Eur Respir Mon 2011; 54: 218–245.
DOI: 10.1183/1025448x.10008410

Pulmonary arteriovenous malformations and other pulmonary aspects of hereditary haemorrhagic telangiectasia

Claire L Shovlin, [1 2] Peter Wilmshurst [3 4] and James E. Jackson [5]

[1]NHLI Cardiovascular Sciences, Imperial College, London, UK. [2]Respiratory Medicine, [5]Imaging, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London UK. [3] Department of Cardiology, Royal Shrewsbury Hospital, UK; [4] University of Keele, UK

Corresponding author: Dr Claire L. Shovlin PhD FRCP, HHTIC London, Respiratory Medicine, Hammersmith Hospital, Du Cane Rd, London, W12 0NN, UK. Phone (44) 208 383 4831; Fax (44) 208 383 1640; c.shovlin@imperial.ac.uk

CLS and JEJ acknowledge support from the NIHR Biomedical Research Centre Funding Scheme.
The authors have no conflicts of interest to declare

KEY WORDS:

Contrast echocardiography, diving, hypoxaemia, pulmonary hypertension, stroke.

SUMMARY:

Pulmonary arteriovenous malformations (PAVMs) are vascular structures that provide a direct capillary-free communication between the pulmonary and systemic circulations. The majority of patients have no PAVM-related symptoms, but are at risk of major complications that can be prevented by appropriate interventions. More than 90% of PAVMs occur as part of hereditary haemorrhagic telangiectasia (HHT), the genetic condition most commonly recognised by nosebleeds, anaemia due to chronic haemorrhage, and/or the presence of arteriovenous malformations in pulmonary, hepatic or cerebral circulations. Patients with HHT are also at higher risk of pulmonary hypertension and pulmonary embolic disease, management of which can be compounded by other aspects of their HHT.

This chapter primarily addresses PAVMs and pulmonary HHT in the clinical setting, in order to improve patient care. Clinical presentation patterns, diagnostic strategies and management options are presented in detail. Relevant pathophysiological mechanisms discussed include new topics for the PAVM literature, such as the alveolar transit of venous bubbles during diving and contrast echocardiography.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that provide a direct capillary-free communication between the pulmonary and systemic circulations [1]. Pulmonary arterial blood passing through these right-to-left (R-L) shunts cannot be oxygenated, leading to hypoxaemia; the fragile wall of the PAVM sac may rupture [2], and the absence of a filtering capillary bed allows particulate matter to reach the systemic circulation resulting in embolic cerebrovascular accidents (CVA) and cerebral abscesses. PAVMs are particularly dangerous during pregnancy and other stresses such as diving. Complications can be limited if the condition is identified and treated, yet until recently, the importance of treatment for PAVMs has been poorly recognised by respiratory physicians (Figure 1).

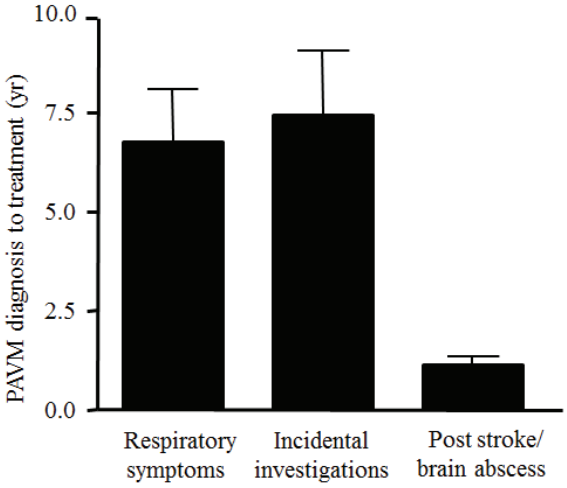

Figure 1: Delays between PAVM diagnosis and treatment according to type of presentation in 219 consecutive patients. Reproduced from Thorax [3] with permission from the publisher.

The majority of pulmonary AVMs ([94%] in the study by Shovlin et al.[3]) occur as part of hereditary haemorrhagic telangiectasia (HHT). HHT is most commonly recognised by nosebleeds (epistaxis) and anaemia due to telangiectasia in the nose and gastrointestinal tract. Arteriovenous malformations (AVMs occur not only in the pulmonary circulation, but also in mucocutaneous [4], hepatic [5], gastrointestinal [6], and cerebrospinal [7, 8] vascular beds. Additionally, patients with HHT are at higher risk of pulmonary hypertension [9], and pulmonary embolic disease [10], management of which can be compounded by other aspects of their HHT.

Most patients with PAVMs and HHT are unaware they have HHT when their PAVMs are diagnosed: in the study by Shovlin et al.[3], 121 (59%) out of 205 were unaware. It is therefore crucial that the respiratory physician is alert to the possibility of HHT in the PAVM patient; aware that mucocutaneous telangiectasia are often subtle (Figure 2); and recognizes that the majority of patients will not volunteer a personal or family history of HHT or nosebleeds, unless specifically asked and allowed time to check with relatives.

OVERVIEW OF HHT

HHT is generally quoted as affecting 1 in 5-8,000, with precise prevalence figures for specific regions in Europe [14, 15], the West Indies (Dutch Antilles) [16], and Japan [17].

Current clinical diagnostic criteria for a definitive diagnosis of HHT require the presence of three out of four key features, namely 1) spontaneous recurrent epistaxis (nosebleeds), 2) telangiectases at characteristic sites, 3) a visceral manifestation (such as PAVMs), and 4) an affected first degree relative [18]. An individual has a diagnosis of "definite HHT" if three

criteria are present; "suspected HHT" if two are present, and "unlikely HHT" if only one is present [18]. For patients with definite clinical HHT, identification of a causative gene mutation is not required to 'confirm' their diagnosis, and at present, does not modify recommended management. HHT disease-causing mutations are not found in approximately 15-20% of HHT families [19-21]: this should not affect a clinical diagnosis of HHT made for individuals within such families.

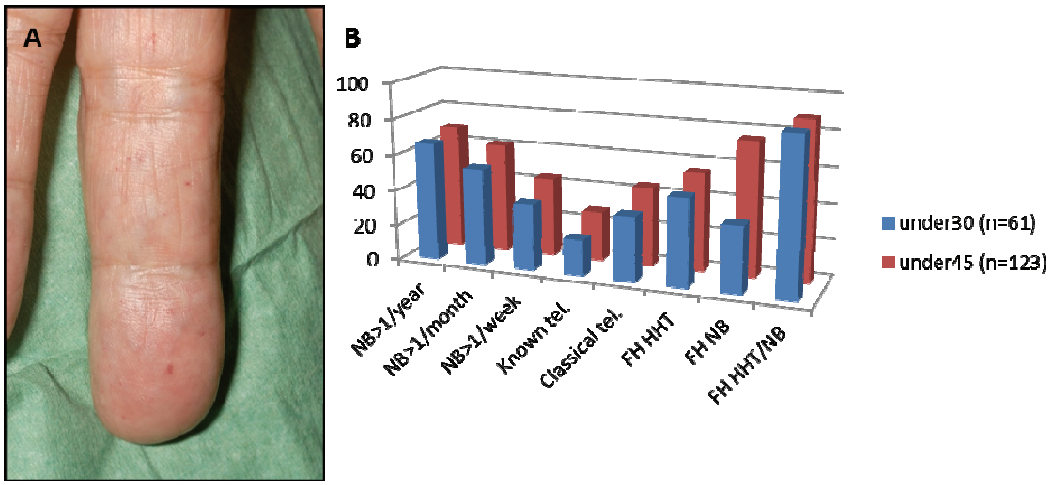

Figure 2: Relative importance of nosebleeds and telangiectasia in making a clinical diagnosis of HHT. In the series of female PAVM patients reported by Shovlin *et al.* [11], the presence of telangiectasia at HHT diagnostic site (lips, internal oral mucosa and tongue, finger tip pads) was recorded at the time of assessment and subsequently classified into 4 categories. **A)** Illustration of typical (3 or more, readily detectable by careful inspection of the sites) compared to florid (as illustrated by Shovlin *et al* [12] and Faughnan *et al* [13]); sparse, or absent. **B)**. Proportions of women demonstrating the clinical features at the age of ≤30ys, and ≤ 45ys. Note that "classical tel." referred to three or more in classical sites (as in a), or more florid. Contrast the high proportions of women that did not demonstrate such telangiectasia with the high proportions who declared a family history of nosebleeds (and/or HHT) when prompted.

Genetics of HHT

HHT is inherited as an autosomal dominant trait. Three disease genes have been identified. HHT type 1 is caused by mutations in *ENG* encoding endoglin [22], and HHT type 2 by mutations in *ACVRL1* encoding activin receptor like kinase (ALK1) [23], and mutations in *MADH4* cause HHT in association with juvenile polyposis (JPHT) [24]. There are at least two further unidentified genes that can cause classical HHT, *HHT3* on chromosome 5q [25, 26], and *HHT4* on chromosome 7p [27]. The genes mutated in HHT encode endothelial cell-expressed proteins that mediate signalling by the TGF-ß superfamily (Figure 3).

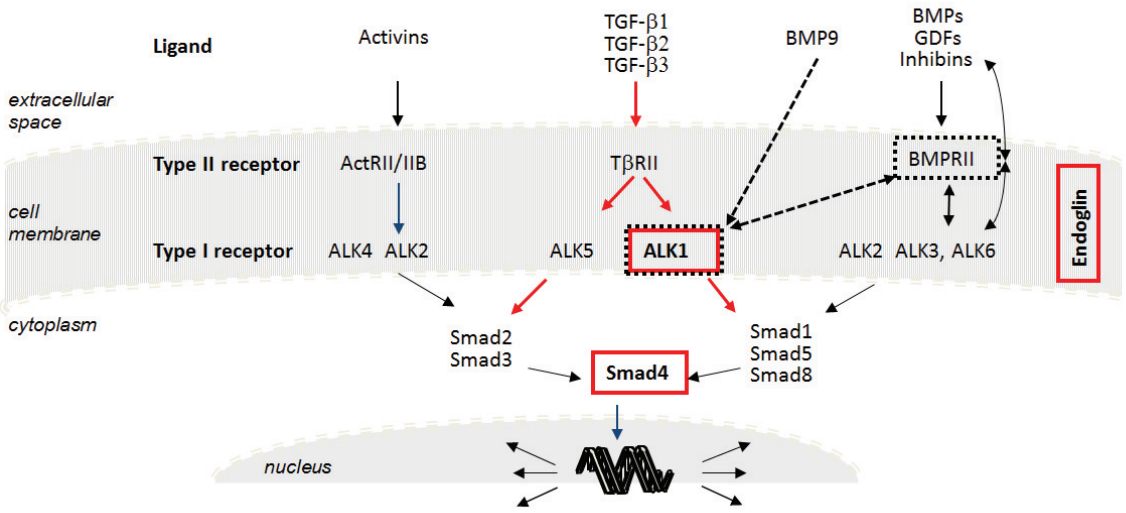

Figure 3: Transforming growth factor (TGF)-ß signalling pathways relevant to pulmonary arteriovenous malformations (PAVMs) and/or hereditary haemorrhagic telangiectasia (HHT). Protein products of mutated genes are boxed in solid lines (HHT/PAVMs) or dotted lines (pulmonary arterial hypertension). BMP: bone morphogenetic protein; GDF: growth and differentiation factor; ActR: activin receptor; T ß R: TGF- ß receptor; BMPR: BMP receptor; ALK: activin receptor-like kinase. Reproduced from[25], with permission from the publisher.

More than 500 different *ENG* and *ACVRL1* mutations have been reported to the HHT Mutation Database at www.hhtmut.org to date, with no common mutations [28]. A body of evidence indicates that HHT mutations result in a non functional allele. Many cannot generate a mutated protein, most obviously entire gene deletions [29]; start codon mutations [30], and mutations with no detectable mutant RNA [31 30, 32]. For endoglin, expression of ~50% of normal is observed in a variety of cells from HHT1 patients [33-37 38], with endogenous mutated endoglin protein species either not detected, or retained intracellularly at low levels [33, 34, 37]. For ALK1, where missense mutations are more common, *in vitro* generated mutated proteins display defective signalling. [39] Although there have been suggestions that the telangiectasia/AVMs may develop at sites in which there was a genetic 'second hit' [40], it is believed that in most if not all cases, HHT results from haploinsufficiency, that is lack of sufficient protein for normal function

Development of HHT telangiectasia

In man, computer reconstruction of serial sections suggest that the smallest HHT cutaneous telangiectatic lesion is a focal dilatation of the post capillary venule which enlarges, connects with dilated arterioles with loss of the intervening capillary bed, and form

arteriovenous communications [41]. The development of *de novo* AVMs can be observed in murine HHT models [42]. In contrast to normal veins exposed to arterial pressures [43], the vessels immediately beyond the new arteriovenous communication do not arterialise [44], and wall thickness remains low compared to the lumen radius [45] (Fig 3B), with disorganised wall structures [11, 46-48].

Since most vessels within HHT-affected vascular beds develop and function normally, endoglin or ALK-1 haploinsufficiency must be deleterious in particular contexts. As discussed elsewhere [44], transgenic models of HHT [42, 49-51] are focussing attention on aberrant vascular responses to injury-induced angiogenic stimuli, when the mutated genes in HHT result in the inability of a blood vessel to mature appropriately [42, 50, 51]. Murine models also provide mechanistic insights into vascular bed specificity of HHT vessel formation, with evidence, for murine endoglin and ALK-1, of differential basal expression levels [52]; dynamic down-regulation in inflammation [53, 54]; different requirements for angiogenesis; [42] and differential generation of reactive oxygen species provoking vascular injury [49, 55] .

Which ligand is important in the pathogenesis of the HHT vascular lesions remains the subject of intense debate and study. Many recent data focus on a defective response to TGF-ß1 signalling, as impaired recruitment of mural cells to vessels [56, 57] may be mediated at least in part via reduced endothelial cell secretion of TGF-ß1 [58, 59] and/or reduced TGF-ß1 induced responses. [56, 58]. Other models suggest that BMP9 may be the ligand most implicated in HHT pathogenesis [60-62]. The association of endoglin with the eNOS/hsp 90 complex leading to uncoupling of eNOS activity in $Eng^{+/-}$ mice [55] may also be crucial in HHT pathogenesis.

Clinical consequences of telangiectasia and AVMs

Fragile-walled nasal telangiectasia are responsible for the nosebleeds (epistaxis) that affect the majority of patients at some point in their lives, often sufficiently frequently to require ENT attention and long term maintenance iron or transfusions. Gastrointestinal telangiectasia, present in a smaller proportion of individuals, also bleed, and may contribute to chronic blood loss. Both gastrointestinal and mucocutaneous telangiectasia become more prevalent with age [4, 44, 63]. Telangiectasia also occur in other HHT-affected vascular beds, where they are usually silent, and overshadowed by the consequences of larger arteriovenous malformations.

For larger arteriovenous malformations in HHT, bleeding is less common, particularly in the pulmonary circulation where AVMs are normally perfused at much lower pressures. Instead the consequences of AVMs tend to result from inappropriate shunting of blood past the relevant capillary beds, resulting in right-to-left (R-L) shunting for PAVMs; left-to-right shunting for systemic AVMs; and hepato-portal shunting for certain hepatic AVMs. Both right-to-left, and left-to-right shunting result in compensatory increases in cardiac output, increases that are generally well tolerated prior to advancing age or concomitant pathologies, particularly the onset of iron deficiency anaemia, or atrial fibrillation.

Other pathologies in HHT

Pulmonary emboli and deep venous thromboses

HHT patients are not protected from prothrombotic risks [10], and when pulmonary emboli occur, they may temporarily occlude pulmonary AVMs [64, 65] and/or lead to paradoxical emboli [65]. Deep venous thromboses and pulmonary emboli affected 6-7% of two separate European HHT populations [10, 66], associated in one series with elevated plasma levels of coagulation factor VIII (FVIII) [10], one of the strongest predictors of recurrent venous thromboembolic events in the general population [67, 68], and also associated with chronic thromboembolic pulmonary hypertension [69-71]. The recent demonstrations that the pulmonary endothelium synthesizes FVIII [72, 73] provides a rationale for why FVIII levels may be higher in HHT patients, but mechanistic data are awaited.

Other respiratory pathologies:

HHT-specific pathologies occur in individuals who may have other respiratory diseases. The natural history of these conditions does not appear to differ in HHT (Shovlin, personal observation).

The remainder of this article will focus primarily on pulmonary AVMs. For further details on other aspects of HHT, the reader is referred to International Guidelines based on systematic assessments of HHT publications up to October 2006 [74], and review articles incorporating the 2006-2010 evidence base [13, 44, 75, 76].

PULMONARY AVMs

Anatomy and development

PAVMs affect approximately 50% of HHT patients [77], with prevalence depending on the genotype. Macroscopic PAVMs are more prevalent in HHT1 than HHT2 [21, 78-82], and in one recent study, 85% of 92 HHT1 patients had evidence of intrapulmonary R-L shunting compared to 36% of 97 HHT2 patients [83].

PAVMs range in size from telangiectases [46] to large 'classical' lesions with hypertrophied feeding arteries, aneurysmal venous sacs and dilated draining veins [84]. (Figure 4A) Approximately 70% are basally-situated [85-88]. In HHT, pulmonary AVMs are usually multiple [3]. Diffuse PAVMs have been defined as multiple small PAVMs affecting every segment of one or more lobes [89] or a single segment [90] (Figure 4B).

Figure 4:

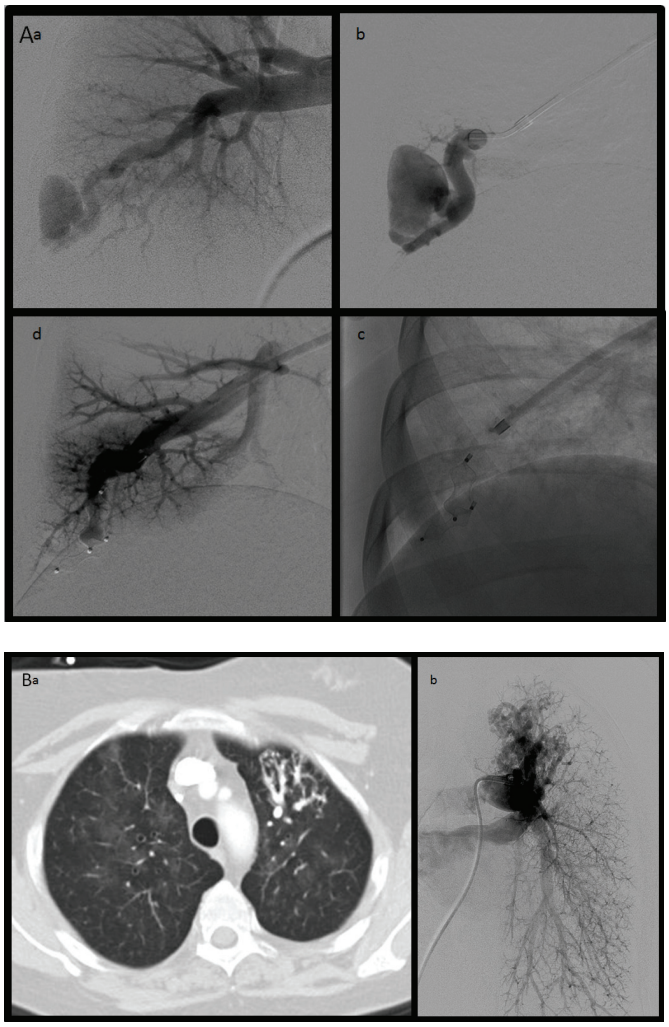

Figure 4. Pulmonary arteriovenous malformations (PAVMs). A) Pulmonary angiogram of a right basal PAVM with two dominant feeding vessels before (a,b) and after (c,d) embolisation with Amplatzer vascular plugs (AGA Medical Corporation, Plymouth, MN, USA). The patient was diagnosed by family screening, but had had a stroke previously. B) Computed tomography (a) and pulmonary angiogram (b) showing a diffuse PAVM in the anterior segment of the left upper lobe. The PAVM had been diagnosed following presentation with a cerebral abscess: post-embolisation, the arterial oxygen saturation increased from 89% supine, 91% erect to 93% supine, 95% erect with symptomatic improvement.

PAVMs can develop in the pre or perinatal period [12], and recent data highlight that PAVMs can be detected in childhood [91, 92]. There are few data available regarding growth of PAVMs once present, but proven times of growth include puberty, pregnancy, and pulmonary venous hypertension [93-97]. Spontaneous regression [98] most likely reflects auto-embolization by a pulmonary embolus, as described in a recent case report where spontaneous recanalisation subsequently occurred [65].

Physiology

Right to left (R-L) Shunt

In normal individuals, the anatomical R–L shunt is less than 2% of the cardiac output, ascribed to the post-pulmonary drainage of bronchial veins into the pulmonary veins and thebesian vessels into the left atrium. In patients with PAVMs, the shunt fraction (proportion of the cardiac output using the shunt pathways) varies, tending to be higher in earlier series where patients were more often symptomatic[88,99-103] than in later series. [3,104,105]

Confirmation that the R–L shunt is the predominant cause of the arterial hypoxaemia in PAVM patients comes from three sources. There is an inverse relationship between the R–L shunt fraction and arterial PO_2 /SaO_2 [106]; calculations from SaO_2 breathing air, are in good agreement with measurements of the anatomic R-L shunt [100]; and temporary occlusion of PAVMs (by an occluding balloon [104], or pulmonary emboli [65]) demonstrated transient 18-20% increases in SaO_2 [65,104]. In occasional patients with significant coexisting lung disease, ventilation–perfusion mismatching may also contribute to hypoxaemia.

Pulmonary haemodynamics.

The pulmonary vascular resistance (PVR) of PAVMs is less than that of the surrounding normal lung due to the absence of a microvascular bed [99]. The effect on the overall PVR depends on the proportion of the cardiac output flowing through the shunt channels. Reduction in PVR in the apparently uninvolved lung [99] most likely reflects the presence of undetected microvascular PAVMs in the apparently normal lung, though there may also be significant vasodilatory stimuli [107]. The overall *P*pa mean is usually low to low-normal [99,104, 105, 108] reflecting the high total pulmonary blood flow.

Pulmonary Function

Sprirometric values are usually normal, [88, 104] but vital capacity may be reduced in the presence of very large PAVMs [103]. DL_{CO} and KCO values less than 70% are unusual, and often signify the presence of widespread small vascular malformations. However, low

DL_{CO}/ K_{CO} values are also found in patients with large R-L shunts [88, 102, 103], when a vascular steal through the low resistance PAVMs contributes to the low diffusion values [104], and improvement may be observed post embolization [104].

Posture

As the majority of PAVMs are at the lung bases [47, 85-88], a frequent finding is orthodeoxia [88, 100, 101, 104, 106] due to a gravity-induced increase in right-to-left shunting on standing [100]. In a recent series of 155 consecutive untreated patients with CT-proven PAVMs, 51 (32.9%) demonstrated an SaO_2 fall of ≥2% in replicate measurements averaged over 4 minutes after standing for 7-10 minutes, compared to the equivalent average supine reading (Santhirapala et al, manuscript in preparation). A smaller fall of 1-2% was present in a further 28 (18%) of patients. (Santhirapala et al, manuscript in preparation).

Exercise

In the healthy lung, PVR falls on exercise to half its value at rest, because of dilation and recruitment of vessels in the pulmonary capillary bed. The effects of exercise on SaO_2 in a PAVM-affected patient depends on the change in vascular resistance through the shunt channels in relation to the change in the resistance of the normal vessels [99 101] (see [109] for further discussion). Overall, work capacity is well preserved in PAVM patients, even when SaO_2 on exercise is <80% [99,104,106]. Recent studies of 88 patients with CT-proven pulmonary AVMs demonstrated little effect of SaO_2 on dyspnoea grade, once age-adjusted. [110]

Pregnancy

In normal pregnancy, complex physiological vasodilatory responses are associated with the increase in cardiac output that approaches 50% in the third trimester [111]. Cardiac chamber [111] and aortic [112] dimensions increase in normal pregnancies. The rise in cardiac output is associated with a fall in PVR, with one study demonstrating PVR values to be 33% lower in 11 healthy women at 16 weeks of pregnancy compared to 15 non-pregnant controls, with mean *P*pa in the groups of 10 and 13 mm Hg respectively [113].

For pregnant PAVM patients, the PAVMs may enlarge [94, 96, 97, 114, 115]. At such times, a fall in arterial PaO_2/SaO_2 may be masked [116], due to the increase in mixed venous oxygenation resulting from progesterone-stimulated increased minute ventilation (VdotE) [117, 118]. Sudden falls in post partum SaO_2, mimicking the presentation of an acute pulmonary embolus, are reported [116].

Diving

During diving, the increased barometric pressures leads to gases dissolving in the tissues on descent. Bubbles liberated from supersaturated tissues on ascent cause decompression illness (DCI) if they are not removed by the alveolar capillary filter. Cardiac [119, 120] and pulmonary R-L shunts[121, 122] are associated with an increased risk of DCI in divers, by allowing paradoxical gas embolism, leading to vascular obstruction and resultant tissue ischaemia. DCI does not occur after bubble contrast echocardiography in people with a R-L shunt, because the gas in a small number of bubble emboli passes down the concentration gradient into the tissues, and the bubble emboli dissolve. After a dive however, tissues are supersaturated with dissolved nitrogen, and bubble emboli are amplified as nitrogen passes from the supersaturated tissues into the bubbles.

The risk of DCI is dependent on the characteristics of the dive which determines the number of venous bubbles liberated and the amount of dissolved nitrogen in tissues that is available to amplify embolic bubbles. However, many individuals experiencing decompression illnesses are affected after dives with acceptable profiles, when it is believed that the R-L shunt allows venous bubbles that form during decompression after many innocuous dives to bypass the alveolar capillary filter. The risk of decompression illness is also affected by the size of the shunt, with the majority of episodes of decompression illness occurring in a small minority of the population who have the largest right to left shunts [121, 122].

Flying

There are theoretical concerns that the reduced barometric pressure and relative immobility associated with flying might exacerbate hypoxaemia and risks of venous thromboembolism for PAVM patients, particularly as many asymptomatic patients with PAVMs have SaO_2 lower than the cut off recommended for flying [123]. A recent retrospective questionnaire-based study examined the frequency of flight-related complications in 3,950 flights in 145 HHT patients, 95 [65%] of whom had PAVMs [124]. 111 (77%) patients reported no complications during or after flights. There was no difference in erect SaO_2 at sea level between the six (4%) who reported dyspnoea, and those who did not [124].

Clinical presentation patterns

Respiratory Symptoms

Dyspnoea is the respiratory symptom most commonly reported by PAVM patients, but may not be appreciated until after the condition has been treated. PAVMs generally result in symptomatic dyspnoea only when resting arterial oxygen saturations are below 80% [3,108], and in a study of 88 patients with CT-proven pulmonary AVMs, no PAVM patients had an MRC dyspnoea grade [126] of higher than two, unless there was major concomitant pathology [110].

Haemorrhage leading to haemoptysis or haemothorax is a relatively rare feature of PAVMs, with three important exceptions: (1) during pregnancy (discussed below); (2) in association with pulmonary hypertension [127], and (3), in the presence of spontaneous or post-embolization [90, 128] systemic arterial blood supply to PAVM sacs.

PAVMs do not usually cause chest pain. Reported series that pleuritic chest pains are present in up to 10% of PAVM patients (Table 1) most likely reflect ascertainment bias, following CTPA investigation of patients for suspected pulmonary embolism.

Neurological features

Ischaemic strokes and cerebral abscess are reported in high proportions of PAVM patients, attributed to paradoxical emboli through PAVMs [87 104 135 140]. In one series of 219 consecutive PAVM patients, corrected for ascertainment bias, 9% of patients had a cerebral abscess and 11.3% an ischemic stroke, with relative risks particularly high in young adults [3]. Anderson Gill extension of Cox proportional hazards models indicated no clear relationship between the risk of ischemic stroke or cerebral abscess with any of six markers of PAVM severity [3], or with conventional neurovascular risk factors. There were strong association between ischaemic stroke and low Ppa mean, and between cerebral abscess, male gender and dental microrganisms [3]. The prevalence of migraine with aura is considerably increased in individuals with any form of right-to-left shunt, and thefrequency of migraine for PAVM patients is approximately doubled compared to general population data, general population controls, or HHT patients without PAVMs [138, 139, 141].

Table 1 : Clinical features of untreated PAVMs

	Published series		
	mean %	range	N
Respiratory			
Asymptomatic	49	25-58	260
Dyspnea	50	27-71	685
Chest pain	12	6-18	390
Haemoptysis	11	4-18	671
Haemothorax	1	0-2	258
Cyanosis	27	9-73	467
Clubbing	28	6-68	459
Bruit	31	3-58	455
Embolic phenomenon			
Cerebral abscess	12.9	0-25	635
CVA/TIA	27	11-55	401
CVA	13.7	9.5-18	262
TIA	22.1	6.3-36	262
Migraine	44.7	38-57	266

Table 1: Clinical features of untreated PAVMs Data derived from figures in references 47, 85-88, 98, 129-140. (Updated from Table originally published in 12).

Pregnancy

Occasional patients have presented during pregnancy or post partum with sudden desaturation due to PAVM growth [94, 96, 97, 114, 115]. Of particular concern however, is the enhanced risk of PAVM haemorrhage [2, 11, 94, 96, 142-145], which may be fatal [11, 97]. Thrombotic complications also occur in PAVM pregnancies, as in the general population in which pulmonary emboli are one of the commonest causes of maternal death [146]. There was no reported difference in miscarriage rates in a retrospective study of 40 HHT patients compared to 80 controls [147]. Normal pregnancy and delivery of a normal baby can occur in the presence of severe arterial hypoxaemia [116].

The rates and types of major complications of PAVMs in pregnancy were examined in a cohort of 484 pregnancies [11]. The predominantly retrospective analyses demonstrated that

1.0% (95% confidence intervals 0.1, 1.9%) of pregnancies resulted in a major PAVM bleed (haemoptysis or haemothorax). Emergency interventions for PAVM haemorrhage included embolization, surgical resection, and induced delivery. One death was attributed to paradoxical emboli causing a myocardial infarction [11]. Overall, in 484 pregnancies in HHT/PAVM patients, 1.0% (0.13 1.9%) of pregnancies resulted in maternal death [11], with all maternal deaths occurring in women previously considered well. In women experiencing a life-threatening event, prior awareness of HHT or PAVM diagnosis was associated with improved survival (p=0.041, Fisher's test) [11].

No means of distinguishing a group more likely to have significant pregnancy-related complications was identified [11]: The severity of PAVMs associated with life-threatening PAVM haemorrhage could be evaluated in four women, only one of whom had low SaO_2/markedly raised R-L shunts, and none of whom had evidence of pulmonary hypertension [11].

Diving and flying

PAVMs may be diagnosed in patients following investigations for decompression illness [121, 122], or in-flight complications. Two cases of in-flight PAVM haemorrhage (one haemoptysis, one haemothorax) were reported recently [148], in addition to cases of ischaemic stroke [3, 124].

Children

PAVMs may present in childhood, with impaired exercise tolerance, dyspnoea, or neurological complications [3, 86, 91], but such presentations are rare. The vast majority of children who will go on to have PAVMs in adult life have no symptoms in childhood. A small proportion present symptomatically at the time of peripubertal growth [1], but the majority remain asymptomatic, as for adults.

Diagnosis

Overview

Figure 5a represents the conventional investigative pathways for generic patients with significant respiratory symptoms such as dyspnoea, haemoptysis or chest pain: PAVMs are infrequently identified as causative pathology in such general population patients.

High proportions of HHT/PAVM patients are undiagnosed at the time of their PAVM-induced ischaemic stroke or cerebral abscess [3,149] , documented at 66.7% and 64.3% respectively in one UK series [3]. There is evidence that PAVM treatments not only improve oxygenation and physiological parameters [104, 108, 135, 136] but also reduce stroke rates [3]. The relative safety of PAVM screening and treatment regimes, and high rate of PAVM detection in the asymptomatic HHT population, has therefore led to the widespread introduction and recommendations for PAVM screening and treatment programmes [74], with pre screening discussions recommended [44, 150].

Common to all PAVM screening programmes are the policies of minimising the radiation burden in an often young population; having a sensitive screen to detect all clinically significant PAVMs; and concern to avoid missing any treatable PAVMs. Early screens were based upon chest radiographs, SaO_2/ PaO_2 and shunt quantitation by 100% oxygen breathing or ^{99m}Tc scans, until it was recognized that there are no cut-offs for these tests which allow adequate sensitivity to rule out very small PAVMs that are still of clinical significance (Table 2). For more sensitive screening tests, the choice lies between thoracic CT and contrast echocardiography. Contrast echocardiography (CE) was recommended by the International Guidelines group as a first line screen [74] (Figure 5b), sparing individuals with negative studies from the radiation burden of thoracic CT scans. At other institutions such as our own, CE has not been used routinely as a first line screen due to resource implications given the majority of echocardiograms are positive, and patient preference for the rapid and cannula-free CT scan (Figure 5c).

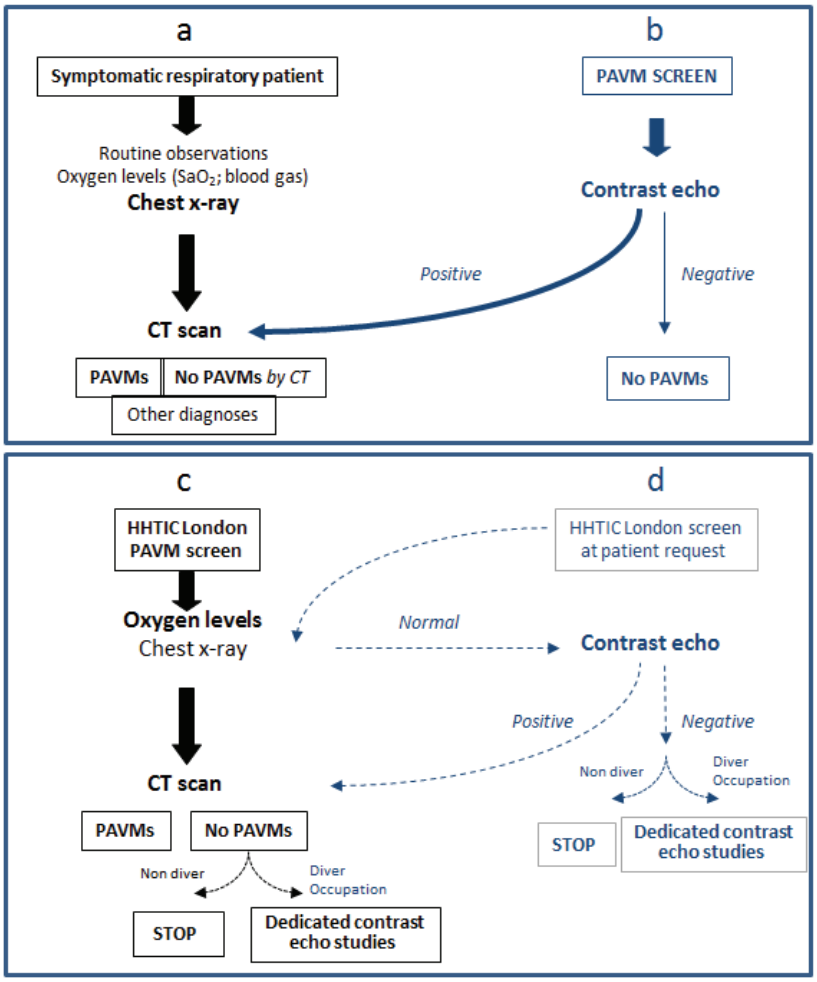

Figure 5: Legend: Alternative pathways for PAVM diagnosis. **a)** Usual pathway for symptomatic patients presenting to general respiratory services. **b)** Pathway recommended by international patient guidelines using contrast echocardiography as first line screen [74]. **c)** 2011 HHTIC London standard pathway. **d)** 2011 HHTIC London option for individuals requesting a first line echocardiogram. Pre echocardiography oxygen saturations and chest x-ray allows avoidance of contrast echo in patients who are significantly desaturated, and most likely to get symptoms (usually migraine /aura), after contrast echocardiography, because they will have masses of bubble emboli. (If symptoms occur, immediate 100% oxygen will get rid of the bubbles and symptoms quickly).

Who to screen?

The international guidelines recommend screening adults and children at the time of initial clinical evaluation for HHT [74], and where initial screening is negative, after puberty, after pregnancy, and within 5 years preceding planned pregnancy. For adults, screening post puberty and post pregnancy may be sufficient as there are no reports of PAVMs developing subsequently, but due to the paucity of published evidence, recommendations are to rescreen every 5-10 years [74].

For children, while appropriate investigation and management of symptomatic children is essential, the question of screening healthy children from HHT families is much more controversial. The international guidelines did not provide a separate recommendation for children as opposed to adults [74]. As previously presented, [3] based on the paucity of evidence for childhood complications from silent PAVMs in previously healthy children, we do not see sufficient indication to conduct a formal PAVM screen before the time of peri-pubertal PAVM growth and maturation, and resolution of the ethical, familial and radiation issues that influence paediatric discussions [3, 75]. Some centres may recommend clinical examination and pulse oxygen saturation measurement in children from HHT families, but this too awaits further evidence that PAVM complications occur in healthy, asymptomatic children.

Screening Methods

Impaired oxygenation

Hypoxemia breathing room air is the simplest method for detecting PAVM R-L shunts. The differential diagnosis is wide, although orthodeoxia may point towards the presence of lower lobe PAVMs. In the past, 100% inspired oxygen rebreathing was considered the gold standard for non-invasive methods of measuring the shunt as a fraction of the cardiac output. There are several practical problems with this method which depends upon good patient technique; two sets of arterial blood gas sampling without contamination by air bubbles; careful calibration of the oxygen electrode for high PaO_2; and inherent estimations that tend to underestimate shunt size [105].

Radiology investigations

Chest radiographs: The radiographic appearances of PAVMs range from normality (particularly if diffuse small telangiectasia are present, or when lower lobe lesions are obscured by the diaphragm on the PA projection), through prominent bronchovascular markings, to the classical rounded mass with visible feeding or draining vessels. The sensitivity of plain radiographs varies widely according to both the size and distribution of PAVMs, and the reported screening intention: Prior to 2007, many screening programs only reported PAVMs with feeding artery diameters greater than 3 mm, since these were widely assumed to be the PAVMs of clinical significance: Data presented in this era were that the chest radiograph was abnormal in 60 to 90% of instances. It is anticipated that the

frequency of positive chest radiographs will fall further as smaller PAVMs are sought, in keeping with the recognition that these also cause neurological complications [3 156].

Table 2: Comparison of early PAVM screening regimes

Modality	Number screened	Population	Threshold value	Sensitivity^ %	Specificity %	1– Specificity %&
PaO_2 ($100\%O_2$)						
Haitjema, 1995 [151]	36	HHT*	< 575 mmHg ‡	88	75	25
Lee, 2003 [152]	59	HHT*	< 575 mmHg ‡	95	8	92
			< 500 mmHg ‡	66	64	36
Kjeldsen, 1999 [153]	24	HHT*	< 500 mmHg‡	100	30	70
Lee, 2003 [152]	29	post-embol#	< 500 mmHg‡	33	85	15
SaO_2 (erect)						
Kjeldsen, 1999 [153]	24	HHT*	≤ 96%	71	100	0
Thompson,1999 [154]	66	post-embol#	≤ 96%	73	35	65
			≤ 95%	61	75	25
^{99m}Tc-MAA shunt						
Thompson, 1999 [154]	66	post-embol#	> 3.5%	87	61	39
			> 5.0%	68	72	28
Contrast echo						
Lee, 2003 [152]	28	post-embol#	bubbles in left heart	100	21	79
Nanthakumar,2001[155]	59	HHT*	bubbles in left heart	94	67	33

Comparison of early PAVM screening regimes: SaO_2, arterial oxygen saturation; ^{99m}Tc-MAA, ^{99m}technetium-labelled albumin macroaggregates; HHT, hereditary haemorrhagic telangiectasia; embol, embolisation.^ Positive likelihood; &, false positive Likelihood. * prospective study of an HHT population; # small residual shunts or no shunts; ‡ 575 and 500 mmHg represent R–L shunts of ~ 5% and 9% respectively.(First published in [109], reproduced with permission from the publisher).

Thoracic CT scanning: Spiral, or helical, computerized tomography (CT) beautifully demonstrates the angiographic anatomy of almost all PAVMs; the radiation burden has been substantially decreased, and the resolution improved, over the past several years by the use of newer multislice, multidetector CT, which limit x-ray exposure to a single short breath-hold acquisition, and which allow elegant multiplanar and three dimensional reconstructions

of the data. In the small number of cases where there are difficulties with interpretation of structures that appear vascular, confirmation of R-L shunting may be helpful.

MRI: To date, MR has been less effective than CT or pulmonary angiography because small PAVMs with rapid blood flow are not visualised [157]. With meticulous technique, the majority of treatable lesions will be visualized and this imaging modality is being used by some centres for pre-embolization assessment and for post-embolization follow-up [158, 159].

Radionuclide scanning: Following intravenous injection of technetium-99m (^{99m}Tc)-labelled albumin microspheres (7-25μm) or macroaggregates (10-80μm), the right-to-left shunt can be assessed by calculating the quantity of tracer reaching the systemic circulation compared to the total quantity received [105] [106].

Angiography: Pre embolization, spiral, or helical, computerized tomography (CT) images are sufficient to beautifully demonstrate the angiographic anatomy of almost all PAVMs to inform on subsequent embolization approaches. Diagnostic angiograms are therefore very rarely required, and in our centre, are only performed at the same session as therapeutic embolization.

Contrast echocardiography

Compared to the previously discussed modalities, respiratory physicians are generally less familiar with contrast echocardiography, recommended by the international guidelines committee as the initial PAVM screening test [74]. The test is therefore discussed in detail.

Bubble contrast echocardiography relies on the normal 100% first pass clearance of a microbubble on passage through the alveolar capillaries as the gas diffuses rapidly out of the microbubble into the alveolus down the concentration gradient. Microbubbles seen in the left heart should therefore be the result of a right to left shunt - either cardiac (most commonly a patent foramen ovale, PFO [160, 161]), or pulmonary. Typically, with an intrapulmonary shunt such as a PAVM, the number of bubbles in the left heart increases over a matter of seconds. The entry of bubbles is not affected by the cardiac cycle or respiration, and though influenced slightly by a Valsalva manoeuvre, this is in a more subtle manner to the changes observed with a PFO. Although PFOs are said to produce earlier opacification, shunting may not occur for many beats after the right heart opacifies, until the

moment when the patient takes a breath in, causing shunting across the PFO. Intrapulmonary shunt origin is certain if the bubble density is greater in the left heart than the right, often requiring 30-60 seconds recording.

In the absence of a R-L shunt, small numbers of bubbles (~< 5/frame) may be seen despite having passed through the alveolar capillaries. Such "alveolar transit" bubbles are smaller than the bubbles in the right heart because most of the gas has been removed, but they have not entirely collapsed. Alveolar transit bubble numbers increase with repeated injection, either because some of the bubbles are left over from the earlier injections, or due to changes/damage to the delicate alveolar capillary interface because of the previous passage of bubbles through alveolar capillaries. Alveolar transit increases as cardiac output increases, and during peak exercise, most people have bubbles detectable in the left heart on contrast echocardiogram (PW, personal observation). Intrapulmonary shunting is also demonstrated in a proportion of healthy subjects at rest (5/19 in [162]; 7% of 100 controls[166]).

CE consistently detects more intrapulmonary R-L shunting in HHT patients than any other PAVM screening modality, and early manuscripts demonstrating high sensitivity [77] and low risk [155, 163], were the reason for the guideline recommendation [74]. While false negatives have been reported [155, 164], the negative predictive value of a negative CE assessed in several specialised units is of the order of 98% [164].

Grade	Definition	PPV	% all HHT [165-167]	% of HHT1 [83]	% of HHT2 [83]
Grade 0	no bubbles	0	25-35	15	65
Grade 1	'minimal LVO'; <20, <30 b/f	0-0.02	20-36	13	21
Grade 2	'moderate LVO Or 30-100 b/f	0 *- 0.56	12-21	26	6
Grade 3 +	'complete LVO' 'extensive LVO'	0.31* - 1.00	5-11	46	8

Table 3: Summary of published graded contrast echo series in HHT: Data in all groups drawn from studies of 71-90"HHT all" [165-167], 92 HHT1 [83], and 97 HHT2 [83] individuals. Posture and exact timings differed between the studies that were conducted in four different specialised HHT centres, but all documented the presence of late shunts after at least 3 cardiac cycles. b/f; bubbles per frame; LVO, left ventricular opacification * in HHT2 [83]

Unfortunately, completely negative scans are not particularly common in HHT patients (Table 3). To attempt to reduce the proportion of screened patients requiring subsequent thoracic CT scans, shunts have been graded, based on the number of microbubbles appearing in the left ventricle on a single frame [163]. Table 3 delineates the data suggesting that Grade 1 and Grade O shunt patients may be spared a CT scan. One prospective series of 105 patients suggested this might extend to a grade 2 shunt [164], but in other studies, Grade 2 positive shunts were associated with PAVMs of a size amenable to embolisation [155 165].

The variations of positive predicted values in these reports may include biological factors such as the variability between hospitals/centres in the local HHT genotypes and hence rates of large PAVMs seen. It is also possible that there was a contribution from the variability in how the contrast echocardiography was performed: The articles referenced in Table 3 used slightly different methods of producing bubble contrast including use [83] and non use [165 166 167] of blood in the syringes, and use of Gelofusine® [167] which produces a similar appearance to bubble contrast on echocardiography, but is not removed on first pass through the lungs. In addition, patient posture, exact timings and other test parameters differed between the studies. Such variation in study methodology is important as adequate opacification of the right heart is essential to demonstrate bubbles appearing in the left heart, and the density of bubbles in the right heart can be altered by varying factors such as the volumes and ratios of air, saline and the patient's blood used; the number of times the mixture is pushed back and forth through a 3-way tap; the size of the IV cannula used; how proximal the injection site is and its relationship to the level of the heart; the patient's posture; anatomic problems such as delayed arrival in muscular men as a result of axillary vein compression by well developed pectoral muscles; autonomic tone; and heart rate.

Even though the studies in Table 3 were performed by highly experienced dedicated PAVM contrast echocardiography centres in which these factors were standardised, positive predicted values varied. Where less dedicated centres choose to use a negative or Grade 1 contrast echocardiographic study to withhold a CT scan for an HHT patient undergoing screening for PAVMs, it is essential that they are confident there were not methodological reasons for a possible false negative.

PAVM Embolization

Methods of embolization

As described elsewhere [168], prophylactic intravenous antibiotics are administered in all cases (1g Vancomycin) one hour before the combined diagnostic and therapeutic procedure. The pulmonary artery pressure is measured in all individuals at the time of angiography. Selective right and/or left pulmonary digital subtraction arteriograms are then obtained via a femoral venous approach to document the anatomy of treatable lesions. In patients in whom previous CT has demonstrated unilateral PAVMs, that side only need be studied at the time of angiography. Selective catheterization of the feeding vessel(s) to each treatable PAVM is then performed and once a suitable position has been achieved as distally as possible within the feeding vessel, embolization is performed with an Amplatzer vascular plug (AVP) (AGA Medical Corporation, Plymouth, Minnesota USA) or metallic coils of an appropriate size for the vessel being occluded. Embolization is ideally performed at the neck of the malformation (i.e. at the site of the arteriovenous communication) in an attempt to avoid the occlusion of normal pulmonary artery branches and to reduce the risk of the development of a bronchial arterial collateral supply to the sac. Additional feeding vessels to this, and other, PAVMs are treated in the same manner.

Amplatzer vascular plugs are rapidly becoming the preferred agent for PAVM embolization as they have a number of important advantages over coils:

- Distal occlusion of the feeding vessel to a PAVM at the neck of the venous sac, is often very difficult to achieve with metallic coils, particularly when the feeding vessel is large, because of the risk of coil migration through the sac into the systemic circulation with potentially disastrous complications. This problem is overcome in most PAVMs by the AVP; the vascular sheath through which the plug is to be deployed can usually be placed at the neck of the PAVM and can, in some instances, be introduced into the venous sac itself. The plug can then be introduced with the sheath in this position and deployed during sheath withdrawal.
- A larger number of PAVMs can be embolized in a single session, because complete occlusion of large diameter feeding arteries (measuring up to 12mm in diameter) can be achieved with a single AVP in the majority of cases, instead of the use of several metallic coils.
- A shorter length of vessel is occluded, reducing the likelihood of occluding vessels supplying normal lung;

The duration of the embolization intervention is determined by the number and complexity of the malformations requiring embolization and patient tolerance to the procedure but, in general, each procedure lasts between 90 and 120 minutes. Post operatively, patients lie semi-erect in bed for 4 hrs before mobilizing. The majority of individuals treated at our institution remain in hospital overnight because of the long distance they have to travel home and we are able, therefore, to obtain post-embolization oxygen saturation data on the morning of discharge to document the immediate response to treatment. Although unlikely, it is possible that thrombus on an embolic device, or within the venous sac of an embolized PAVM, will migrate in the post-embolization period; we consider it reasonable, therefore, to advise patients on discharge to avoid strenuous exercise for several days post-procedure. Those with residual PAVMs of a treatable size are readmitted at approximately three month intervals for further embolization until complete occlusion of all of these lesions has been achieved.

Other embolization techniques such as packing the venous sac with coils or using an occlusion balloon catheter to reduce flow during vessel occlusion are now rarely necessary since the introduction of detachable coils and plugs. Post-embolization, residual shunting through untreatable (< 2 mm diameter) arterial feeding vessels is common. For example, in a series of 192 PAVM patients in whom feeding arteries less than 3 mm in diameter were embolized, [3] 70% had residual disease, a finding supported by other studies [135, 152, 169].

Results of embolization

Embolisation series published to date provide clear evidence for regression of the PAVM sac [170],substantial improvement in oxygenation for patients with pre-embolization hypoxaemia [104, 108, 135, 136, 171-173] and effective treatment of life-threatening haemorrhage [2 97 174]. A recent study demonstrated the clinical efficacy of embolization in improving stroke/abscess risk, [3] though strokes/abscesses do occur in some patients post-embolization due to small untreatable PAVMs. There is also evidence that the prevalence of migraine is reduced [175 139]. Since intracardiac shunt closure also often improves migraine, a current hypothesis is that such shunts allow migraine trigger substances, possibly vasoactive amines liberated in venous blood, to reach the brain by circumventing the alveolar capillaries where they would normally be destroyed on first-pass.

When all feeding arteries to a PAVM sac have been obliterated, the sac regresses, with clear evidence of improvement by 6 months in most cases. However, if all feeding arteries have not been embolized, or if recanalization of occluded vessels occurs, the sac will fail to regress. It is expected that the switch to the use of Amplatzer plugs [168, 176] will reduce the likelihood of post embolization recanalization[156,177,170].

Risks of Embolization

In expert hands, the technique is efficacious, and complications are rare, though the procedure is not without risk. Successive series highlight a learning curve [1, 109], and smaller series have higher complication rates [128]. The most common complication is of transient pleurisy in up to 10% of patients, particularly those with peripheral PAVMs, and higher rates are seen for patients with diffuse PAVMs [90]. The mechanism for the pleurisy is unknown but it appears unrelated to pulmonary infarction [88, 104]. Angina, due to transient air bubble emboli, has been reduced by technical advances in later series. There are occasional reports of long term neurological complications following paradoxical emboli [178].

Development of Systemic Arterial Supply: The risk of massive haemoptysis from PAVM sacs that persist post-embolization and that acquire a systemic arterial collateral blood supply was first highlighted in a small series published in 1998, when haemoptysis was a frequent complication [128]. In a further series, 13 of 32 patients demonstrated abnormally large arteries of bronchial, inferior phrenic, musculophrenic, internal mammary or intercostal origin, but none of these cases experienced haemoptysis [179]. Peri-procedural pulmonary infarction [179] is not a pre- requisite for development of systemic arterial feeders. As elegantly demonstrated using post mortem aortograms and subsequent microradiographs, pulmonary emboli are one of the pulmonary pathologies that stimulate pathological bronchial artery proliferation, resulting in the acquisition of hypertrophied, tortuous systemic to pulmonary collaterals, in which systemic arteries penetrate the pulmonary vascular media and intima [180]. These pathological communications are anatomically distinct from the normal communications between terminal branches of the bronchial microcirculation and peripheral pulmonary artery branches [1, 180].

Where aberrant systemic arterial supply to PAVMs exists but has not manifest by haemoptysis, it is not clear whether embolization therapy is warranted. It is intriguing to recall that there is currently no explanation for the control of the systemic-pulmonary pressure drop in normal bronchopulmonary communications, since the internal longitudinal

muscle bundles present in so called Sperrarterien (blockading arteries) [181, 182] do not reflect sphincter function but are generated by stretching the vessel [183]. Where aberrant systemic arterial supply to PAVMs is present in the setting of haemoptysis, which may be massive, favoured treatment is by selective bronchial artery angiography [184, 185], discussed elsewhere [1, 186].

Effect of embolization on pulmonary artery pressure: PAVM embolization[102, 171, 187, 188] and surgical resection [189] can elevate *P*pa by removal of the PAVM low resistance pathway. However, in the majority of 35 patients with consecutive *P*pa measurements, there was no evidence of a sustained or acute change in *P*pa [108]. In half, embolization led to a fall in *P*pa, attributed to a reduction in cardiac output [171]. PAVM patients clearly differ in their haemodynamic responses to embolization, and it has been suggested that deleterious rises may relate to underlying hepatic AVMs [108, 187, 190]. Temporary balloon occlusion of the PAVM before definitive embolization has been suggested in order to identify which patients are at risk of such an increase [187, 190] but where *P*pa mean did rise following definitive embolization (by 22mmHg), this rise was not predicted by test balloon occlusion [108].

Post embolization follow-up

Following initially complete embolization or surgical resection, residual macroscopic disease may develop several months after treatment, following a period of vascular remodeling, unmasking or apparently provoking the development of additional PAVMs or new pulmonary artery feeder vessels. As a result, review of all patients and right-to-left shunt measurement after several months is generally recommended, and a series of treatments may be needed. The international guidelines [74] recommend post embolization CT at 6-12 months. At our institution we prefer to limit radiation exposure in this often young population: Initial follow up is therefore with CXR and oxygen saturations, with CTs reserved for patients demonstrating new symptoms, deteriorating oxygen saturations, or failure to obliterate a PAVM sac which would have been predicted based on angiographic appearances. Further follow up is recommended for post embolization patients 2-3 yearly, and patients with small untreated PAVMs , or CE positive patients 1-5 yearly [74].

Other treatment options for PAVMs:

Surgery

Embolization has generally supplanted surgical procedures, due to reduced periprocedural risks, parenchymal sparing in patients at risk of recurrent disease, and the documented benefits. Although there are no randomised control trials comparing embolization and surgery, it is recognized that to perform such studies now would be unethical in view of the reported benefits of embolization and recognition that the vast majority of PAVM patients do not have disease suitable for surgery [191].

Surgical resection of PAVMs may be useful however, in two settings. The first is as an adjunctive therapy for highly selective cases where further embolization is not feasible (the commonest reason being that the feeding artery is too small (< 2 mm diameter), but PAVMs are sufficiently localized for thoracoscopic resection). At our institution, we reserve elective surgical approaches for highly selected patients with ongoing ischaemic strokes, transient ischaemic attacks, or significant respiratory symptoms following maximal embolization. Secondly, in emergency situations, particularly associated with massive haemoptysis, lobectomy or pneumonectomy may be appropriate [192,11].

Lung transplantation has been undertaken in a few patients with severe hypoxemia secondary to diffuse disease. [193, 194]. However, the natural history of such disease is more favourable than might be expected: In a retrospective series of 36 patients with diffuse PAVMs for whom follow-up data were available for a mean of 8.5 years (range 0.12- 26 yr), 24 of the 27 survivors were working or studying full time, whereas one of the deaths was transplantation-associated [90]. Three severely hypoxaemic PAVM patients in our clinic who elected not to proceed with lung transplantation after assessments at two different transplant centres have since remained stable over 15-19 years respectively, and one patient has had three successful pregnancies. Thus the long-term complications of untreated PAVMs, are likely in most cases to be less than transplantation-associated morbidity and mortality.

Dental:

In an effort to reduce frequency of cerebral abscess, antibiotic prophylaxis was recommended before dental and surgical procedures for patients with PAVMs and HHT, based on the endocarditis paradigm. The American Heart Association [195] and British NICE

guideline committee [196] have both stated that antibiotic prophylaxis is no longer required for most patients with structural heart disease. PAVM/HHT patients did not fall into the groups considered by AHA/NICE however [197], and individually, are at ~100 fold higher risk than patients with structural heart disease [3]. There is also strengthened evidence for an association between periodontal microorganisms and cerebral abscess [3]. As a result antibiotic prophylaxis is still recommended for PAVM/HHT patients prior to dental procedures, in addition to measures to improve overall dental hygiene [197].

Thromboembolic risk management:

In contrast to advice given to patients in earlier years, it is now recognised that there are settings in which anticoagulants (and/or antiplatelet agents) are required [74] in order to prevent major ischaemic or thromboembolic sequelae. Prophylactic dose anticoagulation for example is required during high risk periods for venous thromboemboli (VTE)[10], particularly for HHT patients hospitalized with pulmonary AVM-induced cerebral abscess [10]. Where VTEs occur, treatment dose heparin and warfarin can be given, though clinical decisions are often compounded by recognition of pre-existing anaemia or concern about visceral haemorrhages [65]. For patients experiencing transient ischemic attacks or ischaemic strokes, we recommend that options such as cessation of hormonal and prothrombotic therapies, and conventional antiplatelet therapy [198], should be considered on a case-by-case basis, even if there is underlying HHT [10]. In our experience, anticoagulation is tolerated surprisingly well by many patients, but primary prevention strategies are difficult to justify. [199].

Pregnancy management:

As a result of case reports and small series, HHT/PAVM specialist centres have recommended PAVM treatment before pregnancy for many years. Radiation assessment studies indicated that embolization may be undertaken during pregnancy [200], and routine embolization in the later stages of pregnancy is performed in some centres where pre-pregnancy treatment was not feasible [74]. Nevertheless, in view of the life threatening nature of the haemorrhages, and uncertainty about the rate at which such complications occurred, some PAVM patients were being advised to avoid pregnancy.

Based on the data from the study of 484 pregnancies in 199 women with HHT and PAVMs demonstrating that that the majority were able to have a normal pregnancy, but a small

proportion did experience life-threatening complications[11], general recommendations for the management of women with HHT/PAVMs were developed[11]. These included management as "high risk" pregnancies; maternal education to consider haemoptysis of any degree or sudden severe dyspnoea as a medical emergency prompting urgent hospitalization; and specific obstetric, and obstetric anaesthetic issues discussed in detail elsewhere [11]. As described in [11], we recommend PAVM screening and treatment pre-pregnancy, but during pregnancy, PAVM embolization is generally not offered unless the pregnant patient is experiencing haemoptysis. This is because of the low risk of PAVM-associated complications, lack of evidence that PAVM embolization during pregnancy in women who have not experienced a complication reduces the risk of haemorrhage in the second and third trimester; and risks associated with PAVM embolization which involves ionizing radiation and, as for any intervention, the potential for inducing pre-term labour.

Diving and HHT /PAVMs:

The international guidelines recommend that patients who have a PAVM, or patients with HHT in whom PAVMs have not been excluded, should avoid diving lifelong [74]. In our experience, while many patients are happy to be informed they should not take up this sport, being cautioned against diving is extremely difficult for active divers, and many others in the large group of HHT/PAVM patients who are highly active and sporty [110]. For existing divers, restricting dive profiles or using breathing gas mixtures that avoid venous bubble liberation should overcome the risk of decompression illness in the presence of a right to left shunt. If there are no venous bubbles, the presence of a right to left shunt cannot increase the risk of decompression illness. Before undertaking diving, we therefore recommend that an individual with a R-L shunt, such as a PAVM, should be counselled by a physician with knowledge of diving medicine.

Anti-angiogenesis strategies

The authors are alarmed about information and enquiries that they are receiving from patients and physicians regarding possible anti-angiogenesis approaches for PAVMs. Interest has arisen as a result of a brief report of a patient whose hepatic AVMs initially responded to the humanized anti VEGF antibody Bevazicimub (Avastin) [201], and evidence of topical efficacy in the treatment of HHT nosebleeds. Thalidomide has also been suggested for use in HHT-related haemorrhage, based on case reports [202, 203] and a very

small uncontrolled short series [51]. The authors are aware of further case reports, and ongoing trials of these agents in carefully selected consenting patients in major HHT centres for other aspects of HHT, but not of any data or ongoing trials for PAVMs.

In our opinion, in the absence of any data for PAVMs, the major toxicities of the currently available systemic approaches [204-207], preclude any use in PAVM patients whose longevity and long-term exercise capacitance have always surprised their physicians (see transplantation section above). There is of course, however, great excitement about the mechanistic insights and potential for future therapeutic developments, but lessons may be learned from the withdrawal of FDA approval for Bevazicimub in the setting of metastatic breast cancer, a disease with a far graver prognosis than PAVMs, because treatment was associated with considerable toxicity, without sufficient evidence of benefit [208].

PULMONARY HYPERTENSION IN HHT

Overview

PH has been recognised in a number of HHT patients [9, 95, 102, 209-212]. As recently reviewed [13, 108], and explored elsewhere in this monograph, two forms of PH predominate in HHT. Post-capillary pulmonary hypertension (PH) develops as a result of long-term increases in left atrial pressure accompanying elevated cardiac output states, particularly in the setting of hepatic AVMs. In many cases, this PCPH is reversible if the causative hepatic AVMs are treated, with liver transplantation the current treatment of choice [74, 213]. In addition, pulmonary arterial hypertension, characterised by elevated intrinsic pulmonary vascular resistance with low pulmonary venous (wedge) pressures, occurs [9, 102, 214], and appears to be independent to other HHT vascular pathologies. Mixed pictures are also observed [108].

Prevalence

The overall prevalence of PH in HHT is low, as shown by catheter-based studies in a group of 143 PAVM/HHT patients undergoing PAVM embolization (Figure 6) [108] and an echocardiographic study from a separate HHT population, where estimated systolic PAP were above the normal range in 9 (20.5%) [215].

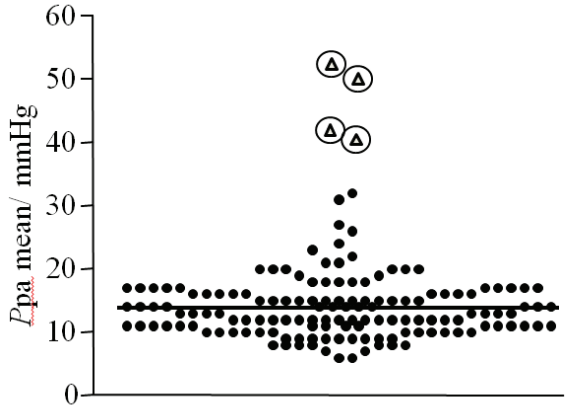

Figure 6: Ppa mean distribution in a UK PAVM series: Comparison of *P*pa mean for 143 patients PAVM patients undergoing embolization (plain symbols), and the four patients not offered embolization (ringed symbols). Reproduced from reference [125] *(ERJ)*. *P*pa mean exceeded 20mmHg in 9/143 (6%), but only two patients referred from services other than specialised pulmonary hypertension units had *P*pa mean exceeding 35mmHg.

Types of pulmonary hypertension

In HHT, pulmonary hypertension occurs predominantly in HHT2 families [214, 216, 217]. In part this reflects the common pathogenic pathways mutated in HHT and PAH (see Figure 3) [9, 79, 214, 218]. However, HHT2 patients are also at higher risk of post capillary pulmonary hypertension (PCPH), as hepatic AVMs, and severe disease due to hepatic AVMs, is more common than in HHT1 [7982, 219]. It is not clear that *ENG* missense polymorphisms reported in association with PAH are HHT-disease causing, and in a recent PAH-HHT series, all cases resulted from ALK1 mutations [217]. Nevertheless, there is evidence from animal models to implicate endoglin mutations in the pathogenesis of pulmonary hypertension [220].

Implications if co-existing PAVMs

Generally the presence of HHT/PAVMs does not modify the sub-speciality management protocols for PH, except for the need to rule out hepatic AVMs that may be a potentially reversible cause of PCPH. When PAH occurs within HHT2/ALK1 patients, it may have a worse prognosis than when due to *BMPR2* mutations [217].

In contrast, the presence of PH substantially modifies risk benefit considerations regarding treatment of PAVMs (Table 4). The risk of paradoxical embolic stroke is substantially lower in individuals with higher *P*pa [125]**,** and symptomatic relief from dyspnoea should not be expected for patients with pulmonary hypertension and higher SaO_2. We conclude that for patients with pre-existing severe pulmonary hypertension, the risks of pulmonary AVM embolization generally outweigh potential benefits. However, the most difficult

judgements relate to individuals with severe PH and major haemoptysis or haemothorax which may be a terminal event [108]. In pregnant women (without PH) in our series [11], and in PH cases known to us, there was time for emergency intervention to be performed after the onset of herald symptoms. In such an emergency setting, patients and their physicians may consider the risks of precipitating a further, potentially fatal increase in *P*pa justifiable.

PAVM Risk	All PAVM patients	Pulmonary hypertension PAVM patients	References
Ischaemic stroke	11.3%	lower (HR 0.89 (95% CI 0.83, 0.95) per mmHg increase, p=$6.2x10^5$)	[3]
Brain abscess	9%	Unchanged	[3]
Dyspnoea ±	1.5; 3.2; 14; 37%	Universal, and more severe	
Haemoptysis	<10%; usually minor	? more common and severe	[190]
Migraine	two fold excess	No data	[137]
Growth	generally nil/slow©	? increased	[95]

Table 4: : PAVM risk-benefit analyses in the presence of pulmonary hypertension. Reproduced from [125]. ±according to SaO_2 quartiles (>96; 93-96; 88-93; <88)% of population reported in [3, 108].©except during puberty and pregnancy. HR hazard ratio; CI confidence intervals.

Conclusions

In summary, due to the risks of paradoxical embolic stroke and pregnancy-related complications, irrespective of symptoms, PAVM patients should be offered embolisation of all vessels of a size amenable to this form of treatment unless there are contraindications. They should also be provided with regular follow-up and advice on dental hygiene, antibiotic prophylaxis, pregnancy and diving. The importance of magnetic resonance imaging to rule out cerebral abscess for PAVM patients presenting with stroke-like symptoms needs to be recognised. Pulmonary hypertension and/or hepatic AVMs with high output cardiac states are relative contraindications to embolisation in the non-emergency situation. Surgery is rarely necessary and should be avoided if possible because of the likelihood of extensive or recurrent disease. There is no current role for anti-angiogenesis strategies.

REFERENCES

1. Shovlin CL, Jackson JE. Pulmonary Arteriovenous Malformations and other pulmonary-vascular abnormalities. In: Mason, Broadbus, Murray, Nadel, eds. Murray and Nadel's Textbook of Respiratory Medicine. 5th ed. Pennsylvania: Elsevier-Saunders; 2010:1261–73
2. Ference BA, Shannon TM, White RI, Zawin M, Burdge CM. Life threatening pulmonary hemorrhage with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia. Chest 1994;106:1387-92.
3. Shovlin CL, Jackson JE, Bamford K, et al. Primary determinants of ischaemic stroke/ brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-66.
4. Plauchu H, deChadarévian J-P, Bideau A, Robert J-M. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 1989;32:291-7.
5. Buscarini E, Buscarini L, Civardi G, Arruzzoli S, Bossalini G, Piantanida M. Hepatic vascular malformations in Hereditary Hemorrhagic Telangiectasia: Imaging findings. Am J Radiol 1994;163:1105-10.
6. Kjeldsen A, Kjeldsen J. Gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. Am J Gastroenterol 2000;95:415-8.
7. Willemse RB, Mager JJ, Westermann CJJ, Overtoom TT, Mauser H, Wolbers JG. Bleeding risk of cerebrovascular malformations in hereditary haemorrhagic telangiectasia. J Neurosurgery 2000;92:779-84.
8. Krings T, Ozanne A, Chng S, Alvarez H, Rodesch G, Lasjaunias P. Neurovascular phenotypes in hereditary haemorrhagic telangiectasia patients according to age. Review of 50 consecutive patients aged 1 day-60 years. Neuroradiology 2005;47:711-20.
9. Trembath R, Thomson J, Machado R, et al. Clinical and molecular features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. New Engl J Med 2001;345:325-34.
10. Shovlin CL, Sulainam NL, Govani FS, Jackson JE, Begbie ME. Elevated Factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. Thrombosis and Haemostasis 2007;98:1031-9.

11. Shovlin CL, Sodhi V, McCarthy A, Lasjaunias P, Jackson JE, Sheppard MN. Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia: suggested approach for obstetric services. BJOG 2008;115:1108-15.
12. Shovlin CL, Letarte M. Hereditary Haemorrhagic Telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-29.
13. Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. Eur Respir J 2009;33:1186-94.
14. Bideau A, Brunet G, Heyer E, Plauchu H, Robert J-M. An abnormal concentration of cases of Rendu-Osler disease in the Valserine valley of the French Jura: a geneological and demographic study. Annals of Human Biology 1992;19:233-47.
15. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. J Intern Med 1999;245:31-9.
16. Jessuron GA, Kamphuis DJ, Zande FHvd, Nossent JC. Cerebral arteriovenous malfomations in the Netherlands Antilles. High prevalence of hereditary hemorrhagic telangiectasia-related single and multiple cerebral arteriovenous malformations. Clin Neurol Neurosurg 1993;95:193-8.
17. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. Hum Mut 2002;19:140-8.
18. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-7.
19. Letteboer TG, Zewald RA, Kamping EJ, et al. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet 2005;116:8-16.
20. Prigoda NL, Savas S, Abdalla SA, et al. Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations. J Med Genet 2006;*in press*.
21. Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat 2006;27:667-75.
22. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-b binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nature Genetics 1994;8:345-51.

23. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nature Genetics 1996;13:189-95.
24. Gallione C, Repetto GM, Legius E, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia is associated with mutations in *MADH4 (SMAD4)*. Lancet 2004;363:852-9.
25. Cole SG, Begbie ME, Wallace GMF, Shovlin CL. A new locus for hereditary haemorrhagic telangiactasia (*HHT3)* maps to chromosome 5. J Med Genet 2005;42:577-82.
26. Govani F, Shovlin C. Fine mapping of the hereditary haemorrhagic telangiectasia (HHT)3 locus on chromosome 5 excludes Sprouty 4, VE-cadherin 2 and other interval genes. J Angiogenesis Research 2010;11:15.
27. Bayrak-Toydemir P, McDonald J, Akarsu N, et al. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. Am J Med Genet 2006;140:2155-62.
28. Shovlin C, Oh S. Hereditary haemorrhagic Telangiectasia. In: F M, ed. Molecular basis of lung disease: Humana Press; 2010.
29. Shoukier M, Teske U, Weise A, Engel W, Argyriou L. Characterization of five novel large deletions causing hereditary haemorrhagic telangiectasia. Clin Genet 2008;73:320-30.
30. Gallione C, Klaus D, Yeh E, et al. Mutation and expression analysis of the endoglin gene in hereditary haemorrhagic telangiectasia. Human Mutation 1998;11:286-94.
31. Shovlin CL, Hughes JM, Scott J, Seidman CE, Seidman JG. Characterization of endoglin and identification of novel mutations in hereditary hemorrhagic telangiectasia. Am J Hum Genet 1997;61:68-79.
32. Shovlin CL. Molecular defects in rare bleeding disorders: Hereditary Haemorrhagic Telangiectasia. Thrombosis and Haemostasis 1997;78:145-50.
33. Pece N, Vera S, Cymerman U, White R, Wrana J, Letarte M. Mutant endoglin in Hereditary Hemorrhagic Telangiectasia type I is transiently expressed intracellularly and is not a dominant negative. J Clin Invest 1997;100:2568-79.
34. Pece-Barbara N, Cymerman U, Vera S, Marchuk D, Letarte M. Expression analysis of four endoglin missense mutations suggests haploinsufficiency is the predominant mechanism for Hereditary Hemorrhagic Telangiectasia type I. Human Molecular Genetics 1999;8:2171-81.

35. Paquet ME, Pece-Barbara N, Vera S, et al. Analysis of several endoglin mutants reveals no endogenous mature or secreted protein capable of interfering with normal endoglin function. Hum Mol Genet 2001;10:1347-57.
36. Bourdeau A, Cymerman U, Paquet ME, et al. Endoglin expression is reduced in normal vessels but still detectable in arteriovenous malformations of patients with hereditary hemorrhagic telangiectasia type 1. Am J Pathol 2000;156:911-23.
37. Cymerman U, Vera S, Pece-Barbara N, et al. Identification of Hereditary Hemorrhagic Telangiectasia type I in newborns by protein expression and mutation analysis of endoglin. Pediatric Research 2000;47:24-35.
38. Fernandez LA, Sanz-Rodriguez F, Zarrabeitia R, et al. Mutation study of Spanish patients with hereditary hemorrhagic telangiectasia and expression analysis of Endoglin and ALK1. Hum Mutat 2006;27:295.
39. Ricard N, Bidart M, Mallet C, et al. Functional analysis of the BMP9 response of ALK1 mutants from HHT2 patients: a diagnostic tool for novel ACVRL1 mutations. Blood 2010;116:1604-12.
40. Knudson AG Jr. Hereditary cancer, oncogenes, and antioncogenes. Cancer Research 1985;45:1437-43.
41. Braverman IM, Keh A, Jacobson BS. Ultrastructure and three-dimensional organization of the telangiectases of hereditary hemorrhagic telangiectasia. J Invest Dermatol 1990;95:422-7.
42. Park S, Wankhede M, Lee Y, et al. Real-time imaging of de novo arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia. J Clin Invest 2009;119:3487-96.
43. Owens CD. Adaptive changes in autogenous vein grafts for arterial reconstruction: clinical implications. J Vasc Surg 2010;51:736-46.
44. Shovlin CL. Hereditary haemorrhagic telangiectasia: Pathogenesis, diagnosis and treatment. Blood Reviews 2010;24:203-19.
45. Wolinsky H, Glagov S. A lamellar unit of aortic medial structure and function in mammals. Circ Res 1967;20:99-111.
46. Hales M. Multiple small arteriovenous fistulas of the lungs. Am J Path 1956;32:927-37.
47. Yater W, Finnegan J, Giffin H. Pulmonary arteriovenous fistula (varix). JAMA 1949;141:581-9.

48. Bourdeau A, Cymerman U, Paquet M-E, et al. Endoglin expression is reduced on normal vessels but still detectable in arteriovenous malformations of patients with Hereditary Haemorrhagic Telangiectasia type I. Am J Pathol 2000;156:911-23.
49. Belik J, Jerkic M, McIntyre B, et al. Age-dependent endothelial nitric oxide synthase uncoupling in pulmonary arteries of endoglin heterozygous mice. Am J Physiol Lung Cell Mol Physiol 2009;297:L1170-8.
50. Mahmoud M, Allinson K, Zhai Z, et al. Pathogenesis of Arteriovenous Malformations in the Absence of Endoglin. Circ Res 2010;Mar 11. [Epub ahead of print].
51. Lebrin F, Srun S, Raymond K, et al. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. Nat Med 2010;16:420-8.
52. Mahmoud M, Borthwick G, Hislop A, Arthur H. Endoglin and activin receptor-like-kinase 1 are co-expressed in the distal vessels of the lung: implications for two familial vascular dysplasias, HHT and PAH. Lab Invest 2009;89:15-25.
53. Li C, Guo B, Ding S, et al. TNF alpha down-regulates CD105 expression in vascular endothelial cells: a comparative study with TGF beta 1. Anticancer Res 2003;23:1189-96.
54. Torsney E, Charlton R, Parums D, Collis M, Arthur HM. Inducible expression of human endoglin during inflammation and wound healing in vivo. Inflammation Research 2002;51:464-70.
55. Toporsian M, Gros R, Kabir M, et al. A role for endoglin in coupling eNOS activity and regulating vascular tone revealed in hereditary hemorrhagic telangiectasia. Circ Res 2005;96:684-92.
56. Oh SP, Seki T, Goss KA, et al. Activin receptor-like kinase 1 modulates transforming growth factor-beta 1 signaling in the regulation of angiogenesis. Proc Natl Acad Sci U S A 2000;97:2626-31.
57. Mancini M, Terzic A, Conley B, Oxburgh L, Nicola T, Vary C. Endoglin plays distinct roles in vascular smooth muscle cell recruitment and regulation of arteriovenous identity during angiogenesis. Dev Dyn 2009;238:2479-93.
58. Carvalho R, Jonker L, Goumans M, et al. Defective paracrine signalling by TGFbeta in yolk sac vasculature of endoglin mutant mice: a paradigm for hereditary haemorrhagic telangiectasia. Development 2004;131:6237-47.
59. Letarte M, McDonald ML, Li C, et al. Reduced endothelial secretion and plasma levels of transforming growth factor-ß1 in patients with hereditary haemorrhagic telangiectasia type 1. Cardiovasc Res 2005;68:155-64.

60. David L, Mallet C, Mazerbourg S, Feige JJ, Bailly S. Identification of BMP9 and BMP10 as functional activators of the orphan activin receptor-like kinase 1 (ALK1) in endothelial cells. Blood 2007;109:1953-61.
61. Scharpfenecker M, van Dinther M, Liu Z, et al. BMP-9 signals via ALK1 and inhibits bFGF-induced endothelial cell proliferation and VEGF-stimulated angiogenesis. J Cell Sci 2007;120:964-72.
62. Bailly S. HHT is not a TGFb disease. Blood 2008;111:478.
63. Letteboer T, Mager H, Snijder R, et al. Genotype-phenotype relationship for localization and age distribution of telangiectases in hereditary hemorrhagic telangiectasia. Am J Med Genet A 2008;146A:2733-9.
64. Sabroe I, Bloom S, Hughes JMB, Shaunak S, Robertson I and Lynn WA. Thromboembolic occlusion of a pulmonary arteriovenous malformation. A very unusual pulmonary embolism. BMJ 1995;311:553-5.
65. Roked F, Jackson J E, Fuld J, et al. Pulmonary thromboemboli modifying the natural history of pulmonary arteriovenous malformations. . Am J Resp Crit Care Med 2011;183:828-9.
66. Riviere S, Pelenc D, Dupuis Girod S, et al. Hereditary haemorrhagic telangiectasia and venous thromboembolism. Hematology Meeting Reports 2009;3:54–5.
67. Kraaijenhagen RA, in'tAnker PS, Koopman MM, et al. High plasma concentration of Factor VIIIc is a major risk factor for venous thromboembolism. Thrombosis and Haemostasis 2000;83:5-9.
68. Kyrle PA, Eichinger S. The risk of recurrent venous thromboembolism: the Austrian study on recurrent venous thromboembolism. Wien Klin Wochenschr 2003;115:471-4.
69. Bonderman D, Turecek PL, Jakowitsch J, et al. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost 2003;90:372-6.
70. Wolf M, Boyer-Neumann C, Parent F, et al. Thrombotic risk factors in pulmonary hypertension. Eur Respir J 2000;15:395-9.
71. Wong CL, Szydlo R, Gibbs S, Laffan M. Hereditary and acquired thrombotic risk factors for chronic thromboembolic pulmonary hypertension. Blood Coagul Fibrinolysis 2010;21:201-6.
72. Jacquemin M, Neyrinck A, Hermanns MI, et al. FVIII production by human lung microvascular endothelial cells. Blood 2006;108:515-7.

73. Shovlin CL, Govani GS, Okoli GN, et al. Endothelial cell processing and alternatively spliced transcripts of Factor VIII. Potential implications for coagulation cascades and pulmonary hypertension. PLOS One 2010;5:e9154.
74. Faughnan M, Palda V, Garcia-Tsao G, et al. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2011;48:73-87.
75. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: A clinical and scientific review. Eur J Hum Genet 2009;17:860-71.
76. Dupuis-Girod S, Bailly S, Plauchu H. Hereditary hemorrhagic telangiectasia (HHT): from molecular biology to patient care. J Thromb Haemost 2010;Mar 19. [Epub ahead of print].
77. Cottin V, Plauchu H, Bayle J-Y, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
78. Kjeldsen AD, Møller TR, Brusgaard K, al e. Clinical symptoms according to genotype amongst patients with hereditary haemorrhagic telangiectasia. J Int Med 2005;258:349-55.
79. Letteboer TGW, Mager JJ, Snijder RJ, et al. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet 2006;43:371-7.
80. Bayrak-Toydemir P, McDonald J, Markewitz B, et al. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia. Am J Med Genet A 2006;140:463-70.
81. Sabbà C, Pasculli G, Lenato GM, et al. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-57.
82. Lesca G, Olivieri C, Burnichon N, et al. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med 2007;9:14-22.
83. van Gent MW, Post MC, Snijder RJ, Westermann CJ, Plokker HW, Mager JJ. Real prevalence of pulmonary right-to-left shunt according to genotype in patients with hereditary hemorrhagic telangiectasia: a transthoracic contrast echocardiography study. Chest 2010;138:833-9.
84. Anabtawi IA, Ellison RG, Ellison LT. Pulmonary arteriovenous aneurysms and fistulas. Annals of Thoracic Surgery 1965;1:277-85.

85. Bosher L, Blake A, Byrd B. An analysis of the pathologic anatomy of pulmonary arteriovenous aneurysms with particular reference to the applicability of local excision. Surgery 1959;45:91-104.
86. Shumacker H, Waldhausen J. Pulmonary arteriovenous fistulas in children. Annals of Surgery 1963;158:713-20.
87. White RIJ, Lynch-Nylan A, Terry P, et al. Pulmonary arteriovenous malformations: Techniques and long-term outcomes of embolotherapy. Radiology 1988;169:663-9.
88. Dutton JAE, Jackson JE, Hughes JMB, et al. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. Am J Roent 1995;165:1119-25.
89. Faughnan ME, Lui YW, Wirth JA, et al. Diffuse pulmonary arteriovenous malformations. Characteristics and prognosis. Chest 2000;117:31-8.
90. Pierucci P MJ, Henderson KJ, Chyun DA, White RI Jr. New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: twenty-seven-year experience. Chest 2008;133:653-61.
91. Curie A, Lesca G, Cottin V, et al. Long-term follow-up in 12 children with pulmonary arteriovenous malformations: confirmation of hereditary hemorrhagic telangiectasia in all cases. J Pediatr Surg 2007;151:299-306.
92. Al-Saleh S, Mei-Zahav M, Faughnan ME, et al. Screening for pulmonary and cerebral arteriovenous malformations in children with hereditary haemorrhagic telangiectasia. Eur Respir J 2009;34:875-81.
93. Livneh A, Langevitz P, Morag B, Catania A, Pras M. Functionally reversible hepatic arteriovenous fistulas during pregnancy in patients with hereditary hemorrhagic telangiectasia. South Med J 1988;81:1047-9.
94. Gammon RB, Miska AK, Keller FS. Osler-Weber-Rendu disease and pulmonary arteriovenous fistulas. Deterioration and embolotherapy during pregnancy. Chest 1990;98:1522-4.
95. Chow LT, Chow WH, Ma KF. Pulmonary arteriovenous malformation. Progressive enlargement with replacement of the entire right middle lobe in a patient with concomitant mitral stenosis. Med J Aus 1993;158:632-4.
96. Swinburne AJ, Fedulla AJ, Gangemi R, Mijangos JA. Hereditary telangiectasia and multiple pulmonary arteriovenous fistulas. Clinical deterioration during pregnancy. Chest 1986;89:459-60.

97. Shovlin CL, Winstock AR, Peters AM, Jackson JE, Hughes JMB. Medical complications of pregnancy in hereditary haemorrhagic telangiectasia. Quart J Med 1995;88:879-87.
98. Vase P, Holm M, Arendrup H. Pulmonary arteriovenous fistulas in hereditary hemorrhagic telangiectasia. Acta Medica Scandinavica 1985;218:105-9.
99. Whyte MKB, Hughes JMB, Jackson JE, et al. Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts. J Appl Physiol 1993;75:321-8.
100. Ueki T, Hughes JMB, Peters AM, et al. Oxygen and ^{99m}Tc-MAA shunt estimations in patients with pulmonary arteriovenous malformations: effects of changes in posture and lung volume. Thorax 1994;49:327-31.
101. Whyte MKB, Peters AM, Hughes JMB, et al. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. Thorax 1992;47:790-6.
102. Pennington D, Gold W, Gordon R, Steiger D, Ring E, Golden J. Treatment of pulmonary arteriovenous malformations by therapeutic embolization. Am Rev Resp Dis 1992;145:1047-51.
103. Chilvers ER, Whyte MKB, Jackson JE, Allison DJ, Hughes JMB. Effect of percutaneous transcatheter embolization on pulmonary function, right-to-left shunt, and arterial oxygenation in patients with pulmonary arteriovenous malformations. Am Rev Respir Dis 1990;142:420-5.
104. Gupta P, Mordin C, Curtis J, Hughes JMB, Shovlin CL, Jackson JE. Pulmonary arteriovenous malformations: Effect of embolization on right-to-left shunt, hypoxaemia and exercise tolerance in 66 patients. Am J Roent 2002;179:347-55.
105. Mager JJ, Zanen P, Verzijbergen F, et al. Quantification of right-to-left shunt with (99m)Tc-labelled albumin macroaggregates and 100% oxygen in patients with hereditary haemorrhagic telangiectasia. Clinical Science (London) 2002;102:127-34.
106. Chilvers ER, Peters AM, George P, Hughes JMB, Allison DJ. Quantification of right to left shunt through pulmonary arteriovenous malformations using ^{99}Tc^{m} albumin microspheres. Clin Radiol 1989;39:611-4.
107. Waldhausen J, Abel F. The circulatory effects of pulmonary arteriovenous fistulas. Surgery 1966;59:76-80.
108. Shovlin CL, Tighe HC, Davies RJ, Gibbs JSR, Jackson JE. Embolisation of pulmonary arteriovenous malformations: no consistent effect on pulmonary artery pressure. Eur Resp J 2008;32:162-9.

109.Shovlin CL, Jackson JE, Hughes JMB. Pulmonary arteriovenous malformations and other pulmonary vascular disorders. In: Mason RJ, Broaddus CVC, Murray JF, Nadel JA, eds. Murray and Nadel's Textbook of Respiratory Medicine, 4th edition. 4th ed. Philadelphia: Elsevier Saunders; 2005:1480-501.
110.Santhirapala V, Springett J T , Wolfenden H, Tighe HC, CL S. Which patients with pulmonary arteriovenous malformations are dyspnoeic? Retrospective analysis of a single centre 2005–2010 cohort. Thorax 2010 2010;65:A92-A3 doi:10.1136/thx.2010.150961.38
111.Silverside CK, Colman JM. Physiological changes during pregnancy. In: Oakley C, Warnes CA, eds. Heart disease in pregnancy. 2nd ed. Oxford: Blackwell; 2007:6-17.
112.Hart MV, Morton MJ, Hosenpud JD, Metcalfe J. Aortic function during normal human pregnancy. Am J Obstet Gynecol 1986;154:887-91.
113.Werko L. Pregnancy and heart disease. Act Obst Gynecol Scand 1954;33:162-210.
114.Hoffman R, Rabens R. Evolving pulmonary nodules: Multiple pulmonary arteriovenous fistulas. Am J Radiol 1974;120:861-4.
115.Eplin MS, Varner MW. Progression of pulmonary arteriovenous malformation during pregnancy: case report and review of the literature. Obstet Gynecol Surv 1997;52:248-53.
116.Shovlin CL, Simonds AK, Hughes JMB. Pulmonary disease and cor pulmonale. In: Oakley C, Warnes CA, eds. Heart disease in pregnancy. 2nd ed. Oxford: Blackwell; 2007:151-72.
117.Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Resp Dis 1980;121:559-81.
118.Templeton A, Kelman G R. Maternal blood gases (PAO_2-PaO_2), physiological shunt and VD/VT in pregnancy. Br J Anaesth 1976;48:1001-4.
119.Moon RE, Camporesi, E.M. and Kisslo, J.A. . Patent foramen and decompression sickness in divers. Lancet 1989;I:513-4.
120.Wilmshurst PT, Byrne, J.C. and Webb-Peploe, M.M. . Relation between interatrial shunts and decompression sickness in divers. Lancet 1989;ii:1302-6.
121.Wilmshurst P. and Bryson P. Relationship between the clinical features of neurological decompression illness and its causes. Clinical Science 2000;99:66-75.
122.Wilmshurst PT PM, Walsh KP, Morrison WL. Relationship between right-to-left shunts and cutaneous decompression illness. Clinical Science 2001;100:539-42.
123.Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 2002;57:289-304.

124.Mason CG, CL S. Flying—safer than we thought? A questionnaire-based study of 156 individuals with hereditary haemorrhagic telangiectasia; 95 with pulmonary AVMs. Thorax 2010 2010;65:A92 doi:10.1136/thx.2010.150961.37.
125.Shovlin CL, Gibbs JSR, Jackson JE. Management of pulmonary arteriovenous malformations in pulmonary hypertensive patients. A pressure to embolise? Eur Respir Rev. Eur Respir Rev 2008;18:4-6.
126.Fletcher(Chairman) CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the aetiology of chronic bronchitis (MRC breathlessness score). BMJ 1960;2:1665.
127.Cottin V, Gamondes D, Schuller A, et al. Near-fatal haemorrhage from pulmonary arteriovenous malformation in HHT with increased cardiac output. Eur Respir Rev 113 2009;18:190–2.
128.Sagara K, Miyazono N, Inoue H, Ueno K, Nishida H, Nakajo M. Recanalization after coil embolotherapy of pulmonary arteriovenous malformations: study of long-term outcome and mechanism for recanalization. Am J Roent 1998;170:727-30.
129.Stringer C, Stanley A, Bates R, Summers J. Pulmonary arteriovenous fistula. Am J Surg 1955;89:1054-80.
130.Sluiter-Eringa H, Orie NGM, Sluiter HJ. Pulmonary arteriovenous fistula. Diagnosis and prognosis in noncomplainant patients. Am Rev Respir Dis 1969;100:177-88.
131.Gomes M, Bernatz P, Dines D. Pulmonary arteriovenous fistulas. Annals of Thoracic Surgery 1969;7:582-93.
132.Dines DE, Arms RA, Bernatz PE, Gomes MR. Pulmonary arteriovenous fistulas. Mayo Clin Proc 1974;49:460-5.
133.Dines DE, Steward JB, Bernatz PE. Pulmonary arteriovenous fistulas. Mayo Clin Proc 1983;58:176-81.
134.Puskas J, Allen M, Moncure A, et al. Pulmonary arteriovenous malformations: therapeutic options. Ann Thor Surg 1993;56:253-8.
135.Haitjema TJ, Overtoom TTC, Westermann CJJ, Lammers JWJ. Embolisation of pulmonary arteriovenous malformations: results and follow-up in 32 patients. Thorax 1995;50:719-23.
136.Lee D, White R, Egglin T, et al. Embolotherapy of large pulmonary arteriovenous malformation: long term results. AnnThor Surg 1997;64:930-40.

137.Moussouttas M, Fayad P, Rosenblatt M, et al. Pulmonary arteriovenous malformations. Cerebral ischaemia and neurologic manifestations. Neurology 2000;55:959-64.
138.Post MC, Letteboer TG, Mager JJ, Plokker TH, Kleider JC, Westermann CJJ. A pulmonary right-to-left shunt in patients with hereditary haemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-9.
139.Thenganatt J, Schneiderman J, Hyland R, Edmeads J, Mandzia J, Faughnan M. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-43.
140.Cottin V CT, Lavolé A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, , "Orphelines" CJGdEedRslM, (GERM"O"P) P. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia patients: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
141.Marziniak M, Jung A, Guralnik V, Evers S, Prudlo J, Geisthoff U. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 2009;29:76-81.
142.Moore BP. Pulmonary arterio-venous fistula. Thorax 1969;24:381.
143.Laroche CM, Wells F, Schneerson J. Massive hemothorax due to enlarging arteriovenous fistula in pregnancy. Chest 1992;101:1452-4.
144.Bevalaqua FA, Ordorica SA, Lefleur R, Young B. Osler Weber Rendu disease. Diagnosis and management of spontaneous hemothorax during pregnancy. New York State J Med 1992;92:551-2.
145.Chanatry BJ. Acute haemothorax owing to pulmonary arteriovenous malformation in pregnancy. Anesth Analg 1992;74:613.
146.CEMACH. Saving mothers lives 2003-2005 (Full report).
147.Goodman RM, Gresham GE, Roberts PL. Outcome of pregnancy in patients with hereditary hemorrhagic telangiectasia. Fertility and Sterility 1967;18:272-7.
148.Pelage JP, Blivet S, Blondel JH, et al. Embolization of ruptured pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia. Hematol Meeting Reports 2009;3:15.
149.Hewes RC, Auster M, White RI. Cerebral embolism--first manifestation of pulmonary arteriovenous malformation in patients with hereditary hemorrhagic telangiectasia. Cardiovasc Intervent Radiol 1985;8:151-5.
150.Raffle A, Gray M. Screening. Evidence and practice: Oxford University Press; 2007.

151.Haitjema T, Disch F, Overtoom TTC, Westermann CJJ, Lammers J-WJ. Screening family members of patients with hereditary haemorrhagic telangiectasia. Am J Med 1995;99:519-24.
152.Lee WL, Graham AF, Pugas RA, et al. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-8.
153.Kjeldsen AD, Oxhøj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: Screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-9.
154.Thompson RD, Jackson J, Peters AM, Doré CJ, Hughes JMB. Sensitivity and specificity of radioisotope right-left shunt measurements and pulse oximetry for the early detection of pulmonary arteriovenous malformations. Chest 1999;115:109-13.
155.Nanthakumar K, Graham A, Robinson T, et al. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-6.
156.Pollak JS, Saluja S, Thabet A, Henderson KJ, White RI. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. Journal of Vascular and Interventional Radiology 2006;17:35-45.
157.Gutierrez F, Glazer H, Levitt R, Moran J. NMR imaging of pulmonary arteriovenous fistulae. J Computer Assisted Tomography 1984;8:750-2.
158.Schneider G UM, Koehler M, Kirchin MA, Massmann A, Buecker A, Geisthoff U. MR angiography for detection of pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. AJR Am J Roentgenol 2008;in press.
159.Boussel L, Cernicanu A, Geerts L, et al. 4D time-resolved magnetic resonance angiography for noninvasive assessment of pulmonary arteriovenous malformations patency. J Magn Reson Imaging 2010;32:1110-6.
160.Hagan PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.
161.Schneider B, Zienkiewicz T, Jansen V, Hofmann T, Noltenius H, Meinertz T. Am J Cardiol. Diagnosis of patent foramen ovale by transoesophageal echocardiography and correlation with autopsy findings 1996;77:1202-9.
162.Feinstein J, Moore P, Rosenthal D, Puchalski M, Brook M. Comparison of contrast echocardiography versus cardiac catheterisation for detection of pulmonary arteriovenous malformations. Am J Cardiol 2002;89:281-5.

163.Barzilai B, Waggoner A, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-10.
164.van Gent M, Post M, Snijder R, et al. Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: does it predict the indication for embolotherapy? Chest 2008;135:1288-92.
165.Gazzaniga P, Buscarini E, Leandro G, et al. Contrast echocardiography for pulmonary arteriovenous malformations (PAVMs) screening: Does any bubble matter? Eur J Echocardiogr 2008;10:513-8. .
166.Parra J, Bueno J, Zarauza J, et al. Graded contrast echocardiography in pulmonary arteriovenous malformations. Eur Respir J 2010;35:1279-85.
167.Zukotynski K, Chan R, Chow C, Cohen J, Faughnan M. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.
168.Hart J, Shovlin C, Jackson J. Embolization of Pulmonary arteriovenous malformations using the Amplatzer vascular plug: successful treatment of 69 consecutive patients Eur J Radiology 2010;in press.
169.Andersen PE, Kjeldsen AD, Oxhoj H, Vase P, White R. Embolotherapy for pulmonary arteriovenous malformations in patients with Hereditary Haemorrhagic Telangiectasia. Acta Radiologica 1998;39:723-6.
170.Remy-Jardin M, Dumont P, Brillet P, Dupuis P, Duhamel A, Remy J. Pulmonary arteriovenous malformations treated with embolotherapy: helical CT evaluation of long-term effectiveness after 2-21-year follow-up. Radiology 2006;239:576-85.
171.Terry P, Barth K, Kaufman S, White R. Balloon embolization for treatment of pulmonary arteriovenous fistulas. New Engl J Med 1980;302:1189-90.
172.Cottin V D-GS, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia
(rendu-osler disease). Respiration 2007;74:4.
173.White R. Pulmonary arteriovenous malformations: how do I embolize? Tech Vasc Interv Radiol 2007;10:283-90.
174.Berg AM, Amirbekian S, Mojibian H, Trow TK, Smith SJ, White RI, Jr. Hemothorax due to rupture of pulmonary arteriovenous malformation: an interventional emergency. Chest 2010;137:705-7.
175.Post M, Thijs V, Schonewille W, et al. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 2006;66:202-5.

176.Letourneau-Guillon L, Faughnan ME, Soulez G, et al. Embolization of pulmonary arteriovenous malformations with amplatzer vascular plugs: safety and midterm effectiveness. J Vasc Interv Radiol 2010;21:649-56.
177.Milic A CR, Cohen JH, Faughnan ME. Reperfusion of pulmonary arteriovenous malformations after embolotherapy. J Vasc Interv Radiol 2005;16:1675-83.
178.Mager HJ, Overtoom TT, Mauser HW, Westermann C. Early cerebral infarction after embolotherapy of a pulmonary arteriovenous malformation. J Vasc Interv Radiol 2001;12:122-3.
179.Brillet PY, Dumont P, Bouaziz N, et al. Pulmonary arteriovenous malformation treated with embolotherapy: systemic collateral supply at multidetector CT angiography after 2-20-year follow-up. Radiology 2007;242:267-76.
180.Turner-Warwick M. Precapillary systemic-pulmonary anastemoses. Thorax 1963;18:225-37.
181.vonHayek H. The Human Lung: Hafner, New York; 1960.
182.Schraufnagel DE PD, Mitzner WA, Wagner EM. Three-dimensional structure of the bronchial microcirculation in sheep. Anat Rec 1995;243:357-66.
183.Weibel E. Die entstehung der Längermuskulatur in den Ästen der A. bronchialis. Zeitschrift für Zellforschung 1958;47:S440-68.
184.Viamonte M. Selective bronchial arteriography in man. Radiology 1964;83:830–9.
185.Rémy J AA, Fardou H, et al. Treatment of hemoptysis by embolization of bronchial arteries. Radiology 1977;122:33–7.
186.Sbano H MA, Ind PW, Jackson JE. Peripheral pulmonary artery pseudoaneurysms and massive haemoptysis. Am J Roentgenology 2005;184:1253-9.
187.Haitjema T, tenBerg J, Overtoom TT, Ernst JM, Westermann CJJ. Unusual complications after embolization of a pulmonary arteriovenous malformation. Chest 1996;109:1401-4.
188.Andrivet P, Lofaso F, Carette M-F, Allegrini J, Adnot S. Haemodynamics and gas exchange before and after coil embolization of pulmonary arteriovenous malformations. Eur Respir J 1995;8:1228-30.
189.Rodan BA, Goodwin JD, Chen JT, Ravin CE. Worsening pulmonary hypertension after resection of arteriovenous fistula. Am J Roentgenology 1981;137:864-7.
190.Montani D, Price L, Girerd D, al E. Fatal rupture of pulmonary arteriovenous malformation in hereditary hemorrhagic telangiectasis and severe pulmonary arterial hypertension. Eur Respir Rev 2008.

191.Hsu CC-T KG, Thompson SA, van Driel ML. Embolisation therapy for pulmonary arteriovenous malformations. Cochrane Database Reviews 2011.
192.Ravasse P, Maragnes P, Petit T, Laloum D. Total pneumonectomy as a salvage procedure for pulmonary arteriovenous malformation in a newborn: Report of one case. J Pediatr Surg 2003;38:254-5.
193.Reynaud-Gaubert M, Thomas P, Gaubert J-Y, et al. Pulmonary arteriovenous malformations: lung transplantation as a therapeutic option. European Respiratory Journal 1999;14:1425-8.
194.Svetliza G, DelaCanal A, Beveraggi E, et al. Lung transplantation in a patient with arteriovenous malformations. J Heart Lung Transplant 2002;21:506-8.
195.Wilson W, Taubert K, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. J Am Dent Assoc 2008;138:739-45; 47-60.
196.Wray D, Ruiz F, Richey R, Stokes T. Guideline Development Group. Prophylaxis against infective endocarditis for dental procedures-summary of the NICE guideline. Br Dental J 2008;204:555-7.
197.Shovlin CL, Bamford KB, Wray D. Post-NICE 2008: Antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J 2008;2008.
198.Physicians RCo. National Clinical Guidelines for Stroke. wwwrcplondonacuk/ceeu_stroke_homehtm 2000.
199.Shovlin CL, Govani FS. Hereditary haemorrhagic telangiectasia and genetic thrombophilia. Eur J Hum Genet 2009;18:405-6.
200.Gershon A, Faughnan M, Chon K, et al. Transcatheter embolotherapy of maternal pulmonary arteriovenous malformations during pregnancy. Chest 2001;119:470-7.
201.Mitchell A, Adams LA, MacQuillan G, Tibballs J, vandenDriesen R, Delriviere L. Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic telangiectasia. . Liver Transpl 2008;14:210-3.
202.Kurstin R. Using thalidomide in a patient with epithelioid leiomyosarcoma and Osler-Weber-Rendu disease. Oncology (Willeston Park) 2002;16:21-4.

203.Pérez-Encinas M, Rabuñal Martínez M, Bello López J. Is thalidomide effective for the treatment of gastrointestinal bleeding in hereditary hemorrhagic telangiectasia? Haematologica 2002;87:ELT34.
204.Buscarini E, Manfredi G, Zambelli A. Bevacizumab to treat complicated liver vascular malformations in hereditary hemorrhagic telangiectasia: a word of caution. Liver Transpl 2008;14:1685-6.
205.Vargesson N. Thalidomide-induced limb defects: resolving a 50-year-old puzzle. Bioessays 2009;31:1327-36.
206.BNF. British National Formulary: Royal Pharmaceutical Society of Great Britain British Medical Association; 2011.
207.Akhurst R. Taking thalidomide out of rehab. Nature Medicine 2010;16:370-2.
208.Reynolds S. FDA Advisory Committee Recommends against Bevacizumab for Metastatic Breast Cancer. National Cancer Institute 2010;7.
209.Sapru R, Hutchison D, Hall J. Pulmonary hypertension in patients with pulmonary arteriovenous fistulae. Br Heart J 1968;31:559.
210.leRoux B, Gibb B, Wainwright J. Pulmonary arteriovenous fistula with bilharzial pulmonry hypertension. Br Heart J 1970;32:571-4.
211.Trell E, Johansson BW, Linell F, Ripa J. Familial pulmonary hypertension and multiple abnormalities of large systemic arteries in Osler's disease. Am J Med 1972;53:50-63.
212.Olivieri C, Lanzarini L, Pagella F, et al. Echocardiographic screening discloses increased values of pulmonary artery systolic pressure in 9 of 68 unselected patients affected with hereditary hemorrhagic telangiectasia. Genetics in Medicine 2006;8:183-90.
213.Buscarini E, Plauchu H, GarciaTsao G, et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. Liver International 2006;26:1040-6.
214.Harrison RE, Flanagan JA, Sankelo M, et al. Molecular and functional analysis identifies ALK-1 as the predominant cause of pulmonary hypertension related to hereditary haemorrhagic telangiectasia. J Med Genet 2003;40:865-71.
215.Olivieri C LL, Pagella F, Semino L, Corno S, Valacca C, Plauchu H,, Lesca G BM, Buscarini E, Danesino C. Echocardiographic screening discloses increased values of pulmonary artery systolic pressure in 9 of 68 unselected patients affected with hereditary hemorrhagic telangiectasia. Genet Med 2006;8:183-90.

216.Abdalla SA, Gallione CJ, Barst RJ, et al. Primary pulmonary hypertension in families with hereditary haemorrhagic telangiectasia. Eur Respir J 2004;23:373-7.
217.Girerd B, Montani D, Coulet F, et al. Clinical outcomes of pulmonary arterial hypertension in patients carrying an ACVRL1 (ALK1) mutation. Am J Respir Crit Care Med 2010;181:851-61.
218.Chaouat A, Coulet F, Favre C, et al. Endoglin germline mutation in a patient with hereditary haemorrhagic telangiectasia and dexfenfluramine associated pulmonary arterial hypertension. Thorax 2004;59:446-8.
219.Gincul R, Lesca G, Gelas-Dore B, et al. Evaluation of previously nonscreened hereditary hemorrhagic telangiectasia patients shows frequent liver involvement and early cardiac consequences. Hepatology 2008;48:1377-9.
220.Toporsian M, Jerkic M, Zhou Y, et al. Spontaneous adult-onset pulmonary arterial hypertension attributable to increased endothelial oxidative stress in a murine model of hereditary hemorrhagic telangiectasia. Arterioscler Thromb Vasc Biol 2010;30:509-17.
221.Abdalla S, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 2006;43:97-110.
222.Lebrin F, Mummery C. Endoglin-mediated vascular remodeling: mechanisms underlying hereditary hemorrhagic telangiectasia. Trends Cardiovasc Med 2008;18:25-32.
223.Lopez-Novoa JM, Bernabeu C. The physiological role of endoglin in the cardiovascular system. Am J Physiol Heart Circ Physiol 2010;299:H959-74.
224.Bertolino P, Deckers M, Lebrin F, ten Dijke P. Transforming growth factor-beta signal transduction in angiogenesis and vascular disorders. Chest 2005;128:585S-90S.
225.Upton P, Davies R, Trembath R, Morrell N. BMP and activin type-II receptors balance BMP9 signals mediated by activin receptor-like kinase-1 in human pulmonary artery endothelial cells. J Biol Chem 2009; 284:15794-804.
226.Pardali E, Goumans MJ, ten Dijke P. Signaling by members of the TGF-beta family in vascular morphogenesis and disease. Trends Cell Biol 2010;20:556-67.
227.Goumans MJ, Valdimarsdottir G, Itoh S, Rosendahl A, Sideras P, ten Dijke P. Balancing the activation state of the endothelium via two distinct TGF-beta type I receptors. EMBO J 2002;21:1743-53.
228.Goumans MJ, Lebrin F, Valdimarsdottir G. Controlling the angiogenic switch: a balance between two distinct TGF-b receptor signaling pathways. Trends Cardiovasc Med 2003;13:301-7.

229.Blanco FJ, Santibanez JF, Guerrro-Esteo M, Langa C, Vary CP, Bernabeu C. Interactions and functional interplay between endoglin and ALK-1, two components of the endothelial transforming growth factor-beta receptor complex. J Cell Physiol 2005;204:574-84.
230.Lebrin F, Goumans MJ, Jonker L, et al. Endoglin promotes endothelial cell proliferation and TGF-beta/ALK1 signal transduction. EMBO J 2004;23:4018-28.
231.Pece-Barbara N, Vera S, Kathirkamathamby K, et al. Endoglin null endothelial cells proliferate faster and are more responsive to transforming growth factor beta1 with higher affinity receptors and an activated Alk1 pathway. J Biol Chem 2005;280:27800-8.
232.Guo X, Wang XF. Signaling cross-talk between TGF-beta/BMP and other pathways. Cell Res 2009;19:71-88.