SERIES "PULMONARY HYPERTENSION: BASIC CONCEPTS FOR PRACTICAL MANAGEMENT"
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The pulmonary vascular complications of hereditary haemorrhagic telangiectasia

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ABSTRACT: Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder, characterised by the presence of vascular malformations. The pulmonary vascular complications of HHT include pulmonary arteriovenous malformations, pulmonary hypertension associated with high-output heart failure and liver vascular malformations and, finally, pulmonary arterial hypertension secondary to HHT. In the present review, the authors describe the clinical presentation, diagnosis and management of all three pulmonary vascular presentations of HHT, as well as the underlying genetics and pathophysiology.

KEYWORDS: Hereditary haemorrhagic telangiectasia, pulmonary arterial hypertension, pulmonary arteriovenous malformation, pulmonary hypertension

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Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder, with an estimated prevalence of 1 in 5000, characterised by vascular malformations in the nose, mouth, brain, lungs, liver and gastro-intestinal (GI) tract, as well as on the skin. Pulmonary vascular complications of HHT are frequent and varied in presentation. Pulmonary arteriovenous malformations (PAVMs) are the most frequent complication, occurring in 15–45% of HHT patients, and can be treated preventatively. Pulmonary hypertension (PH) is a recognised complication of liver vascular malformations (VMs) associated with high cardiac output, in HHT. PH can also occur in HHT patients without liver VMs, albeit more rarely, mimicking idiopathic pulmonary arterial hypertension (PAH). The clinical, molecular and pathophysiological aspects of all three pulmonary vascular presentations of HHT will be described.

The present review is part of a series of articles summarising the latest developments in pulmonary vascular disease [1], including reviews to date of current therapies for PAH [2–4] and of PH secondary to interstitial lung disease [5].

PULMONARY ARTERIOVENOUS MALFORMATIONS
Clinical presentation and pathophysiology
PAVMs are present in 15–45% of patients with HHT [6, 7] and HHT is the underlying cause in at least 80% of PAVMs. The prevalence of PAVMs appears to be higher in patients with endoglin mutation, in the range of 49–75%, compared with 5–44% in patients with activin receptor-like kinase (ALK)-1 mutation [8–10]. Families with endoglin mutation also have a higher prevalence of cerebral arteriovenous malformations (AVMs) than those with ALK-1 mutation [9, 10]. PAVMs are also reported in the small number of families with SMAD4 mutation, characteristic of the combined juvenile polyposis and HHT syndrome [11], but also found in approximately 3% of HHT families [12]. Basic research has uncovered alterations in transforming growth factor (TGF)-β signalling, endothelial nitric oxide synthase activity and angiogenesis in HHT in recent years [13–16].

Previous articles in this series: **No. 1:** Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 407–415. **No. 2:** Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 891–901. **No. 3:** Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; 31: 1357–1367. **No. 4:** Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008; 32: 198–209. **No. 5:** Warwick G, Thomas PS, Yates DH. Biomarkers in pulmonary hypertension. *Eur Respir J* 2008; 32: 503–512. **No. 6:** Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385. **No. 7:** Montani D, Price LC, Dorfmuller P, *et al.* Pulmonary veno-occlusive disease. *Eur Respir J* 2009; 33: 189–200.

However, the exact cell biological mechanisms of how endoglin, ALK-1 or SMAD4 mutations actually lead to the development of AVMs remain uncertain.

Adults with untreated PAVMs are at risk of life-threatening haemorrhage and of neurological complications. In the larger series to date [17–20], previous stroke is reported in 10–36%, transient ischaemic attack in 6–37%, cerebral abscess in 8–19% and massive haemoptysis or spontaneous haemothorax in 4–20% of patients. Similar complications occur in children [21–23], although the rates are uncertain because of the smaller size of paediatric series and their inclusion of more severe cases with diffuse PAVMs.

The haemorrhagic complications of PAVMs can be life-threatening, and the risk may be increased during pregnancy [24, 25], possibly due to increased cardiac output or due to changes in PAVM wall stability. Transient ischaemic attack and stroke are presumed to result from the paradoxical embolisation of asymptomatic leg vein thrombus though PAVMs to the left-sided arterial circulation. Alternatively, the thrombus can occasionally originate *in situ* in PAVMs, embolising to the left-sided circulation. Although patients with HHT are not clearly at increased risk of venous thromboembolism, those patients that do develop venous thromboembolism appear to have higher factor VIII levels [26]. Multiplicity of PAVMs has been associated with a higher risk of previous stroke in HHT patients [20]. Cerebral abscess presumably occurs secondary to paradoxical embolisation of bio-films of bacteria. The pathogens are often from an oral source [27] and the risk may be highest following dental procedures. Male sex and hypoxaemia also appear to increase the risk of cerebral abscess in patients with PAVMs [27]. PAVMs are also associated with migraine [28], particularly with aura [29], in HHT patients. There are no prospective cohort studies to precisely define the natural history of untreated PAVMs. Since experts believe that a ''no treatment arm'' would be unethical, our understanding of the complications of PAVMs are limited to these retrospective studies.

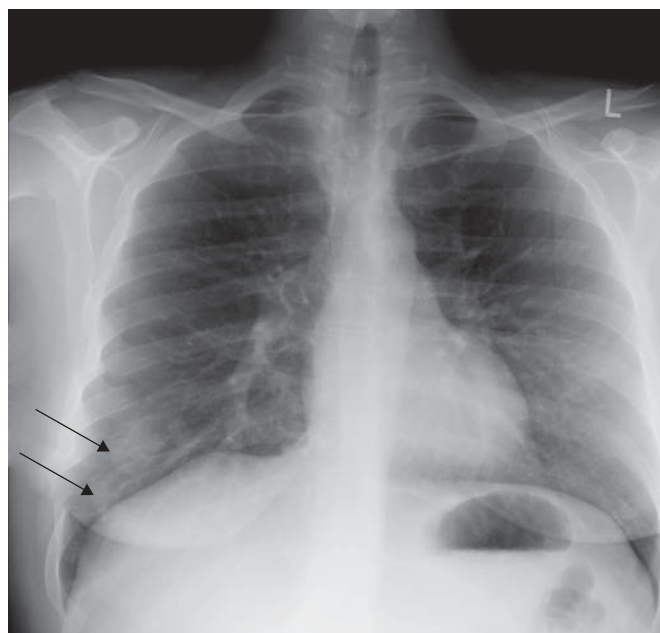PAVMs in HHT are usually multiple (mean of three per patient) [30]. In approximately 5% of cases, PAVMs are diffuse and innumerable [31, 32] and present special problems because of the difficulty in treating them. Approximately 80% of PAVMs in HHT are simple fistulas [33] with one or more feeding arteries. The remainder are complex, with feeding arteries from more than one segment and/or a septated or nidus-like structure. Figure 1 demonstrates typical lip and tongue telangiectasias and figures 2 and 3 demonstrate PAVMs, in a typical HHT family.

Clinical evaluation

Given the serious nature of the complications that can occur from untreated PAVMs, and the availability of safe and effective preventative therapy, most authors have recommended routine screening of all HHT patients for PAVMs [34]. The classical findings of PAVMs are cyanosis, clubbing and a pulmonary bruit. Although these findings are highly indicative of PAVMs, they are found in <10% of HHT patients with PAVMs, so that clinical screening is clearly insufficient for detecting PAVMs in most HHT patients. Contrast echocardiography is the screening test of choice, with a sensitivity of >90% [7, 35] for detection of PAVMs in HHT patients. It involves no radiation exposure and is much more sensitive than oxygen shunt testing, oximetry, or chest radiography. Computed tomography (CT) thorax is the current accepted diagnostic gold standard [22] and is used to confirm and measure the size of PAVMs in patients with positive contrast echocardiography. Standard pulmonary angiography has a lower resolution than current multidetector CT and is not performed as an initial diagnostic procedure. It is important to note that, with current multidetector CT technology, contrast enhancement is not required to detect even small PAVMs [30].

Treatment

Transcatheter embolotherapy is the current standard treatment for PAVMs. There is no longer any role for surgery in

FIGURE 1. Typical telangiectasias in a 50-yr-old male with hereditary haemorrhagic telangiectasia (endoglin mutation), who also has pulmonary arteriovenous malformations.

FIGURE 2. Chest radiograph of the 26-yr-old daughter of the patient shown in figure 1, demonstrating two pulmonary arteriovenous malformations in the right lung (arrows). L: left side.
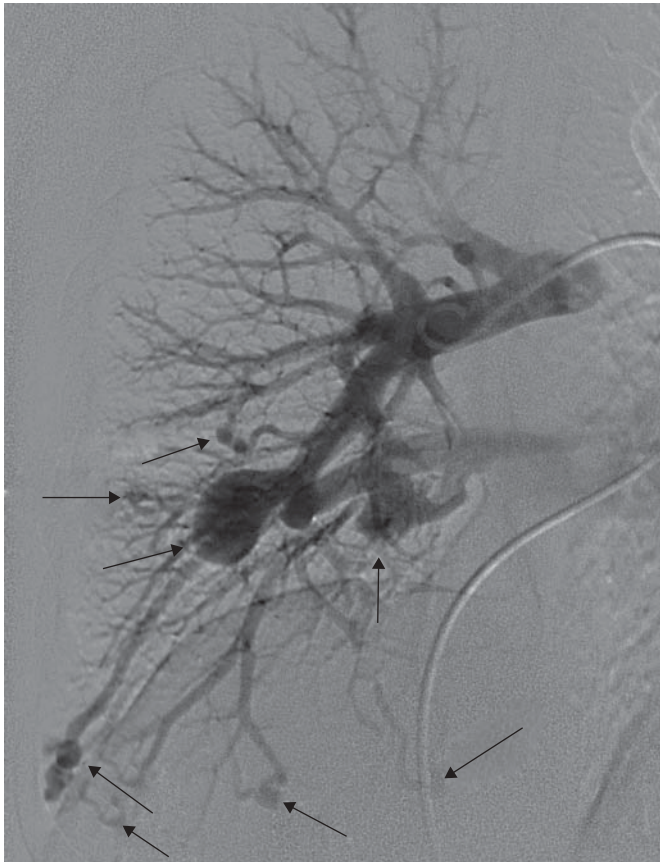
FIGURE 3. Right pulmonary angiogram of the same 26-yr-old patient as in figure 2, demonstrating multiple pulmonary arteriovenous malformations of variable size (arrows).

managing PAVMs. There have been several long-term, although uncontrolled, series demonstrating excellent procedural success (close to 100%) and long-term efficacy (>83%) for occlusion of PAVMs [18, 19, 36]. The most common complication of embolisation is pleuritic chest pain [18, 19, 36], which is most often self-limited. There is a <1% rate of paradoxical device embolisation [18, 19, 36], with distal complications occurring only very rarely. In the studies with at least 5 yrs follow-up, long-term complications from PAVMs were rare. When they occurred, complications were typically associated with residual significant (at least 3-mm) untreated PAVMs or reperfused PAVMs [30]. A feeding artery of at least 3 mm is currently the threshold for treatment of PAVMs, in most centres, as most complications of untreated PAVMs have been described in patients with a feeding artery of at least 3 mm [18], although some centres consider embolisation of smaller PAVMs. Since the reperfusion rate of PAVMs is approximately 10–17% [19, 30], early and long-term follow-up are essential to detect PAVMs that need repeat embolisation. In addition, approximately 50% of patients have small detectable residual PAVMs [37], which should be followed and embolised when significant. Most authors recommend a minimum follow-up with CT at 1 yr and every 3–5 yrs thereafter [19, 30, 37]. It is important to note that the efficacy and safety data are all reported from centres with considerable expertise in PAVM embolotherapy. Thus, the efficacy and safety of these

procedures may be less optimal in less experienced centres and, generally, patients should be referred to centres with substantial experience.

Certain precautions are also recommended to patients with PAVMs, even once they are embolised. Antibiotic prophylaxis for bacteraemic procedures continues to be routinely recommended to prevent cerebral abscess [6]. This is important as this complication does not seem to correlate with the feeding artery diameter of PAVMs and can occur even in patients with only <3-mm feeding arteries. In addition, use of intravenous air filters are typically recommended to prevent transient ischaemic attack from air embolism during *i.v.* infusions. Patients are also recommended to avoid SCUBA diving [37].

PULMONARY HYPERTENSION
In the context of HHT, it is important to recognise that PH may be categorised into two very distinct types (table 1). Most commonly, PH occurs in association with liver VMs, secondary to the high cardiac output, typically after the onset of left heart failure. These patients usually have mildly elevated left atrial pressures and low pulmonary vascular resistance (PVR). Less commonly, patients have elevated pulmonary artery pressures, normal left atrial pressure, normal or reduced cardiac output and significantly increased PVR. These latter patients have PAH and have a true pulmonary arteriopathy (see later section). The key differentiating variable is the transpulmonary gradient (TPG; mean pulmonary artery pressure ($\bar{P}$pa) minus an estimate of left atrial pressure; normally <12 mmHg). The TPG is normal in the high-output cardiac failure-related PH but increased in patients with PAH.

PH and high-output heart failure
In patients with HHT, PH most often results from the high pulmonary blood flow and left heart failure that accompanies the high cardiac output state associated with liver VMs. Mutations in the ALK-1 gene are typically present in these patients, although cases of liver VMs in HHT due to endoglin mutations have also been reported [8, 9, 38]. Liver VMs are detected in as many as 40–75% of patients with HHT using sensitive imaging techniques (fig. 4) [39, 40], but most are small and do not lead to symptoms. However, more significant liver VMs do cause symptoms in 5–8% of patients with HHT

TABLE 1	Haemodynamic profiles in patients with hereditary haemorrhagic telangiectasia and pulmonary hypertension (PH)				
Profile	$\bar{P}$pa	CO	PAOP	TPG	PVR
PH, high flow, LV failure	↑	↑↑	High-normal or ↑	Normal	Normal
PAH	↑↑	↓	Normal	↑	↑↑

$\bar{P}$pa: mean pulmonary arterial pressure; CO: cardiac output; PAOP: pulmonary artery occlusion pressure; TPG: transpulmonary gradient; PVR: pulmonary vascular resistance; LV: left ventricular; PAH: pulmonary arterial hypertension; ↑: increase; ↑↑: large increase; ↓: decrease.

FIGURE 4. Gadolinium-enhanced T1-weighted magnetic resonance image of diffuse liver vascular malformations. There is evidence of diffuse telangiectasia and confluent vascular malformations (arrows). In addition, this arterial phase image shows early enhancement of the hepatic veins, compatible with hepatic artery to hepatic vein shunting.

FIGURE 5. Pathophysiology of pulmonary hypertension in patients with hereditary haemorrhagic telangiectasia and liver vascular malformations. LA: left atrial; RV: right ventricle.

[41–43]. Most commonly, these patients have exertional dyspnoea and fatigue, palpitations and peripheral oedema related to high-output cardiac failure [41, 42].

Liver VMs are associated less commonly with a variety of other symptoms. Shunting of blood from the hepatic artery to veins causes steal syndromes with abdominal pain from either biliary or mesenteric ischaemia [41–43]. Communications between the hepatic artery and portal veins can result in portal hypertension with gastrointestinal bleeding or ascites [41, 42]. Portal vein to hepatic vein shunts predispose to hepatic encephalopathy manifested by confusion and asterixis [41, 42]. CT scanning generally identifies these vascular abnormalities, but does not specifically predict the predominant clinical manifestations in individual patients [44]. Although most patients initially manifest one symptom type, clinical overlap can occur with the development of biliary ischaemia or hepatic encephalopathy in heart failure patients [41].

The most common clinical manifestation of liver VMs is high-output heart failure [45], accounting for over 80% of patients in larger series [41, 42, 45]. For unknown reasons, heart failure occurs much more commonly in females than in males [41]. Patients often develop symptoms of heart failure in their seventh decade of life, although symptoms can develop in females during pregnancy [46]. Heart failure occurs in patients with two- to three-fold elevations in cardiac output due to elevated hepatic blood flow, which can approach 5–10 L·min^{-1} [41]. Shunting of blood through the liver sometimes results in the oxygen content of hepatic venous blood approaching that of arterial blood. A large step-up between the mid inferior vena cava and right atrium is often present and indicates significant hepatic artery to vein shunting. The high flow through the liver also results in elevated central mixed venous saturations that mimic those seen with atrial septal defects and other large intra-cardiac left-to-right shunts.
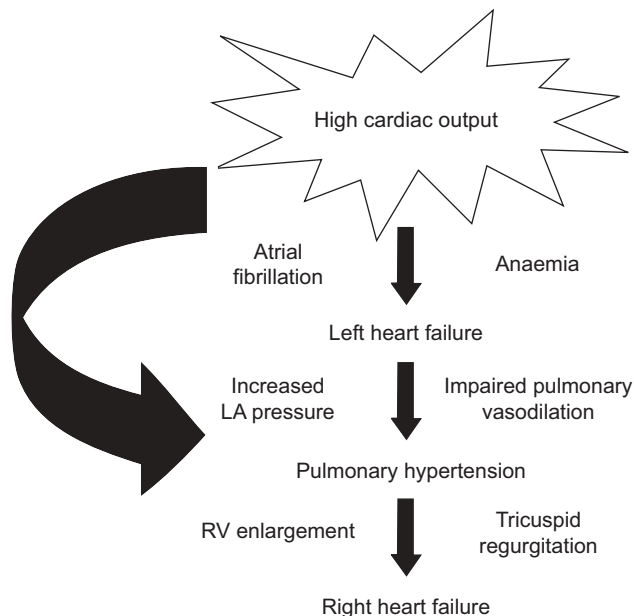
Pathophysiology

In healthy patients with liver VMs and high cardiac output, the pulmonary vasculature dilates adequately to maintain normal pulmonary artery pressures. The mechanisms responsible for the development of left ventricular failure and PH in patients with high cardiac output are outlined in figure 5. PH most often occurs in patients with liver VMs from the high pulmonary blood flow in combination with an elevation in pulmonary venous pressure from left ventricular failure [41]. Importantly, left ventricular failure occurs in patients with liver VMs in the absence of overt left ventricular systolic dysfunction [41]. Elevation in pulmonary capillary wedge pressures [41] reflects the combination of high pulmonary venous flow and left ventricular diastolic dysfunction.

Symptoms of heart failure are often precipitated by the development of atrial fibrillation or severe anaemia [41]. Patients with liver VMs and high cardiac output are predisposed to atrial fibrillation, because they often have left atrial enlargement. The loss of atrial contraction with the onset of atrial fibrillation impairs ventricular filling and triggers haemodynamic decompensation in susceptible patients. Severe anaemia also reduces systemic oxygen delivery and exacerbates the symptoms of heart failure [42]. The extent to which remodelling of the pulmonary vasculature also occurs with chronic high flow from liver VMs is uncertain. Nonetheless, once pulmonary arterial pressures are elevated, the combination of volume and pressure overload potentially strains the right ventricle (RV) leading to right ventricular enlargement and contractile dysfunction, secondary tricuspid regurgitation and right heart failure [41–43].

Evaluation of high-output heart failure

PH is often detected first by echocardiography during the evaluation of patients with HHT who are experiencing

exertional dyspnoea. Such patients should always undergo evaluation for liver VMs, since high cardiac output is the most common cause of PH in HHT and is potentially improved with therapy. In most cases, clinical features readily distinguish PH associated with high-output heart failure from PAH associated with HHT. In high-output heart failure, bedside evaluation typically reveals a wide arterial pulse pressure with a low diastolic pressure due to the reduced systemic vascular resistance with rapid run-off of the cardiac stroke volume through the liver VMs [42]. Pulses are bounding, the precordium is active and a systolic ejection murmur is readily detected at the left sternal border [41]. Auscultation of the abdomen generally reveals a hepatic bruit and the liver is often pulsatile. Thus, the triad of a wide arterial pulse pressure, systolic murmur and liver bruit is virtually diagnostic for liver VMs with high output in patients with HHT.

Doppler echocardiography is a useful diagnostic tool in patients with suspected high-output cardiac failure and secondary PH. Although left ventricular systolic function is normal, left ventricle size is at the upper limits of normal and left atrial enlargement is almost always present. Doppler flow velocities in the left ventricular outflow track and aortic valve are often elevated, sometimes incorrectly interpreted as suggestive of aortic stenosis. The right ventricular findings vary according to the severity and duration of disease. Early in the disease, the RV appears normal, but later the RV enlarges. In patients with significant PH the RV can develop contractile dysfunction and tricuspid regurgitation. In patients with PH, the Doppler-derived measurement of the tricuspid regurgitant jet provides a reasonable estimate of peak RV and pulmonary arterial systolic pressure. The development of a D-shaped septum is an ominous sign, but is much less common than in patients with PAH.

Right heart catheterisation is the gold standard for the diagnosis of PH associated with liver VMs [41, 47]. High cardiac output, elevated pulmonary capillary wedge pressures and a normal PVR readily distinguish high-output failure from patients with PAH (table 1). Specifically, PVR is typically normal even in the presence of moderate PH. In patients with more advanced disease, or those who have been treated with diuretics, the right heart catheterisation findings are often less typical and more difficult to interpret. Diuretics lower pulmonary capillary wedge pressures, but the cardiac output remains elevated and the PVR is often still low or normal.

Treatment
Treatment of high cardiac output failure in patients with liver VMs is directed at the treatment of left heart failure, anaemia and atrial fibrillation [41, 42]. Aggressive treatment with diuretics is a mainstay of treatment in that it reduces the pulmonary venous pressures and often significantly lowers the pulmonary artery pressures. Correction of severe anaemia is essential to minimise the stress on the heart [41] and many patients are considerably less symptomatic when the haemoglobin concentration is maintained greater than 10 g·dL^{-1}. Since iron deficiency often results from recurrent epistaxis or gastrointestinal bleeding from telangiectasias, aggressive iron replacement and sometimes blood transfusion are required. In patients with atrial fibrillation, an aggressive approach to

cardioversion and the subsequent maintenance of sinus rhythm with anti-arrhythmic therapy should be considered.

The utility of pulmonary vasodilators in the treatment of PH associated with liver VMs is uncertain. There are important theoretical concerns that any systemic vasodilatation would have adverse consequences on left heart failure. Thus, the use of pulmonary vasodilators should be limited to patients with PAH (see later section) [48].

Surgical hepatic artery ligation [49] and percutaneous hepatic artery embolisation [50] have been used at some centres for the treatment of liver VMs. However, these interventions can lead to the development of biliary ischaemia and in some cases serious hepatic necrosis [41, 42]. Thus, sub-selective hepatic artery embolisation is reserved only for highly selected patients who have failed medical therapy and who are not considered candidates for liver transplantation [42, 47]. Liver transplantation has been used for highly symptomatic individuals with high-output heart failure due to extensive liver VMs [51, 52]. Excellent success in reducing cardiac output and alleviating symptoms has been reported in some patients. Although patients with severe PH, right ventricular dysfunction or severe tricuspid regurgitation are typically excluded from transplant consideration, those with mild PH, normal PVR, high cardiac output and normal right ventricular function are potentially candidates for transplantation. Due to the inherent risks of surgery and the long-term immunosuppressive therapy after liver transplantation, alternatives for the treatment of high-output failure would be highly desirable. One recent case report raised the possibility that anti-angiogenic therapy with anti-vascular endothelial growth factor antibody (bevacizumab) might be effective in reducing the size of liver VMs and useful in the treatment of patients with high-output heart failure [53]. Additional investigations of the long-term risks and benefits of this approach and of other anti-angiogenic therapies are required.

PAH in HHT
Although rare, PAH is increasingly recognised as a complication of HHT [13, 54]. Symptoms of fatigue and breathlessness are relatively nonspecific and could potentially be related to anaemia, PAVMs or liver VMs in HHT patients. However, the development of unexplained shortness of breath with features indicating right heart pressure or volume overload should prompt evaluation for the presence of PAH.

The exact prevalence of PAH in the population of HHT patients, however, has not been systematically evaluated. In a recent genotype–phenotype study of 111 patients with HHT, no case of PAH was documented [55]. However there did not appear to be a systematic evaluation of each patient, making it difficult to determine how many of that cohort actually underwent echocardiographic screening for PH. In a recent echocardiographic study of 68 patients with PAH, elevated tricuspid regurgitant Doppler velocities indicative of right ventricular systolic pressure was present in nine out of 44 of evaluable patients (24 patients could not have peak pulmonary pressure measured) [56]. Three were family members of a patient with known PAH, one patient had undiagnosed mitral valve disease and others had liver VMs. Echocardiographic estimates of pulmonary pressure are of limited value,

particularly in patients who may have high cardiac output [57]. Invasive haemodynamics were not obtained and consequently the actual prevalence of PAH in the study cohort is not known.

Genetics

Gene mutations have been described in some cases of PAH. Mutations in the bone morphogenetic protein receptor (BMPR) type II are responsible for the majority of patients with familial PAH and occasionally for sporadic forms of the disease [58]. Haploinsufficiency for BMPR-II is felt to be the predominant molecular mechanism underlying the familial predisposition to PH [59]. The prevalence of mutations or polymorphisms in the BMPR-II gene in the general population is probably very low. However, in kindred studies of patients with PAH, the presence of a BMPR-II mutation confers an increased, but not absolute, risk of developing PAH. To this end it has been proposed that a "two-hit" phenomenon is required in "at risk" individuals before PAH becomes manifest [60]. In the presence of a BMPR-II mutation, however, PAH, when it does occur, appears more severe than in patients who do not carry a BMPR-II mutation. In a recent study, 68 BMPR-II carriers with PAH were compared with 155 noncarriers with PAH [61]. Those with a BMPR-II mutation were younger at diagnosis (36.5 ± 14.5 versus 46.0 ± 16.1 yrs; $p < 0.0001$) and had worse haemodynamics and shorter survival or time to lung transplantation.

Mutations in BMPR-II have not been found in patients with HHT-related PAH (HHT-PAH). However mutations in ALK-1 have been implicated. Since the seminal publication by TREMBATH et al. [62], a variety of mutations in the ALK-1 gene appear to predispose patients with HHT to the development of PAH [54, 62, 63]. In contrast, mutation in the endoglin gene in HHT-PAH patients is uncommon and may be attributable to other causes such as pulmonary embolism, exposure to anorexogens, or liver VMs [56, 64]. Although an initial report suggested that there was an age-related reduction in endoglin in PAH patients with either HHT1 or HHT2 [65], this was not confirmed in a subsequent study [13], demonstrating that the level of newly synthesised endoglin protein, as measured by metabolic labelling, was not altered in 61 patients with HHT2 and PH.

The association between mutations in the ALK-1 gene and HHT-PAH highlights the potential relevance of perturbations in the TGF-β signalling pathway on angiogenesis and endothelial function/repair [59, 66, 67]. Although ALK-1 and BMPR-II operate on different TGF-β receptors, they share a common intracellular intermediary pathway through activation of SMADs 1/5/8 [68]. Further evidence for the importance of TGF-β signalling stems from observations that alterations in exons 8 and 10 of the ALK-1 gene appear to be common in patients with PAH and HHT [13]. Mutations in exon 10 are relevant in that they have been demonstrated to occur within a conserved carboxyl-terminal region of ALK-1 (the non-activating non-downregulating box (NANDOR BOX)), an alteration that may have effects on TGF-β-induced receptor signalling [54, 63, 66]. The finding that juvenile polyposis is associated with mutations in either SMAD4, as in the juvenile polyposis-hereditary telangiectasia syndrome [11], or BMPR-IA [69] further supports the importance of BMPR signalling and the potential link between HHT and PAH [69].

Intimal hyperplasia, medial thickening, in situ thrombosis and plexiform lesions characterise the arteriopathy seen in idiopathic and other forms of PAH, including HHT-PAH. There is also one report of pulmonary capillary haemangiomatosis in a patient with HHT [70]. Although the authors did not report upon this patient's genotype, they commented that there was no difference in ALK-1 expression in diseased versus normal endothelial cells. Given the angioproliferative features of pulmonary capillary haemangiomatosis, the potential link between it and HHT is intriguing but, fortunately, seems rare.

Haemodynamics

The typical haemodynamic profile of PAH is that of an elevation of $\bar{P}$pa (defined as >25 mmHg at rest and >30 mmHg with exercise) and normal left atrial pressure, and is further characterised by a low cardiac output and elevated PVR. These findings contrast with the haemodynamic findings described in PH secondary to liver VMs (table 1) [54, 62, 63]. In the few reports of HHT patients with PAH that have provided haemodynamic data, the haemodynamic pattern has been one of a low cardiac output, high PVR state as seen in idiopathic PAH [54, 62, 63]. Therefore, these patients are likely to share both the haemodynamics and natural history of progressive right heart failure that is seen in their idiopathic PAH counterparts.

Right heart failure

The presence of right heart dysfunction and high RV afterload may present unique challenges in the patient with HHT and PAH. In the setting of GI bleeding and/or epistaxis, the hypovolaemia can precipitate low cardiac output. Bleeding can also result in anaemia, which decreases oxygen delivery and increases cardiac demand that might not be able to be met by a failing RV.

Special considerations are warranted with regard to the unusual patients with PAVMs and PAH. Since PAVMs unload the RV, embolisation of PAVMs in the patient with PAH theoretically can lead to an increase in right ventricular afterload and precipitate right heart failure. Little reassurance about this possibility is provided by a recent publication of pulmonary embolisation in 143 patients with PAVMs [71]. In their report, SHOVLIN et al. [71] found no elevation in pulmonary pressures or ensuing right heart failure following embolisation. However, as pointed out in the accompanying editorial, patients with PAH were not included in this report. Indeed, four patients with established PAH were excluded from embolisation. Thus, it remains critical to identify patients with low cardiac output and reduced RV function who might develop worsening in RV function after embolisation. Interestingly, there is a reported case of a male infant with PAH, who later manifested HHT, with the development of PAVMs associated with a reduction in $\bar{P}$pa and improvement in the PVR [72]. Presumably the development of PAVMs led to a reduction in RV afterload.

Treatment

Several medical treatment strategies have been shown to be efficacious in PAH and one would anticipate that they would be useful in the management of HHT-PAH. In controlled clinical trials, parenteral prostanoids, endothelin inhibitors and

phosphodiesterase inhibitors have been shown to improve haemodynamics, exercise capacity and symptoms in patients with PAH from a variety of causes [2–4, 73]. Although these therapies have been shown to improve outcome compared with historical cohorts, only flolan has been shown to improve survival within a controlled clinical trial [74]. It is interesting that, irrespective of the cause of PAH, most of these therapies have been shown to be of benefit, perhaps implying commonalities in pathophysiology as it relates to the prostaglandin, endothelin and nitric oxide pathways in PAH. In this regard, it is not surprising that there are cases showing benefit of these therapies in HHT patients with PAH.

There are no systematic reports evaluating outcomes of patients with HHT-PAH. However, one would anticipate that these patients share the poor prognosis of other patients with PAH. Consequently, there is an imperative to provide treatment options to these patients. At present, the experience with medical treatments is sparse and limited to case reports. Minai et al. [75] reported a patient with HHT-PAH without a detectable ALK-1 or endoglin mutation treated for PAH over a period of 10 yrs. Interestingly, this patient demonstrated an initial acute haemodynamic response to calcium channel blockers with a reduction in $\bar{P}_{pa}$ from 110 to 58 mmHg, and stabilisation of $\bar{P}_{pa}$ with nifedipine over a 5-yr period. Subsequently, epoprostenol and then treprostinil were used intravenously over the next 4 yrs. Over the period of observation there was an improvement in functional capacity and symptoms. Acute response to vasodilators in HHT-PAH has not been reported previously [62]. Thus, there is probably no role for the use of calcium channel blockers in this population. Therefore, the case report by Minai et al. [75] not withstanding, the current authors do not advocate for the routine use of vasodilator testing or use of calcium channel blockers in patients with HHT-PAH. In another report, bosentan (a nonselective endothelin inhibitor) was shown to improve haemodynamics, exercise capacity (as measured by 6-min walk distance) and pro-brain natriuretic peptide levels in two patients with HHT-PAH [48].

Owing to the rarity of HHT-PAH, prospective randomised trials are unlikely to be feasible. At present, many jurisdictions are not able to use these medications beyond certain diagnostic causes of PAH. Carefully conducted case series that evaluate changes in haemodynamics, exercise capacity, symptoms and quality-of-life measures with therapy hopefully will provide evidence to support the efficacy of these often costly therapies.

CONCLUSIONS
Advances in the understanding of hereditary haemorrhagic telangiectasia have highlighted the importance of pulmonary vascular disease in these patients and, in turn, have led to specific therapies to treat the pulmonary manifestations of this disease. Early screening and embolisation for pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia is recommended to prevent the haemorrhagic and neurological complications of pulmonary arteriovenous malformations. In patients with pulmonary hypertension, distinguishing between pulmonary hypertension associated with liver vascular malformations and pulmonary arterial hypertension is critical. Formal haemodynamic assessment of patients with pulmonary hypertension and investigations for liver vascular malformations should be completed for prognostic reasons and to help guide treatment.

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