The lung in hereditary hemorrhagic telangiectasia

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Abstract

Hereditary hemorrhagic telangiectasia is a dominantly inherited genetic vascular disorder with an estimated prevalence of 1 in 6,000, characterized by recurrent epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVM) that affect many organs, including the lungs, gastrointestinal tract, liver and brain. Diagnosis is based on the Curaçao criteria and is considered definite if at least three of the four following criteria are fulfilled[1]: 1) spontaneous and recurrent epistaxis, 2) telangiectasia, 3) family history and 4) visceral arteriovenous malformations (AVMs) such as pulmonary, liver, cerebral or spinal AVMs, or gastrointestinal AVMs.

The focus of this review is to delineate how HHT affects the lung. In brief:

- **Pulmonary arteriovenous malformations (PAVMs)** affect around 50% of all HHT patients. PAVMs result in an anatomical right-to-left shunt, cause hypoxemia, and place patients at high risk of paradoxical embolic strokes and cerebral abscess.
- Around 20% of HHT patients with no evidence of PAVMs on thoracic CT scan also display evidence of **intrapulmonary right-to-left shunting** by contrast echocardiography, and there is limited appreciation that this can be a normal variant in the general population.
- Although the focus of many publications, significant **pulmonary hypertension** is rare in HHT. This is usually secondary to high pulmonary blood flow because of elevated cardiac outputs required to meet the wider circulatory demands imposed by hepatic AVMs. Pulmonary arterial hypertensive phenotypes are rare.
- There appear to be minor modifications in the incidence of non-vascular pulmonary conditions, particularly lung cancer and sleep apnea.

Introduction

Hereditary hemorrhagic telangiectasia (HHT; Online Mendelian Inheritance in Man® #187300) is a dominantly inherited genetic vascular disorder with an estimated prevalence of 1 in 6,000, characterized by recurrent epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVM) that affect many organs, including the lungs, gastrointestinal tract, liver and brain. Diagnosis is based on the Curaçao criteria and is considered definite if at least three of the four following criteria are fulfilled[1]: 1) spontaneous and recurrent epistaxis, 2) telangiectasia, 3) family history and 4) visceral arteriovenous malformations (AVMs) such as pulmonary, liver, cerebral or spinal AVMs, or gastrointestinal AVMs (Table 1).

HHT is caused by a single pathogenic variant ("mutation"), usually in either *ENG* (encoding endoglin)[2], or *ACVRL1* (encoding activin receptor-like kinase one[3]). Smaller proportions of HHT cases (<5%) are caused by *SMAD4 (*syn. *MADH4*, encoding SMAD4)[4], and unidentified mutations, likely in the promoter or intronic regions of these genes, or other genes affecting the same signaling pathway. Endoglin, ALK1 and SMAD4 proteins are components of transforming growth factor ß/bone morphogenetic protein signaling pathways: ALK1 is a type I transmembrane serine threonine receptor kinase; endoglin an auxiliary receptor, and SMAD4 the common partner for canonical (SMAD-based) signaling.[5] While the exact pathogenic mechanisms are yet to be determined, HHT vascular abnormalities are thought to arise due to resultant imbalances in response to angiogenic factors such as vascular endothelial growth factor (VEGF),[6] defective vascular repair,[7] and/or modified vessel maturation[8]. Recently, heterozygous missense substitutions in the *GDF2* gene, which

encodes the protein bone morphogenetic protein 9, have been reported in individuals with some cutaneous vascular lesions similar to those seen in HHT [9, 10] although pathogenicity of the gene variants remains uncertain. Vascular lesions similar to those present in HHT (such as skin telangiectasia, and certain high flow AVMs) may also be found in other hereditary vasculopathies due to *RASA1, TIE2* which appear to mediate different signaling pathways.[11, 12]

ENG, *ACVRL1* and *SMAD4* pathogenic sequence variants can generate the full spectrum of HHT vascular lesions including pulmonary, cerebral, hepatic and spinal involvement, though *ENG* mutations are associated with an increased risk of PAVMs and CAVMs, (~3-6 fold) whereas *ACVRL1* variants more frequently cause hepatic AVMs (~3-6 fold)[13-15]. The vascular abnormalities have been reproduced in animal models by heterozygous inactivation of the *ENG* or *ACVRL1* genes.[16, 17]

The focus of this review is to delineate how HHT affects the lung. In brief:

- **Pulmonary arteriovenous malformations (PAVMs)** affect ~50% of all HHT patients.[18] PAVMs result in an anatomical right-to-left shunt, cause hypoxemia, and place patients at high risk of paradoxical embolic strokes and cerebral abscess,[19] but their importance remains under-recognised.[20]
- ~20% of HHT patients with no evidence of PAVMs on thoracic CT scan also display evidence of **intrapulmonary right-to-left shunting** by contrast echocardiography,[21] and there is limited appreciation that this can be a normal variant in the general population.[22]
- Although the focus of many publications, significant **pulmonary hypertension** is rare in HHT. Supranormal pulmonary artery pressures are identified in up to 20% of

unselected HHT patients,[23] but this is usually secondary to high pulmonary blood flow[24] because of elevated cardiac outputs required to meet the wider circulatory demands imposed by hepatic AVMs and other HHT complications.[25] Pulmonary arterial hypertensive phenotypes are rare.[26-29]

- There appear to be minor modifications in the incidence of non-vascular pulmonary conditions, particularly lung cancer and sleep apnea.

PULMONARY ARTERIOVENOUS MALFORMATIONS

Definition, prevalence and anatomical considerations

Pulmonary arteriovenous malformations (PAVMs) are structurally abnormal vessels (Figure 1) that provide direct capillary-free communication between the pulmonary and systemic circulations and result in an anatomical right-to-left (R-L) shunt. They may occur sporadically, but more usually are associated with HHT. The major consequences of PAVMs are impairment of gas exchange (resulting in hypoxemia), and paradoxical emboli (Figure 2). In less than 2% of untreated cases, the PAVM may involve a systemic artery rather than pulmonary artery.[30] PAVMs vascularized by more than one branch of a pulmonary artery or drained by multiple segmental pulmonary veins are labelled complex PAVMs.

PAVMs comprise an aneurismal or serpiginous sac with one or more afferent feeding arteries and one or more efferent draining veins. Based on cross sectional and angiographic imaging,

PAVMs are classified as single (only one macroscopic PAVM) or multiple (several lesions distributed in different lobes or lung segments), noting each PAVM can itself be complex in structure. The term "diffuse" is used to describe the rare situation of PAVMs, usually small, affecting multiple segmental branches of one lobe or all branches of one segment [31], raising specific treatment challenges. The severity of right-to-left shunting is defined as the proportion of the cardiac output passing through the PAVMs, and may be massive (>40%) in patients with large single PAVMs, as well as patients with more diffuse, smaller PAVMs.

In HHT patients, PAVMs predominate in the lower lobes (60 to 95%) and are multiple in at least half of all HHT cases[30](Figure 2). In published series, PAVMs do not appear to directly influence spirometric values[32, 33].

The prevalence of PAVMs differs according to HHT genotype, being higher in HHT1 due to *ENG* (up to 58%) compared to HHT2 due to *ACVRL1* (18%) ($P < 0.001$).[18-21] PAVMs may be present from birth and have usually completed development by adult life although they can enlarge later in life, for example during pregnancy or following other alterations in pulmonary haemodynamics.

Clinical manifestations and complications

Most patients with PAVMs that place them at risk of preventable strokes and brain abscess are unaware that they have a problem within their lungs. PAVMs continue to be more commonly diagnosed by incidental imaging, systematic screening, or investigations after neurological complications, than by respiratory symptoms.[18, 34, 35] As HHT patients should undergo screening for PAVMs, this should be the main circumstance for the detection of PAVMs.

Paradoxical emboli:

The major risks of PAVMs are neurological due to compromised pulmonary capillary bed filtration, and include cerebral abscess, ischemic stroke, transient ischemic attacks and asymptomatic cerebral infarction. Such complications frequently reveal the diagnosis of PAVM(s), and even of HHT itself. Cerebral abscesses commonly occur in asymptomatic individuals without a prior diagnosis of PAVM or HHT [34, 35] and leave approximately 50% of survivors with residual life-changing neurological deficits [35]. Cerebral abscesses are estimated to affect 5 to 19% of patients with PAVMs at a median age of 53 years [18, 34-39]. This translated to an increased rate for HHT patients of 155/100,000/year compared to 0.4/100,000/year in the general population.[39] Cerebral abscess are frequently due to multiple organisms, may follow dental or other interventional procedures, and occur in immunocompetent patients at a median age of 33 years [18].

Crucially, the cerebral abscess data dispel previously proposed myths about the importance of respiratory symptoms, hypoxemia or feeding artery diameter in establishing which PAVMs require treatment: Not only do cerebral abscesses commonly occur in patients with no respiratory symptoms and normal SaO_2, but also, across two separate series, in 14/65 (21.5%) of cases, all PAVM feeding arteries had a diameter of 1-3mm, i.e. at or below the limits of what is commonly considered treatable.[34, 35] That said, in multivariate analyses of a recent series of 445 consecutive patients with PAVMs, cerebral abscess was more common in patients with lower SaO_2 , with the risk of cerebral abscess increasing by 10.47% (95% confidence intervals 4.18, 16.36%) for every 1% fall in SaO_2.[35] Thus overall, the risk of cerebral abscess is increased, whatever the size of the PAVM or feeding artery, in individuals with more severe right-to-left shunting. In multivariate analyses, cerebral abscess was also

associated with indices of iron loading (higher transferrin iron saturation index; intravenous iron use for anemia); male gender; and venous thromboemboli.[35] Other severe infections may occur as a result of PAVMs[38] including abscesses in other viscera, the spinal cord, or soft tissues, as well as meningitis, septicemia, endocarditis, and bacterial spondylodiscitis.

PAVMs are also strongly associated with an enhanced risk of cerebral ischemia and infarction, again attributed to paradoxical emboli. The rate of a clinical ischemic stroke (duration >24hrs) has been reported between 9 to 18% [18, 34, 40-42], 11.3% when adjusting for ascertainment bias[34] , with a median age of 53 years, and is reduced after embolization of PAVMs[34]. Transient cerebral ischemic attacks affect 6 to 37% of PAVM patients.[18, 43] The burden of asymptomatic cerebral infarction is greater still: in one series 34/67 (51%) of patients with PAVMs had CT-evidence of cerebral infarcts at median age 41ys[44] and in a more recent series of MRIs performed for cerebral AVM screening at median age 42.9ys, 'incidental' cerebral ischemic changes were reported in 13/24 (54.2%) of HHT patients with PAVMs (PAVM age/gender-adjusted odds ratio 80.1 (95% CI 2.0, 3145, p=0.019)).[45] Ischemic strokes commonly occur in previously asymptomatic individuals without a prior diagnosis of PAVM or HHT.[34, 40] Recent studies highlight that for a patient with a PAVM, the strongest stroke risk factors are low serum iron[40] (which is associated with exuberant platelet aggregation to 5HT [40, 46]), and high serum fibrinogen[40], which is the predominant circulating plasma protein for platelet adhesion[47]. These emphasize the importance of anti-platelet therapies as utilized in conventional ischemic stroke management. Anticoagulants are only recommended if there is separate evidence of deep venous thrombosis or pulmonary emboli, which are rare in PAVM-ischemic stroke patients.[40, 48]

Respiratory:

The most striking clinical finding for this patient group is the presence of asymptomatic hypoxemia[49]: significantly hypoxemic patients with $SaO_2 < 85\%$ are often able to pursue sporting activities to a very high level,[50] emphasising the powerful hematological[49, 51] and hemodynamic[52, 53] compensatory responses that can be employed. Crucially, these compensatory responses are then lost after treatment of PAVMs, and exercise capacity/oxygen delivery usually returns to pre-treatment levels.[49, 51, 53] There is no clear relationship between the severity of right-to-left shunting and dyspnea: instead dyspnea appears to be more common in patients with airflow obstruction related to another condition, higher pulmonary artery pressures, anemia or other indices of ill health.[49, 52].

Cyanosis and clubbing may be present in hypoxemic patients with PAVMs, but cyanosis is masked by anemia, and clubbing severity does not seem to be predictable unless right-to-left shunting is severe. Patients with PAVMs occasionally exhibit orthodeoxia[54], attributed to basal predominance of PAVMs, but this is usually asymptomatic, and platypnea (dyspnea on assuming the upright position) is very rare.[54]

Other respiratory symptoms due to untreated PAVMs include hemoptysis and hemothorax resulting from intrabronchial or intrapleural rupture of PAVMs respectively.[55] These are rare, reflecting the low pressures of the pulmonary circulation, but are more common in pregnancy (see below)[56, 57]; if PAVMs acquire a systemic arterial feeder after PAVM embolization;[58] or in the setting of pulmonary hypertension.[31, 59, 60] Emergency PAVM treatment by embolization or surgery is effective.

Chest pain is rarely attributable to untreated PAVMs. The apparent association between chest pain and PAVMs in the literature most likely reflects incidental occurrence that precipitated diagnostic imaging.

The presence of PAVMs is also associated with a significant increase in the prevalence of migraine. The risk is approximately doubled if HHT patients have PAVMs and migraines often improve after PAVM treatment[36, 61-64]. Similarly, the prevalence of PAVM is higher in patients with migraine among the HHT population (50% versus 36%)[64]. Recent data suggest the pathophysiological mechanisms may again include paradoxical embolism of particulate matter[65].

Pregnancy and PAVMs

During pregnancy, the risk of PAVM haemorrhage and of maternal death are each in the order of 1% (in 484 pregnancies, 1.0% (95% CI 0.1-1.9), resulting in a major PAVM bleed, and 1.0% (0.13-1.9%) in maternal death)[56]. Both hemoptysis and hemothorax are described.[56, 57] To reduce maternal and fetal complications related to PAVMs during pregnancy, systematic screening and treatment of PAVM are recommended prior to pregnancy. PAVMs often increase in size and number during pregnancy, likely due to increased blood volume and cardiac output. In pregnancy, there are also enhanced risks of pulmonary emboli, and myocardial infarction with normal coronary arteries.[56] Pregnant HHT patients with PAVM should be offered close follow-up throughout pregnancy: arterial oxygen content (CaO_2) appears a more relevant and helpful index than SaO_2 which may be misleadingly high[51]. If

necessary, transcatheter embolotherapy of maternal pulmonary AVMs can be performed[66] though in our practice this is restricted to women who are experiencing hemoptysis.

Diagnosis of PAVM

Thoracic CT scans using helical multidetectors are the gold standard for the diagnosis of PAVMs, with the ability to detect anatomical PAVMs far below the technical limitations of treatment. Expertise is wide-spread, though diagnostic confusion can result: distinguishing features of possible "PAVM mimics," such as a pulmonary varix, bronchoceles, or pulmonary malinosculations, are presented elsewhere[67]. It is important that CT use is restricted: In a single-center study of 246 patients with PAVMs (mean age, 53 yrs), the mean cumulative effective dose (CED) over an 11-year period was 51.7 mSv: CT scans repeated according to recommended protocols[68] accounted for 46% of the CED, compared with 51% from interventional procedures.[69] Due to potential radiation exposure, recent consensus statements emphasize that CT scans should not be repeated unless there is a new clinical indication.[48] CT should be performed without contrast injection for screening, with injection only if required for confirmation of the diagnosis or pretreatment. Similarly, pulmonary angiography should not be performed as a diagnostic test, and in experienced centres, is usually only performed at the time of embolization after PAVMs have been anatomically defined by a thoracic CT scan.

Screening for PAVMs in the HHT Population:

Either a negative contrast echocardiogram (CE) performed in experienced hands, or a negative thoracic CT scan (with or without contrast), excludes clinically significant PAVMs.

Transthoracic contrast echocardiography (TTCE) has been recommended as the initial screening test for PAVMs[68] due to high sensitivity[70] and low risk.[71] TTCE 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. TTCE is performed by injecting 4-5 ml of agitated modified fluid gelatin or isotonic saline solution with 0.5 ml room air into a peripheral vein, while simultaneously imaging the atria with 2-D echocardiography. Microbubbles seen in the left heart indicate an intracardiac or intrapulmonary right-to-left shunt. A low-dose chest X-ray is often performed prior to TTCE to detect large PAVMs and obviate the need for microbubble injection in patients with high-flow right-to-left shunting. If negative in expert hands, no further imaging is required to exclude PAVMs, and the study should not need to be repeated. Although TTCE is the recommended screening method in international guidelines, some HHT centers prefer to perform a single thoracic CT to screen for PAVMs in HHT patients, especially because less experienced sonographers in wider respiratory unit practice may overlook relatively small numbers of bubbles. Even using this approach, echocardiography (not TTCE) may be useful to ensure that pulmonary arterial pressures, cardiac output and right heart cavities are normal. The choice between using CT or TTCE to screen for PAVM may therefore depend on physicians' and patients' preferences, patient's age and gender, and resources.

Key interpretive points for TTCE include:

- TTCE is considered positive for an intra-pulmonary right-to-left shunting if microbubbles appear in the left atrium after a delay (usually 3-4 cardiac cycles is

considered a cut off) or ramp in intensity (in contrast to intracardiac shunts). Intrapulmonary shunt origin is certain if the bubble density is greater in the left heart than the right, often requiring 30-60 seconds recording.[72]

- Pulmonary AVMs are one cause of intrapulmonary right-to-left shunting: intrapulmonary shunting demonstrable by TTCE is also evident in ~10% of the general population at rest, and the majority of healthy individuals on exercise, and/or after adrenergic stimuli.[22, 73, 74]
- A positive intrapulmonary shunt study is also more likely after injury to the delicate pulmonary capillaries, for example following a second injection of contrast.[72]
- TTCE is usually positive in HHT1 patients (85%)[21], and often positive in HHT2 (35%)[21]. Semi-quantification of the shunt may help distinguish from physiological shunting and enhance positive predictive value for a PAVM amenable to treatment[75] or complication risk[76].
- In the absence of PAVMs visible on CT scan, a contrast echocardiogram demonstrating an intrapulmonary shunt does not appear to be associated with enhanced neurological risk in HHT patients.[76] TTCE is therefore not indicated when presence of a PAVM has already been established by CT or in follow-up of patients with treated PAVMs. There is also reassuring data in the general population, indicating very few exercise-induced arterialized gas bubbles reach the cerebral vasculature,[77] although it is not clear that the same would apply for non-gaseous paradoxical emboli.

Different algorithms have been proposed for the screening and follow-up in adult patients with HHT, according to the degree of local expertise with contrast echocardiography (Figure 3).

Interventional Treatment of PAVMs

Treatment of PAVMs in HHT aims at preventing severe complications, especially cerebral abscess, ischemic stroke, and haemorrhage. Interventional treatment is thus warranted in all patients with PAVMs of a size amenable to treatment, irrespective of symptoms[49, 61, 78-80]. PAVM treatment also reduces migraines[61, 81], HHT nosebleeds[82], polycythaemia[49, 51] and haemodynamic sequelae of PAVMs[52, 53]. Patients should not undergo embolization expecting improved exercise tolerance, although this may be observed.

PAVM embolization

Transcatheter vasoocclusion (embolisation) of PAVMs previously used balloons and/or detachable coils with thrombogenic fibres to accelerate platelet thrombus formation[83]. Increasingly Amplatzer vascular plugs are recommended as these have greater efficacy and appear to have lower risk of recanalisation[67, 84-86]. Other devices are occasionally used, especially for PAVMs with very large feeding arteries[84]. There is no size threshold (other than technical feasibility) for treatment.[34, 35, 48, 67] Multiple PAVMs can be occluded within one procedure, but several procedures can be required to occlude all visible PAVMs, and high proportions of HHT patients are left with residual PAVMs below the technical limits of vasoocclusion. As for all procedures, it is important that the vasoocclusion be performed by radiologists experienced in the management and treatment of HHT-related PAVMs to decrease the risk of complications and improve efficacy: 20 procedures is required for

interventional radiologists to meet VASCERN eligibility requirements.[87] Risks appear to be low in expert hands and major complications are usually quoted in the order of 1%. These include symptomatic lung infarction, systemic migration of embolization devices, air embolism, and exceptionally transient angina, cardiac arrhythmia, deep venous thrombosis, or pneumothorax. Infections related to the procedure are minimised by scrupulous aseptic technique, and prophylactic antibiotherapy. More benign complications such as transient pleurisy are reported in approximately 10% of patients, more frequently in patients with diffuse or peripheral PAVMs[31].

Successful vaso-occlusion of PAVMs immediately decreases right-to-left shunting, and improves arterial blood gases, however, residual hypoxemia and positive cardiac contrast echocardiography are frequent. Long-term follow-up is mandatory in all HHT patients diagnosed with PAVMs as they are likely to require ongoing medical management. Once the PAVM sac and dilated draining veins regress, PAVMs rarely recur- this can be demonstrated by simple chest x-ray in most cases. In a small proportion of cases, PAVMs may recanalise, acquire new arterial feeders, and vaso-occlusion of large PAVMs may unmask or facilitate the development of new PAVMs.[86] Detection is recommended, as they may be successfully treated by repeated vaso-occlusion. The 2006 international guidelines recommended post-embolization CT scans at 6 to 12 months then every 3 years thereafter, with CT scans every 1 to 5 years for other patients with CT-evident PAVMs or positive contrast echocardiographic studies[68]. These recommendation however, may be revisited, given the evidence of cumulative radiation burdens pursuing this strategy,[69] and CT-sparing follow up strategies may be preferred (Figure 3) [48].

Surgery

Surgical treatment of PAVMs consisting of conservative resection of lung lobes or segments is currently rare, and restricted to complex or multiple PAVMs not amenable to transcatheter therapy. Lung transplantation has been performed in occasional HHT/PAVM patients[31, 88] although PAVMs very rarely cause severe respiratory insufficiency reducing survival expectancy and leading to consider lung transplant, and the longevity of patients declining lung transplantation for PAVMs exceeds the most optimistic lung transplantation figures.[89]

Medical Management of Patients with PAVMs

As an adjunct to embolization treatments, there are a number of relatively simple lifestyle and medical management recommendations to reduce complication rates from PAVMs.[19]

Antibiotic prophylaxis

It is often overlooked that in the general population, multiple procedures result in transient bacteraemias that are cleared within minutes in the absence of antibiotics, but prevented or resolved earlier with prior antibiotic administration.[90] Antibiotic prophylaxis immediately prior to dental and surgical procedures has been recommended for many years in patients with PAVMs, and this advice was not changed by the restrictions placed on prophylactic antibiotic to prevent infective endocarditis.[91] Based on earlier endocarditis guidance, oral administration is conventionally 1-2hs before a procedure, with a further dose post procedure. Amoxicillin/clavulanic acid is the preferred agent[90, 91]with metronidazole or clindamycin suggested for penicillin-allergic patients.[91] Whether specifically high risk patients should have intravenous administration is currently under discussion.[35, 48, 90] Whether

prophylactic treatment may be useful in any HHT patient with positive contrast echocardiography including those with no visible PAVM on chest CT is debated.

Judicious dental hygiene is recommended for patients with PAVMs.[91] Recent data highlight the importance of scrupulous aseptic technique, prompt treatment of other infections, and prophylactic antibiotics prior to other interventional procedures[35] to attempt to reduce the rate of cerebral abscess.

Air emboli: Scuba diving is not recommended due to the risk of air embolism.[68] In some countries, the use of air filters is recommended for intravenous infusion to prevent air embolism and transient ischemic attacks- in other countries, expert nursing practice already includes these as "never events" and the risks of modifying protocols may be counterproductive.

Oxygen for hypoxemic patients: Supplementary oxygen can be prescribed for symptomatic patients: there is anecdotal evidence of benefit and there may be an additional rationale with recent studies demonstrating that low PaO_2 (not arterial oxygen content, CaO_2) is the stimulus that mediates opening of normal intrapulmonary shunts.[74] There is no rationale for prophylactic oxygen use to prevent hypoxic pulmonary hypertension, because there is no alveolar hypoxia[52, 54].

Iron deficiency: Optimization of iron status is emerging as a core principle for the management of patients with PAVMs, particularly those with HHT and substantial iron losses from nosebleeds.[92] Iron deficiency restricts hemoglobin synthesis/erythrocytosis, and this is an even greater problem for patients with hypoxemia as they depend on polycythemia to maintain arterial oxygen content[49, 51], and for patients needing to achieve enhanced cardiac

outputs due to low systemic vascular resistance (eg AVMs, sepsis) and/or hypoxemia.[52, 53]. Iron deficiency is also associated with enhanced risks of venous[93] and arterial[40] thromboses in the HHT/PAVM population. However, iron deficiency treatments may inadvertently place patients with prior iron deficiency into at least transient iron overload states,[35, 94, 95] and with recent evidence that this may enhance the risk of cerebral abscess,[35] and other bacterial infections[96], some caution is required.

PULMONARY HYPERTENSION IN HHT

Significant pulmonary hypertension (PH) is observed in around 8% of HHT patients, usually secondary to high cardiac output[24], particularly in association with liver vascular malformations.[97-100] This is distinct to the rarer, pulmonary arterial hypertension (PAH) phenotype, with different physiopathology and treatment algorithms (table 2 and Figure). The key differentiating variables is the pulmonary artery wedge pressure (table 2). The pre-capillary pulmonary gradient (diastolic pulmonary artery pressure minus the pulmonary artery wedge pressure as an estimate of left atrial pressure; normal < 7 mmHg) may also contribute in difficult cases especially combined postcapillary and precapillary pulmonary hypertension; it is normal in the high-output cardiac failure-related PH but increased in patients with PAH.

Types of PH in HHT (table 2)

AVM-associated, secondary to high cardiac output and high pulmonary blood flow:

Where PH is present in HHT, it is usually secondary to high pulmonary flow and increased cardiac output (in older classifications, referred to as "post-capillary PH"). Although technically falling within the current Group 2 Pulmonary Hypertension umbrella [101], this is not a disorder of the left ventricle, and again, diagnostics and therapeutic algorithms should differ.

Systemic AVMs are one of the classical pathologies associated with high cardiac output states: reduced systemic vascular resistance leads to a fall in arterial blood pressure, activation of sympathetic and neurohormonal systems, and increased cardiac output to maintain vital organ perfusion at the expense of salt and water retention.[102-104] High left atrial filling pressures lead to pulmonary venous hypertension,[102-104] and the increases in

cardiac output may exceed the pump capacity of healthy left ventricles, leading to high output cardiac failure (HOCF).[103, 104]

Such patients usually have elevated cardiac output (CO), mildly elevated left atrial pressures and low pulmonary vascular resistance (PVR). The pulmonary hypertension improves following treatment of hepatic AVMs: in one study, after liver transplantation that removed hepatic AVMs, the mean cardiac index fell from 5.75L/min/m^2 to 3.4L/min/m^2.[105] However, some hepatic AVM patients show secondary decreases in CO, at an advanced stage of heart failure[26], which can be misleading if no previous data on cardiac index are available.

Other types of PH that may occur in HHT patients

More rarely, pulmonary arterial hypertension (PAH), is observed (Group 1) and is a "true" pulmonary arteriopathy. Patients have elevated pulmonary artery pressures, normal left atrial pressure, normal or reduced cardiac output and significantly increased PVR.

There is a third, rarer group of HHT patients with liver involvement and chronic high cardiac output, or with portal hypertension, in which post- and pre-capillary PH can be observed. It is not yet known whether chronic exposure to increased flow leads to remodelling of the pulmonary vascular bed as in Eisenmenger's syndrome, but intriguingly, one such case resolved following liver transplantation (Shovlin, unpublished observation).

Finally, it is also possible for patients with HHT, as for people without HHT, to suffer from thromboembolic PH, hypoxic PH in the setting of parenchymal lung disease, and other forms

of PH: there are no data to indicate whether these pathologies are more or less common in HHT. Importantly, hypoxemia due to pulmonary AVMs does not lead to hypoxic PH which depends on pulmonary vasoconstriction secondary to alveolar hypoxia, not arterial hypoxemia.

PAH is predominantly recognised in HHT2 patients due to *ACVRL1* mutations: whether specific *ACVRL1* genotypes influence the development of HHT (potentially with PAVM, or liver AVM and hyperdynamic PH), or idiopathic PAH is not yet clear. Other major genes, modifier genes, and/ or environmental factors are likely to contribute to pathogenesis.

Screening and investigation of PH

Systematic screening for PH is not recommended in asymptomatic HHT patients. However, PH investigations should be incorporated into the diagnostic algorithms for any patient with unexplained shortness of breath or exercise limitation: echocardiography with estimation of atrioventricular pressure gradient and cardiac index measurement should be systematically performed and liver evaluation and follow-up are mandatory to interpret the cardiac data.

Echocardiography is therefore an important investigation in patients with HHT, contributing to both screening for PAVM and right-to-left shunting using the contrast method, and further evaluating possible PH whatever its mechanism (high cardiac output, or high pulmonary vascular resistance). The presence of dilated right sided chambers and/or increased velocity of the tricuspid regurgitation jet should prompt right heart catheterization, which is required to confirm PH and to characterize its mechanism.

Mechanism and management of pulmonary hypertension due to increased cardiac output and hyperdynamic state in HHT (Group 2 PH)

While in principle, any systemic AVM will result in reduced systemic vascular resistance and activation of the renin/angiotensin/aldosterone system[104], in practice in HHT, this is usually observed in the setting of large hepatic AVMs.[26, 103, 106]

Liver involvement in HHT is detected in 41 to 78% of HHT patients using sensitive imaging technique,[100, 107-109] though more commonly in HHT 2 patients with pathogenic variants in *ACVRL1*. The evolution of vascular lesions consists in the progressive enlargement and creation of multiple direct AVMs.[110] The Doppler ultrasound grade evaluates multiple anatomical and dynamic features, and ranges from 0+ for hepatic artery diameter 5-6 mm, peak flow velocity <80 cm/sec, and vascular resistivity index <0.55, through grades 1-4 defined by enlargement and increased flow velocity of the hepatic artery, hepatic artery branches (developing tortuosity), and hepatic veins, together with modifications of portal vein flow.[98] As emphasized by the recent EASL guidelines[111], 8% of patients with liver VMs will be symptomatic,[100, 112, 113] and intense medical treatment successfully treats the majority of these[111][109].

However, liver VMs in HHT can result in three important complications including high output cardiac failure (HOCF) at a rate of 1.2 per 100 person years[111] (in addition to portal hypertension, and biliary necrosis). In the literature, HOCF symptoms were often observed in the sixth or seventh decade, including dyspnea, decreased exercise tolerance and fatigue, palpitations, peripheral edema, and ascites. [26, 100, 112, 114, 115]

Ginon et al proposed a tentative description of disease course based on cardiac complications (Figure 4) and severity of pulmonary hypertension, starting with a high output state,

preceding left cardiac failure, and eventually further pulmonary hypertension and right cardiac failure. Only few data are available about natural history, follow up and prognosis in HHT, and these focus more on the clinical phenotype of HOCF than pulmonary hypertension: In the largest prospective series, onset of iron deficiency anemia was the most common precipitant of high output cardiac failure,[112] supported by a second series in which HOCF appeared more commonly following a worsening of nose bleeds[114]. Progressive left atrium (LA) enlargement and likely increased adrenergic drive appear to initiate a particularly difficult cycle with the development of atrial fibrillation that reduces stroke volume.

Importantly for respiratory physicians, treatment of pulmonary hypertension in the setting of hepatic AVMs and high cardiac output will differ substantially to the more usual PAH algorithms: Symptomatic treatment includes salt restriction and diuretics, and optimal correction of iron deficiency, anemia and atrial fibrillation, although this is not always efficacious. ACE inhibitors or beta-blockers have been tried, but were not evaluated in patients with HOCF.[104] The majority of patients treated in this way demonstrate complete or partial resolution of symptoms, but these are not curative.[111]

Liver transplantation, (LT) is the only curative option for liver involvement in HHT[99, 105, 116], and associated with complete or partial reversibility of HOCF and pulmonary hypertension[105]. However, optimal timing for LT remains unclear, as morbidity is higher in patients at an advanced stage and in poor medical condition, with concurrent pulmonary hypertension associated with stormier perioperative courses: a PVR <240dynes sec cm^{-5} has been suggested as a cut off [99]. Despite the risks, when undertaken, post-operative OLT mortality in HHT is modest at 7-10%, and the long term survival (>10 years) is excellent,

ranging from 82-92%.[105, 116] Although hepatic artery ligation, banding, and embolization have been associated with improved cardiac symptoms, the significant associated morbidity and mortality means these are no longer recommended.[68, 111]

Anti-angiogenic therapy with anti-vascular endothelial growth factor antibody (bevacizumab) might be effective in reducing liver size and may be an interesting option in treating HOCF.[117-119] However, as relapses are observed after the end of treatment, OLT is still now the only radical cure for liver VMs, in patients under the age of 65 years. Bevacizumab is recommended, either for patients over the age of 65 years, or those who are poor candidates for surgery; if these latter respond to bevacizumab they can be re-evaluated for OLT (with a"fast-track")[120].

Mechanism and management of pulmonary arterial hypertension (Group 1 or PAH)

PAH is caused by remodeling of small pulmonary arteries with lumen narrowing, subsequent right heart failure and death. PAH in the absence of liver AVM is very rare in HHT: the prevalence has been recently evaluated in France and estimated to be lower than 5% of confirmed PH in HHT (Revuz S et al, 2017 in review), however, it has not been systematically evaluated.

PAH in HHT is clinically indistinguishable from idiopathic PAH (with severe, progressive dyspnea on exertion, and progressive right heart failure), and histologically similar to idiopathic PAH, with intimal hyperplasia, medial thickening and remodelling, *in situ* thrombosis, and plexiform lesions[27-29, 121-123].

PAVMs and PH in HHT

Special considerations are warranted with regard to the unusual HHT patients with both PAVMs and PH. Anecdotally, vasooclusion of PAVMs in a patient with PH can lead to a sudden increase in right ventricular afterload and precipitate right heart failure. However, in a large series, pulmonary arterial pressure was not generally modified by PAVM embolization.[80] Testing the hemodynamic consequences of PAVM vaso-occlusion by transient occlusion of the feeding vessel by an inflatable balloon has been proposed but did not predict the outcome in one published case.[80] Thus as rehearsed some years ago,[124] while vasoocclusion of PAVMs in patients with known PH is technically possible, for patients with severe PH, based on current evidence, we would not usually interpret risk–benefit considerations in favour of PAVM embolization, unless the patient had life-threatening haemoptysis or haemothorax. The risk of rapid increase in size of PAVMs and of hemorrhage related to PAVMs rupture might be increased in individuals with severe pulmonary hypertension[60].

The natural history and long-term outcome of HHT-associated PAH is unknown but it is no better than that of PAH due to *BMPR2,* with one series suggesting the outcome is worse than for patients with PAH due to *ACVRL1*.[29] To what extent patients with HHT and PAH may benefit from modification of PAH management algorithms remains to be determined.

HHT and other lung pathologies.

There is no evidence to date that HHT influences the likelihood of patients developing common respiratory conditions such as asthma, COPD, or interstitial lung disease, though as noted above, the presence of such conditions may limit an individual's ability to generate the

exuberant ventilatory responses required for PAVM compensation.[52] There are tantalising data that sleep apnea may be ~2.6 fold more common in patients with HHT[125], with a prevalence of 69/100,000 in comparison to 27/100,000 in the general population. Recent data have suggested that HHT may be associated with a reduced incidence of cancer in general,[126, 127] and specifically primary or secondary lung cancer.[127] Mechanisms remain speculative.

In conclusion, HHT is an important condition for the practising pulmonologist. Where formalised regional or national screening/treatment programmes are instituted, life expectancy is increased compared to historical controls and similar countries operating less well-implemented screening programmes[127, 128]. The recent approval of the European Reference Network (VASCERN HHT) (https://vascern.eu/expertise/rare-diseases-wgs/hht-wg/) is likely to improve visibility, transborder care, training, educational opportunities and hopefully research for clinicians seeking wider exposure to this important, and long-overlooked condition.

Table and figures

Table 1: Visceral manifestations of HHT and complications

Table 2: Pulmonary hemodynamics associated with HHT.

Figure 1: PAVM on CT scan

Figure 2: Schematic of systemic and pulmonary circulations indicating vascular beds commonly affected by HHT. Red arrows denote AVMs. The pulmonary circulation indicates pulmonary AVMs, and distinguishes sites of pulmonary arterial (PAH), and post capillary (Group 2) pulmonary hypertension. The hepatic and portal circulations indicate the three anatomical forms of aberrant hepatic vascular communications: 1: hepatic artery to hepatic vein (arteriovenous, associated with high output states and Group 2 PH), 2: hepato-portal (hepatic artery to portal vein, associated with portal hypertension), and 3, porto-venous (portal vein to hepatic vein).

Figure 3: Algorithms proposed for the screening and follow-up in adult patients with HHT. Radiation-sparing follow up is recommended, limiting follow-up CT scans to situations when clinically indicated.

Figure 4: **Relationship between pulmonary hypertension and hepatic VMs in HHT** adapted from Ginon et al[26].

Legend: Further mechanistic contributions from A: Other causes of reduced systemic vascular resistance (eg other AVMs, sepsis); B: Other mechanisms of reduced arterial oxygen content (eg hypoxemia). C: Mechanisms include left atrial enlargement, and adrenergic stimuli to meet increased cardiac demands. D: Right heart failure develops with severe pulmonary hypertension. Repeated echocardiography with CI measurements and classification with other cardiac parameters is important to follow patients with liver VMs and possible evolution over time.

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Table 1: Visceral manifestations of HHT and complications

Manifestation / lesion	**Prevalence**	**Diagnosis**	**Complication**
Epistaxis / telangiectasia of nasal mucosa	>90%	Epistaxis beginning in childhood, often inaugural of HHT.	Anaemia; Acute haemorrhage
Mucocutaneous telangiectasia (lips, oral cavity, tongue, fingertips)	80%	Evident	Cosmetic haemorrhage
Telangiectasia of the gastrointestinal tract	15-30%	Endoscopy (upper/lower)	Anaemia; Gastrointestinal haemorrhage
Pulmonary AVMs	50%	CT Scan Transthoracic contrast echocardiography (TTCE)	**Most asymptopmatic** **Right-to-left shunt:** Stroke, Brain abscess, Hypoxaemia +/- dyspnoea; Migraine **Haemorrhage :** Haemoptysis, Haemothorax
Hepatic vascular malformations	30 - 70%	Doppler US CT can	**Most asymptomatic** **Hepatic AVMs:** High cardiac output ± failure, post-capillary pulmonary hypertension **Hepato-portal VMs:** Portal hypertension **Porto-venous VMs:** Biliary ischaemia
Cerebral AVMs	10-20%	MRI Angiography	**Most asymptomatic** **Haemorrhage** depends on type: **Headache** **Epilepsy**
Spinal AVMs	<1%	Spinal MRI	**Haemorrhage;** Paraplegia (acute, subacute or progressive)

Table 2: Pulmonary hemodynamics associated with HHT.

	Hyperdynamic circulatory state	**Excess fluid volume**	**PAH**
Mean Pulmonary Artery Pressure	↑	↑	↑↑
Pulmonary Vascular Resistance	↓	→	↑↑
Cardiac output	↑	↑	**→ or ↓**
Pulmonary artery wedge pressure	↓	↑	**→ or ↓**
Precapillary pressure gradient (diastolic pulmonary artery pressure – pulmonary artery wedge pressure)	→	→	↑

Legends: PAH= Pulmonary artery hypertension (Group 1), ↑ = increased, ↓ = decreased, → = unchanged

Figure 1

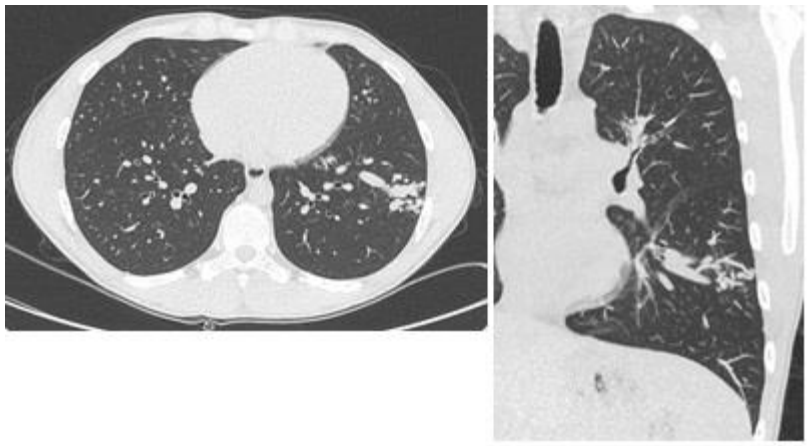

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Figure 2

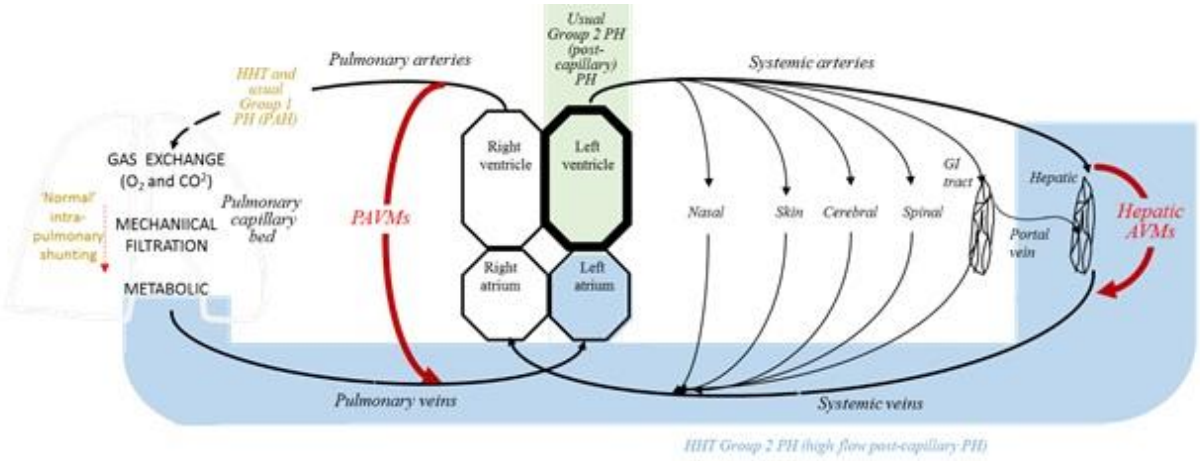

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Figure 3

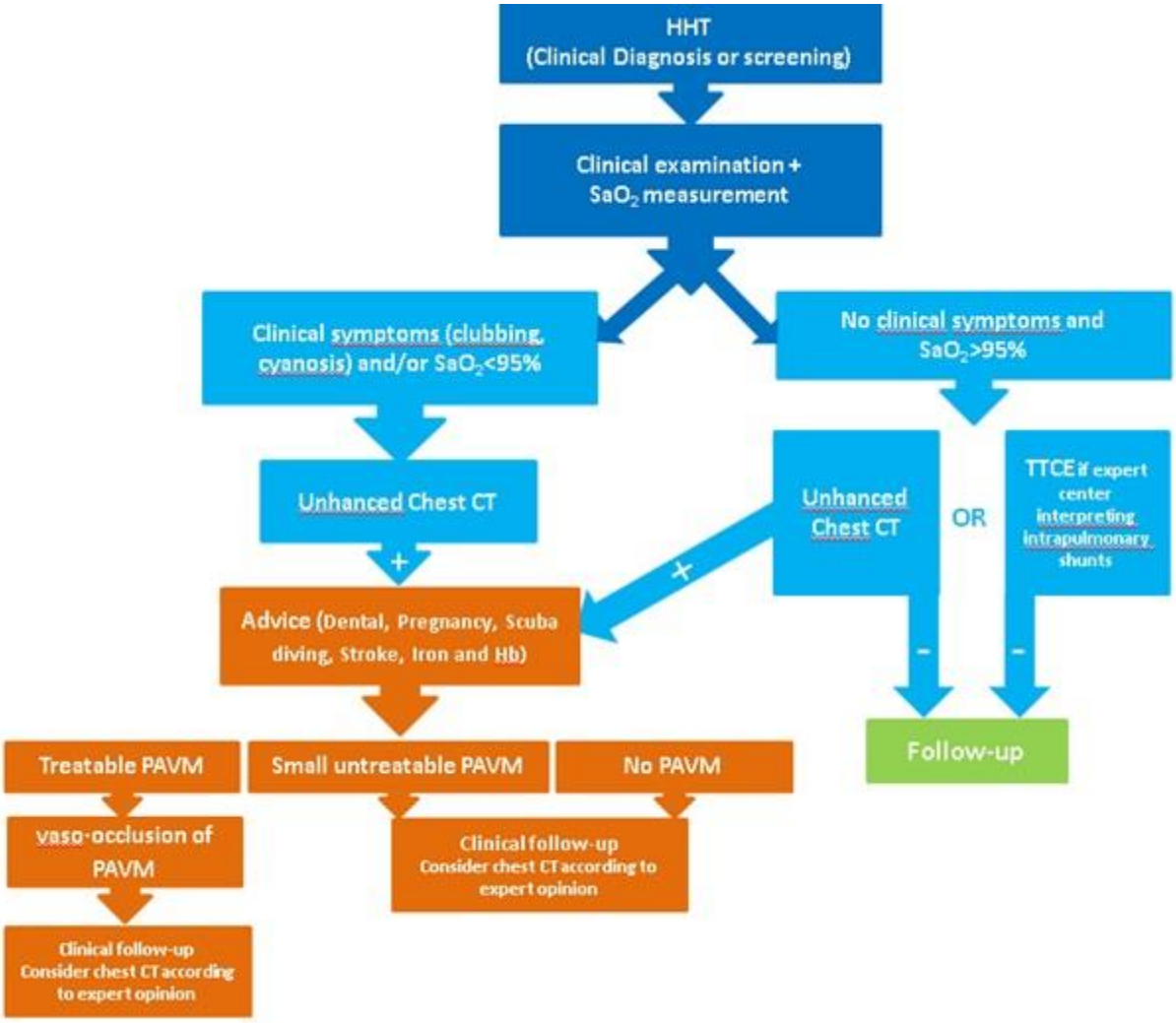

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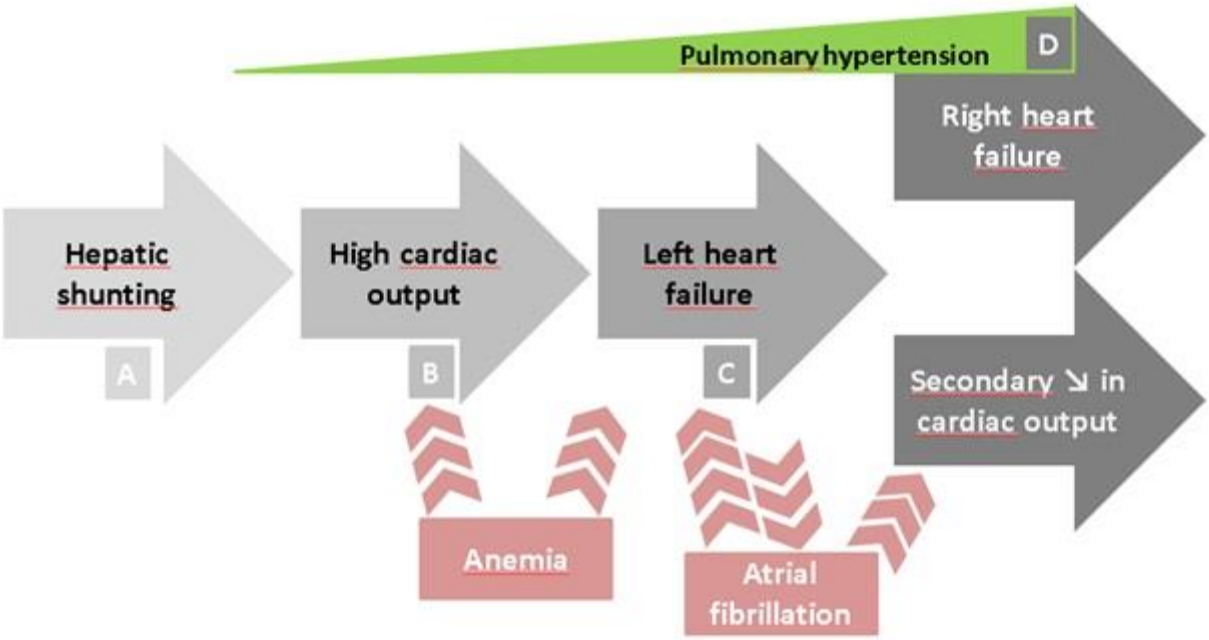
Figure 4



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