a compensatory increase in cardiac output via increases in both stroke volume and heart rate. As the high output state persists, left ventricular filling pressures increase and secondary pulmonary hypertension follows<sup>25</sup>. Right heart catheterization demonstrating increased pulmonary artery pressures with high cardiac output and elevated pulmonary artery and capillary wedge pressures confirms the diagnosis in the presence of sufficient intrahepatic shunting. Pulmonary vascular resistance (PVR) is typically normal.

Patients with HHT will less commonly manifest a familial pulmonary arterial hypertension (PAH) syndrome. Most cases of familial transmission of PAH in patients with HHT are attributed to mutations in bone morphogenetic protein 2 (BMP2), another member of the TGF- $\beta$  superfamily of receptors, but nearly 30% of cases of familial PAH occur in the absence of mutations in BMP2. Mutations in the HHT-causative genes ACVRL1 and, to a lesser extent, endoglin have been implicated in many of these cases. PAH in these patients is clinically and histologically identical to PAH associated with BMP2 mutations, except that most of these patients will manifest symptoms of HHT in addition to PAH, presenting unique challenges. Fortunately, this is very rare, estimated to affect less than 1% of patients with HHT. But because of the significant morbidity and

mortality associated with PAH, any HHT patient with evidence of PH on screening echo should undergo a thorough evaluation for PAH.

### **Managing Pulmonary Vascular Manifestations of HHT**

Disrupting blood flow through PAVMs reduces the risk of both hemorrhagic and embolic complications. Until the 1970s this was accomplished through surgical resection of PAVMs. Resection was generally reserved for cases where complications had arisen or were felt to be imminent, although many surgeons advocated preventive resection for large AVMs. Presently, surgical resection is rarely pursued except in unusual circumstances or when an AVM is mistaken for a neoplastic mass or nodule. Lung transplantation has been performed on patients with diffuse PAVMs not amenable to other therapies, but that practice has largely been abandoned. Even severely hypoxemic patients may remain stable for decades, significantly longer than would be expected following lung transplantation. In one series of 821 patients with PAVMs, 36 had diffuse AVMs resulting in significant hypoxemia. Of those, only one patient was referred for lung transplantation and died during the operation<sup>26</sup>.

Nonsurgical disruption via transcatheter embolization is now standard therapy for PAVMs. The first reported case of successful embolotherapy of a PAVM was published in the mid-1970s using metal coils fashioned by the operator specifically for the procedure. An early concern focused on the risk of the occluding device transiting the AVM into the systemic circulation, with catastrophic potential. To mitigate that risk, steel coils and/or nylon brushes were attached to baffles, but instances of systemic embolization still occurred. In some reports surgical silk was added to complete the occlusion. Detachable silicone and latex balloons have also been used as occluding devices but have fallen out of favor.

Embolization techniques and devices have evolved significantly since then. MR-compatible steel, platinum or titanium coils, with attached synthetic fibers to promote clot formation and maximize occlusion, became the preferred occlusion devices and are still used in some cases today. These metallic coils must be deployed with particular care, typically at the most distal feasible position adjacent to the AVM nidus to avoid occluding proximal pulmonary artery branches. However, the benefits of distal coil placement, especially in larger vessels, must be balanced against the increased risk of migration across the AVM into the systemic circulation, so expertise in performing the procedure and proper device selection are critical. Coils that are too small may embolize across the AVM; large coils may not fully retract once deployed, preventing effective vessel occlusion.

Vascular plugs have largely replaced metal coils for PAVM embolotherapy. Amplatzer vascular plugs are particularly suited to occlusion of high flow vessels. The plugs consist of nitinol mesh that can be deployed directly adjacent to the AVM sac, where it expands and anchors in place with less risk of systemic migration. Vascular plugs have several advantages over metal coils. Successful occlusion can often be achieved with a single plug, shortening procedure duration. Plugs are also capable of safely and effectively occluding even very small feeding vessels with low risk of systemic embolization<sup>27</sup> in part because stable positioning within the vessel can be confirmed prior to detaching the plug.

Current practice guidelines recommend closure of PAVMs with feeding vessels  $\geq$  3 mm diameter. Doing so reduces paradoxical embolic and hemorrhagic complications associated with untreated AVMs. These guidelines are likely to soon change - most HHT Centers including ours will now treat smaller AVMs with feeding arteries  $\geq$  2 mm.

While effective, transcatheter embolotherapy has certain limitations. PAVMs with feeding vessels smaller than 2 mm are difficult or impossible to treat yet still pose a risk of embolic complications. In addition, up to  $\frac{1}{4}$  of treated vessels will demonstrate reperfusion on follow up imaging, requiring re-treatment. The vast majority that reperfuse do so via recanalization of the occluded feeding vessel; however, around 12-15% will reperfuse via collateral circulation, usually from an adjacent pulmonary artery branch. In rare instances, systemic arteries will perfuse previously embolized PAVMs. When that occurs, CT scans timed for contrast to fill the pulmonary artery circulation may not demonstrate reperfusion.

Outcomes following transcatheter embolization of pulmonary AVMs are favorable. The procedure can be completed as an outpatient, and, with newer devices and techniques, complications are rare. It is generally accepted that the procedure significantly reduces the risk of embolic and hemorrhagic complications related to PAVMs, but exactly how much is not known since a controlled study is not ethically feasible or appropriate. Regardless, plenty of observational data supports the effectiveness of PAVM closure, including one study in which no patient with successfully treated PAVMs experienced embolic stroke or brain abscess<sup>17</sup>.

## **Conclusions**

HHT is genetic disorder of blood vessel formation that affects more people than most clinicians realize. Of the various clinical manifestations of HHT, pulmonary vascular complications are among the most common and potentially serious, ranging from asymptomatic hypoxemia to pulmonary hypertension to potentially fatal embolic and hemorrhagic complications. Transcatheter embolization of

PAVMs is effective at reducing embolic and hemorrhagic complications, but unfortunately, most patients who experience complications do so before being diagnosed with HHT. Increased awareness of HHT and its manifestations will hopefully lead to earlier diagnosis and treatments to prevent these serious complications.

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