CONCISE CLINICAL REVIEWS

Pulmonary arteriovenous malformations

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Funding: European Respiratory Society: Rare Disease Achievement Award (CLS), NIHR: London (NW) Comprehensive Local Research Network, HHT patient donations.

Running head: PAVMs- state of the art in 2014

Subject category 17.03 (Pulm Circ Gen);

Word Count 5310

Key words: embolization; HHT, hypoxemia/hypoxia; iron deficiency; radiation

At a glance: **WHAT IS KNOWN ON THIS SUBJECT:** PAVMs are a rare curiosity, often associated with hereditary hemorrhagic telangiectasia, and should be treated by embolization to prevent strokes, brain abscess and hemorrhage. **WHAT THIS PAPER ADDS:** This article synthesises material from recent manuscripts that have advanced our understanding of PAVM prevalence, hypoxemia compensations, phenotypic modifiers, and the need for radiation-limiting management strategies.

Abstract 250 words

Within the past decade, pulmonary arteriovenous malformations (PAVMs) have evolved from rare curiosities, to not uncommon clinical states, with latest estimates suggesting a prevalence of ~1 in 2,600. PAVMs provide anatomic right-to-left shunts, allowing systemic venous blood to bypass gas exchange and pulmonary capillary bed processing. Hypoxemia and enhanced ventilatory demands result, though both are usually asymptomatic. Paradoxical emboli lead to strokes and cerebral abscesses, and these commonly occur in individuals with previously undiagnosed PAVMs. PAVM hemorrhage is rare, but is the main cause of maternal death in pregnancy. PAVM occlusion by embolization is the standard of care to reduce these risks. However, recent data demonstrate that currently recommended management protocols can result in levels of radiation exposure that would be classified as harmful. Recent publications also provide a better appreciation of the hematologic and cardiovascular demands required to maintain arterial oxygen content and oxygen consumption in hypoxemic patients; identify patient subgroups at higher risk of complications; and emphasise the proportion of radiologically-visible PAVMs too small to treat by embolization. This review therefore additionally outlines medical states that exacerbate the consequences of PAVMs. Chief amongst these is iron deficiency which is commonly present due to concurrent hereditary hemorrhagic telangiectasia: iron deficiency impairs hypoxemia compensations by restricting erythropoiesis, and increases the risk of ischemic strokes. Management of periodontal disease, dental interventions, pulmonary hypertension, and pregnancy also require specific consideration in the setting of PAVMs. The review concludes by discussing to what extent previously recommended protocols may benefit from modification or revision.

INTRODUCTION:

Pulmonary arteriovenous malformations (PAVMs) are structurally abnormal vessels that provide a direct capillary-free communication between the pulmonary and systemic circulations (Figure 1), and hence an anatomic 'right-to-left' shunt (Figure 2). Gas exchange, filtration, and other processing of systemic venous blood is impaired. Surprisingly, the dilated, thin wall structures rarely hemorrhage, although this is the most common contributor to the 1% rate of maternal death in pregnancy.

PAVMs are substantially more prevalent than suggested by autopsy studies of the 1950s, and now barely meet the definition of a rare disease: Population-wide cancer screening programs using thoracic computerised tomography (CT) suggest PAVMs sufficiently large for detection by CT affect 1 in 2,630 (95% confidence intervals 1 in 1,315-1 in 5,555).[1]

Previous review articles summarise the pathophysiology and management recommendations using evidence available in 1998,[2,3] 2006,[4,5] and 2011-2013.[6-11] As first proposed 60ys ago,[12] treatment of asymptomatic PAVM patients is recommended to prevent later complications, with embolization now the standard of care (Figure 3).

However, the last 12 months have witnessed the publication of many PAVM data manuscripts that challenge concepts utilised in current management practice. Most importantly, new data demonstrate that currently employed protocols can result in levels of radiation exposure that would be classified as harmful:[13] It therefore seems imperative to reconsider risk-benefit considerations. The remainder of this review places the new PAVM evidence base in context for the practising pulmonologist, before considering to what extent previously recommended protocols may benefit from modification or revision.

ETIOLOGY OF PAVMs

Hereditary hemorrhagic telangiectasia (HHT)

The most common cause of PAVMs is hereditary hemorrhagic telangiectasia (HHT), a condition discussed in detail in HHT guidelines[5] and more recent HHT review articles.[14-17] Some brief comments are appropriate here, due to the HHT-bias of the PAVM evidence base, and impact of HHT features on PAVM presentation patterns.

HHT affects ~1 in 5-8,000, is transmitted from parent to child as an autosomal dominant trait, and is most commonly caused by mutations in *endoglin* (HHT1), *ACVLI*/ALK1 (HHT2) or *Smad4* (HTJP) Arteriovenous malformations (AVMs) and smaller telangiectatic vessels develop at multiple sites including nasal, mucocutaneous, pulmonary, hepatic, gastrointestinal and cerebrovascular beds. HHT patients usually present with recurrent nosebleeds, iron deficiency anemia, and/or complications attributable to previously silent AVMs. There is also an increased risk of pulmonary hypertension.

The prevalence of PAVMs differs according to HHT genotype, though screening is recommended across all genotypes.[5,6,7,14-17]. One series of 199 HHT patients demonstrated CT-evident PAVMs in 58% with *ENG* mutations, compared to 18% with mutations in *ACVLI*/ALK1 ($p<0.001$).[18] Conversely, pulmonary arterial hypertension, and pulmonary venous hypertension attributed to hepatic AVMs and high output states, are more common in HHT2,[19] but are only clinically significant in <5% of HHT patients.[20]

The diagnosis of HHT can be difficult, and is further influenced by socioeconomic and geographical factors.[21] With enhanced awareness of HHT, the reported proportion of PAVM cases with HHT rose from ~70% pre 1998,[2,3] to 93.6% in one series,[22] with 59% (121/205) PAVM/HHT patients previously unaware they had HHT.[22]

Non HHT PAVMs

In a broad PAVM referral practice, the second most common etiology of single PAVMs appears to be sporadic, though this diagnosis should not be considered until HHT has been formally sought in the proband and family members. The respective HHT/PAVM prevalences suggest that the proportion of

sporadic PAVMs will rise, as more asymptomatic PAVMs are detected in the general population through the increasing use of CT scans in medical practice.

Treatment of cyanotic congenital heart disease by surgical generation of a cavo-pulmonary shunt frequently leads to PAVM development in the lung not receiving hepatic venous effluent.[23,24] Rare etiological causes include gestational trophoblastic disease, and arteriovenous fistulae induced by trauma. The case report-biased literature (27% of PubMed retrievals for "pulmonary arteriovenous malformations" from 2003-2012 were single case reports) suggests other causes that may reflect chance associations or alternate diagnoses.

CLINICAL FEATURES OF PAVMs

Presentation patterns

Clinical features observed in PAVM patients vary widely, and are summarised in Table 1.

Dyspnea and asymptomatic hypoxemia

Hypoxemia due to right-to-left shunting may be severe, but the most striking clinical finding for this patient group is the presence of asymptomatic hypoxemia.[26]

Relatively few patients present because of dyspnea, or describe dyspnea on exertion. Dyspnea was the reason for presentation in 51% (25/49) of cases by 1949,[25] 47% (201/427) by 1998[3], but only 14.6% (32/219) of a more recent series.[22] In 165 consecutive patients, MRC dyspnea grades did not exceed 3 (dyspnea after ~1 mile on the flat) unless there was significant co-existing cardiopulmonary disease.[27]Significantly hypoxemic patients with SaO_2 <85% were able to pursue sporting activities to a very high level.[26,28] Formal cardiopulmonary exercise tests (CPET) of 21 PAVM patients with SaO_2

80%-96%, demonstrated that Borg scale dyspnea, maximal work-rates and peak oxygen consumption ($V[dot]O_2$) did not differ according to hypoxemia severity.[28]

PAVM patients frequently exhibit orthodeoxia,[27] attributed to basal predominance of PAVMs. Although the cardiac literature might suggest platypnea (dyspnea relieved by lying down) should be evident,[29] in 257 consecutive patients with PAVMs, platypnea was not described by any of the 75 patients whose SaO_2 fell by at least 2% on standing.[27]

Only six of 95 patients completing a retrospective questionnaire of flight tolerance reported in-flight dyspnea, and there was no difference in sea-level SaO_2 between those reporting dyspnea, and those who did not.[30]

Most strikingly, 86/98 (87.8%) of consecutive patients reported no improvement in dypsnea/exercise capacity after embolization had corrected their hypoxaemia.[26] Those who did note an improvement were more likely to have coexisting concurrent diseases such as airflow obstruction, and/or elevated pulmonary artery pressure.[26,27] CPET studies in five patients where median SaO_2 increased from 90% pre-embolization to 96% post-embolization (p=0.009), demonstrated no difference in peak work-rate or peak $V[dot]O_2$ (medians 119W, 1.69L min^{-1} pre; 113W, 1.72L min^{-1} post-embolization).[28] Four patients reset their peak oxygen pulse (oxygen consumption per heart beat) to values almost identical to their pre-embolization values.[28]

Hemorrhage

PAVM hemorrhage leading to haemoptysis or hemothorax can be fatal, but is a relatively rare feature of PAVMs. The two main exceptions are if the patient is pregnant,[31,32] or if PAVMs are perfused at systemic pressures, for example due to pulmonary hypertension, or systemic arterial supply (from bronchial or non-bronchial systemic arteries) to PAVM sacs. Systemic arterial supplies may be spontaneous, but more commonly develop following PAVM embolization.[33-36] In patients with coexisting HHT, hemoptysis also results from nasopharyngeal and endobronchial telangiectasia.

Chest Pain

Pleuritic chest pain has been described in up to 10% of PAVM patients. In our experience, and as reported,[25,37] for untreated PAVMs, chest pain is much more commonly a reason for the diagnostic imaging to be performed, rather than attributable to the PAVM itself.

Neurological risks due to compromised capillary bed filtration

Neurological PAVM-associated risks are common, and remain poorly recognised. Even in recent series, the majority of PAVM- induced ischemic strokes or cerebral abscess occurred in patients who had not yet received their diagnosis of PAVMs.[22,38] The median delay from cerebral event to PAVM diagnosis was 2ys.[22]

Cerebral abscess

A Danish epidemiological study demonstrated cerebral abscess rates of 0.4/100,000/year in the general population but 155/100,000/year in HHT/PAVM patients.[38] Cross sectional rates of 7.8-19.0% are reported in different series,[2-11,22] including 9.05% in 219 consecutive PAVM/HHT patients, adjusting for ascertainment bias.[22]

Ischemic strokes

Cross-sectional studies indicate ischemic stroke[2] rates of 9-18%,[2-11,22] and 11.3% adjusting for ascertainment bias.[22] Modelling suggests that by 65ys, at least 25% of untreated PAVM patients will have a clinical stroke (symptoms lasting >24hs),[20,22] while a 1999 imaging study identified cortical or subcortical infarcts in 34/67 (51%) patients, at a median age of 41 years.[39] Ischemic stroke risk was reduced following embolization of PAVMs.[22]

Migraine headaches

Multiple studies demonstrate the risk of migraine in HHT patients is approximately doubled if they have pulmonary AVMs,[40-44] and suggest that migraines improve following PAVM treatment.[40,43] Migraine features and precipitants appear indistinguishable to migraines in the general population.[44]

Myocardial infarctions

Myocardial infarctions also occur as a result of paradoxical emboli,[45]and may have similar risk factors as ischemic strokes.[20]

Pregnancy-related deaths

Pregnancy is a hazardous period for women with PAVMs. Absolute risks were quantified in two separate series of 487[31] and 244[32] pregnancies. In one series, 1.0% of pregnancies (95% confidence intervals 0.1-1.9) resulted in a major PAVM bleed,[31] and the maternal death rate was 1.00% (95% CI 0.13, 1.92%).[31] There are also enhanced risks of pulmonary emboli, and myocardial infarction with normal coronary arteries.[31] In women experiencing a life-threatening event, prior awareness of the PAVM of HHT diagnosis was associated with improved survival ($p = 0.041$).[31]

Longevity

PAVM development is usually completed by the end of puberty, but despite the clear risks, cross sectional series include large proportions of older patients. In our recent series of 497 consecutive patients, a quarter were 60ys or older at presentation, and it was not uncommon for patients describing cyanosis in childhood to become grandparents and even great-grandparents in their lifetime.[20]

Diagnosis and assessment of PAVMS

Radiological methods:

Imaging modalities define PAVM number, size, nature, and suitability for embolization.[36,46] 'Simple' lesions consist of an aneurysmal venous sac communicating with a dilated feeding artery and draining vein (Figure 1A). Other PAVMs are complex plexiform masses with multiple afferent and efferent

vessels. Diffuse PAVMs have been defined as multiple small PAVMs affecting a single segment, or every segment of one or more lobes.[35,47] Distinguishing features of possible "PAVM mimics" such as a pulmonary varix or bronchocele are presented elsewhere. [46]

Although PAVMs may be clearly visible on chest radiographs, many are not, and the chest radiograph has been reported as being normal in 10 to 40% of instances where clinically significant PAVMs were present.[7] Computed tomography (CT) is generally considered the gold-standard investigation for diagnosing PAVMs and demonstrating their size and extent prior to therapy, and will detect lesions far below the size for which embolization is feasible. This modality is preferred to magnetic resonance (MR) imaging because of its greater resolution. Elegant CT demonstration of angiographic anatomy means that diagnostic angiograms are very rarely required: in our center, they are performed at the same session as therapeutic embolization, and limited to the lung where PAVMs are sited.[6,7,46,48]

Evaluation of right-to-left shunts

PAVMs provide an anatomic right-to-left shunt: pulmonary arterial blood passing through PAVMs is not exposed to ventilated alveoli. This contrasts to the hepatopulmonary syndrome where shunting is considered to arise as a result of perfusion-diffusion defects in dilated microvascular channels.

Gas exchange

Classically, shunts were measured by arterial PaO_2 breathing 100% oxygen. More commonly, arterial PaO_2 and/or oxygen saturation (SaO_2), are measured on air: each is inversely related to the proportion of the cardiac output flowing through the shunt (Figure 4). Other methods such as the multiple inert gas technique (MIGET) have not been utilised in large PAVM series.

Technetium perfusion scans

Perfusion scans using technetium-labelled albumin macroaggregates permit precise shunt quantification (Figure 4). As for 100% oxygen quantifications, this method is no longer in general use for diagnosis or follow up of PAVMs.

Contrast echocardiography(CE)

More commonly in PAVM practice, the circulatory transit of microbubbles generated by intravenously injected echocontrast material is detected, imaging bubbles arriving in the left heart or systemic circulation (Figure 2). Microbubbles of gas behave differently to albumin particles on pulmonary capillary transit, because the gas rapidly diffuses into the alveolus down the concentration gradient, leading to microbubble shrinkage, then collapse.[7] With the sensitivity to detect single microbubble transits, such studies should detect all anatomic shunts, which is the reason why transthoracic CE was recommended by the international HHT guidelines committee as the initial PAVM screening test.[5]

However, CE studies are also frequently positive in normal lungs, without any detectable impairment of gas exchange.[49,50] Approximately 8% of the general population exhibit this phenomenon at rest, rising to up to 90% on exercise and in other high cardiac output states.[49-52] There is interest and debate regarding the implications and basis of these findings in the general population. The proportion attributable to "alveolar transit" bubbles (bubbles that have passed through the capillaries but not fully collapsed)[7] is not known.

In HHT patients, one study demonstrated positive CEs in 85% of patients with HHT1, and 35% with HHT2.[18] However, in HHT1, a positive CE study only provided a 36.3% positive predictive value for a treatable PAVM.[18] The remainder likely reflect both PAVMs below the limits of CT scan detection, and normal physiological responses in a state characterised by high cardiac outputs (compensating for anaemia,[53] hypoxemia,[26-28,,54,55] hepatic and/or other AVMs[56]).

Careful grading of the number of bubbles visible in the left ventricle can facilitate distinction between PAVMs and more normal variation. In a combined Dutch-Italian study, Grade 3 shunts (>100 bubbles per frame) had a positive predictive value [PPV] for CT-evident PAVMs of 92.5%, compared to a PPV of 13.4% for the lowest positive contrast shunt grade (Grade 1, <30 bubbles per frame). [57]

NEW INSIGHTS INTO PAVM PHYSIOLOGY AND CLINICAL CONSEQUENCES

Mechanisms to preserve oxygen delivery to the tissues

During chronic compensation, a graded secondary erythrocytotic ('polycythemic') response operates to maintain arterial oxygen content (CaO_2). CaO_2 is determined both by oxygenation and hemoglobin, with CaO_2 breathing room air approximating to $SaO_2 \times hemoglobin \times \frac{1.34}{100}$ where hemoglobin is expressed in g/dl, and SaO_2 as a percentage.[58] In 165 consecutive PAVM patients with SaO_2 varying from 78.5-99% (median 95%), there was a hemoglobin rise of 0.82g/dl for every 1% fall in SaO_2 ($p<0.0001$).[26] Thus, healthy PAVM patients appeared to preserve CaO_2 at just over 18mls/dL on air,[26-28] as reported at altitude.[59] Self-reported exercise tolerance was worse in patients with lower CaO_2 ($p<0.0001$).[26] After correction of hypoxemia by PAVM embolization, secondary eythrocytotic responses were lost, hemoglobin fell, and CaO_2 returned to pre-embolization values within months.[26]

PAVM patients have high cardiac outputs at rest and on exercise.[54,55,60] On exercise, one study demonstrated an excessive increase in total pulmonary blood flow (142% of predicted) in relation to the observed oxygen consumption ({Vdot}O_2), resulting in higher than predicted tissue oxygen delivery on exercise.[54] Data from two studies suggest that on exercise, hypoxemic patients utilise increased stroke volumes, with similar heart rates to controls,[28,54] and this may be regulated through maintenance of the oxygen pulse (oxygen delivered/utilised per heart beat).[28] Cardiac output and stroke volume fall after embolization.[55]

Apparently separately, acute falls in SaO_2/CaO_2 (for example on standing) appear to be compensated by increased heart rate: Orthostatic tachycardia was more pronounced in 257 PAVM patients than 40 controls without orthodeoxia: The age-adjusted pulse rate was 0.79 min^{-1} higher for every 1% fall in SaO_2 on standing ($p<0.001$).[27] Unlike the postural orthostatic tachycardia syndrome (POTS), for PAVM patients, more exuberant postural tachycardias predicted better exercise tolerance.[27]

Understanding of these findings, and multiple PAVM case reports, [61] may be improved using the analogy of a train line delivering oxygen to the tissues:[62] hypoxemia leads to an increased number of train carriages (hemoglobin), and/or cardiac work such that blood hypoxemia does not lead to tissue hypoxia. The train line analogy also provides an intuitive understanding of why compensation may be less successful for hypoxemic patients who have concurrent cardiac disease, or airways/alveolar pathologies, particularly in the setting of iron-restricted erythropoeisis.[62]

Exercise adaptations:

Studies published earlier this year[26,28] suggest that PAVM patients who participate in intense sporting activity may enhance compensatory mechanisms, facilitating oxygen delivery. A CPET study of 21 patients suggested the strongest predictors of maximal work-rate were lower body mass index, and higher anerobic threshold, both of which reflect better aerobic conditioning.[28] Of 117 consecutive PAVM patients with normal exercise tolerance, a pre-defined athletic group displayed higher hemoglobin for their degree of hypoxemia (resulting in higher CaO_2),[26] mirroring general population data that exercise training can stimulate bone marrow erythropoiesis, increasing hemoglobin and red cell mass.[63]

One PAVM study[26] suggests mechanisms may include modified iron handling: the median serum ferritin was 38ug/L in athletes (IQR 19-77 ug/L) and non-athletic normals (IQR 16-73 ug/L), but serum iron was higher in athletes (median 19.5 [IQR 13-28] μmol/l) than non-athletic normals (median 14 [IQR 9-17]μmol/l, p=0.01).[26] This difference could be predicted if intense physical activity enhanced skeletal muscle production of erythroferrone:[64] Erythroferrone was recently identified as an erythroblast-synthesized hormone that suppresses hepcidin production[64] (and hence promotes gastrointestinal iron absorption and mobilisation of iron from stores[65]). However, the same protein appears to be synthesised by skeletal muscle,[66] providing a plausible mechanism for an aerobically advantageous adaptation to exercise.

Impaired CO_2 clearance

The impairment of gas exchange by right-to-left shunting through PAVMs also impairs H^+/CO_2 clearance,[58] resulting in abnormally high ventilator drives.[28,54,60] On exercise, PAVM patients increase minute ventilation (V[dot]E) more than controls for a given increase in CO_2 production (V[dot]CO_2),[28] with a steeper V[dot]E/V[dot]CO_2 slope in patients with lower SaO_2.[28] It is of some surprise that recent[28] and earlier[54,60] studies indicate that the ventilatory stimulus from the combined O_2 and CO_2 shunts not only maintains normocapnia, but appears to cause an overshoot, resulting in lower end-tidal PCO_2 and venous bicarbonate.[28,54,60] Following successful embolization, end-tidal PCO_2, V[dot]E/V[dot]CO_2 slopes, and lower ventilatory equivalent for CO_2 ($EqCO_2$) at nadir normalise.[28]

The increased ventilation was not captured as dyspnea by Borg scale testing during CPET.[28] In a large observational series, a small group of individuals did notice that ventilatory patterns they had experienced during yoga, swimming, and singing resolved following embolization.[26]

Mechanisms of paradoxical emboli

Ischemic stroke

The 2011 American Heart Association Stroke Guidelines recommended use of anti-platelets agents for secondary prophylaxis of ischemic strokes due to PAVMs.[67] Recent data highlight that HHT/PAVM patients with nosebleeds often tolerate antiplatelet and anticoagulant therapies better than expected.[68]

In the PAVM population, ischemic strokes are not attributable to conventional vascular risk factors such as hypertension, hypercholesterolemia, diabetes, or arrhythmias.[20,22] It was expected that risks would increase with the severity of PAVM-induced shunting. An earlier proposed “3mm rule” for a

feeding artery luminal diameter of clinical consequence was withdrawn,[69] though 3mm is still referred to as a possible threshold for PAVMs requiring embolization.[9]

Paradoxical embolic events are more common in patients with the higher grade contrast echocardiography shunts that are more likely to be associated with visible PAVMs seen on CT.[70] In one study, Grade 3 shunts ([PPV]for CT-evident PAVMs 92.5%[57]) were associated with a 10.4 fold increase in stroke/abscess, whereas patients with Grade 1 shunts (PPV for CT-evident PAVMs 13.4%[57]) had no enhanced risk.[70] Such findings are reassuring for the members of general and HHT populations with low grade intrapulmonary shunts by contrast echocardiography, and no evidence of PAVMs on a formal CT scan.

Once PAVMs are sufficiently large for CT detection, or grade 3 shunts, there is little evidence that stroke risk is substantially influenced by further increase in shunt size: A prospective series of 219 consecutive PAVM cases provided no evidence of increased stroke risk with PAVM severity judged by six different biomarkers,[22] and only a marginal association with low SaO_2 in an extended series of 497 patients.[20] The strongest stroke risk factors identified to date are low serum iron[20] (common due to inadequate iron intake for HHT hemorrhagic losses[71]); low pulmonary artery pressure (proposed to facilitate the paradoxical embolic process[20,22]); and serum fibrinogen,[20] the predominant circulating plasma protein for platelet adhesion.[72] Both iron deficiency[73] and serum fibrinogen[74] are emerging as risk factors for ischemic stroke in the general population, a third of whom have a patent foramen ovale that can also lead to paradoxical emboli at specific times.[67,75]

The low hemoglobin caused by iron deficiency has been suggested to contribute to stroke risk through impaired oxygen delivery.[73] However, PAVM-induced ischemic strokes are not global hypoxic insults, but conventional, focal infarcts, resulting in partial anterior or posterior circulation syndromes.[20] Iron deficiency is associated with increased blood viscosity,[76] higher factor VIII[77] and venous thrombemboli (VTE).[77] Conventional VTE can lead to ischemic strokes following paradoxical embolism of a pulmonary embolus,[78] but this is uncommon in PAVM patients.[20,22] Given the AHA

recommended antiplatelet agents for prevention of ischemic strokes in PAVM patients,[67] the recently rediscovered exuberant platelet aggregation in iron deficiency seems a more plausible mechanistic link:[20] Platelets from iron deficient patients (with and without HHT)[20,79] demonstrate enhanced *ex vivo* aggregation to 5HT (serotonin), providing potential new therapeutic targets.[20,79]

Cerebral abscess

The organisms most commonly isolated from PAVM-associated cerebral abscesses are anaerobic or facultative anaerobic organisms of periodontal origin.[22,80]Risk factors identified for PAVM-associated cerebral abscess include male gender,[22] dental hygiene and interventions;[22] and, once adjusted for male gender, a lower SaO_2.[22] A genetic predisposition is suspected due to the frequent recurrence in siblings.

Migraines

Modified pulmonary metabolism of vasoactive amines is usually proposed as a plausible mechanistic link between PAVMs and migraines. The precipitation of migraines following contrast injection for nuclear medicine scans[20] suggests to the current author, that paradoxical emboli may also contribute to migraine pathogenesis.

Impact of concurrent cardiopulmonary disease

Airflow obstruction emerged as a surprising predictor of dyspnea, and improvement in exercise tolerance after embolization.[26] Suggested reasons why patients with airflow obstruction may be less able to compensate for PAVMs included impaired ability to achieve the supranormal ventilation required for CO_2 clearance.[6]

Significant pulmonary hypertension results in enhanced risk of PAVM growth and rupture/hemoptysis, greater dyspnea (with attendant greater likelihood of symptomatic improvement post embolization),[26] and reduced risk of paradoxical ischemic stroke.[20,22] PAVM embolization in the presence of severe pulmonary hypertension is more hazardous, can be fatal, and temporary balloon occlusion does not predict subsequent rises in pulmonary artery pressure.[81]

Physiological and pathological states associated with higher cardiac outputs also appear to impact on symptomatic status (Table 1), and often modify risks of PAVM treatment. Such states include pregnancy and iron deficiency (each discussed above), HHT-related hepatic AVMs[56] and sepsis. Formal data are required, but it is this author's impression that more athletically-trained individuals fare better when they encounter such stresses.

Altered barometric pressure

Theoretical concerns that the reduced barometric pressure and relative immobility associated with flying might be detrimental were not substantiated in a retrospective questionnaire-based study of 3,950 flights in 145 HHT patients including 95 with PAVMs.[30] Scuba divers with right-to-left shunts, including PAVMs, are at increased risk of decompression illness, through paradoxical gas embolism, leading to vascular obstruction and resultant tissue ischemia.[7]

MANAGEMENT STRATEGIES:

Embolization

PAVM embolization is recommended for first line treatment of PAVMs amenable to treatment.[10] Detailed descriptions of embolization techniques are beyond the scope of this text, and the reader is referred to recent manuscripts.[6,7,8,10,34,36,46,48,81] Amplatzer vascular plugs have rapidly become the preferred agent for embolization, compared to coils.[36,48,82,83] Advantages include the ability to occlude large diameter feeding arteries with single plugs (thus reducing procedure time and radiation exposure), easier occlusion at the neck of the sac, and occlusion over a shorter length of vessel, thereby reducing the likelihood of occluding vessels supplying normal lung.[6,7,48]

Benefits of embolization

Following successful embolization, assuming feeding arteries remain occluded and the PAVM does not recruit a new vascular supply from neighbouring pulmonary and/or systemic arteries,[34,36] organization and remodelling leads to regression of the PAVM sac, and normalization of diameters of former feeding arteries/draining veins (Figure 1).[28] Multiple series have demonstrated anatomic resolution of PAVMs; reduction in right-to-left shunting; and improvement in oxygenation following embolization (reviewed[2,3,6-11]). More recent publications highlight reduction in strokes,[20] migraines,[40,43] and reduced hematologic (hemoglobin),[26] cardiac, [28,55] and ventilatory[28] demands.

Limitations of embolization

There are technical limitations to embolization feasibility: Feeding arteries with luminal diameters <2-3 mm diameter are technically untreatable using current catheterization methods. This may be why more proximal occlusions (with attendant risks) have been utilized in some centers. The now obsolete '3mm rule' means that PAVMs purely supplied by such vessels were not included in many of the efficacy series. HHT patients often have multiple PAVMs, only a proportion of which are suitable for embolization. In these cases, improvement in shunting, as opposed to complete obliteration of PAVMs, is the most realistic outcome that can be offered.

As detailed elsewhere,[36] PAVM sac persistence after embolization occurred in up to 25% of cases in the pre-Amplatzer plug era. One series with an overall persistence rate of 5%, demonstrated recanalization through previously embolized feeding arteries accounted for 91% (48/53) of persistent PAVMs.[36] A separate series indicated recanalization was more likely if coils were used singly, or placed >1cm from the PAVM sac,[84] and there are suggestions in the literature that recanalization rates may be higher in childhood.[11] A recent study demonstrated no recanalization 6-40 months after embolization of 28 PAVMs with Amplatzer plugs and coils.[82]

PAVM sacs that persist after embolization may acquire new pulmonary, and more hazardously systemic arterial feeders.[34,36] This mirrors findings reported for spontanous pulmonary embolic occlusions of normal pulmonary arteries.[85] The neovascular supplies are less amenable to subsequent

re-embolization, than recanalized feeding arteries.[36] With appropriate evaluations of systemic arteries, the development of a systemic arterial supply appears to be frequent (13/32 in [34]).

Risks

Risks appear to be low in experienced hands where long-term follow up of patients is employed but are not zero. Generally, the most common complication of embolization is transient pleurisy which is reported in approximately 10% of patients, and can occur in the absence of pulmonary infarction. Rates appear higher with peripheral, or diffuse PAVMs.[35] Paradoxical embolism of devices, thrombi, or air bubbles (leading to angina, strokes, or need for retrieval) are rare, and seem to have been reduced by technical advances reported in later series. Potential massive hemoptysis from systemic arterial collaterals that develop in the months following embolization remains a concern, requiring dual systemic (bronchial) and pulmonary angiographic approaches for embolization.[7,9,36]

Specific considerations apply in the setting of pre-existing pulmonary hypertension when occlusion of PAVMs can result in acute and fatal increases in PAP. A detailed discussion using data available in 2008 was presented in [86] Our current interpretation of the evidence base is that severe pulmonary hypertension remains a relative, if not absolute contraindication to elective embolization. However, further data are needed, particularly since patients with higher PAP are more likely to report a symptomatic benefit if PAVMs can be safely occluded.[26]

Radiation limitation strategies

In the last few months, the management strategies recommended in Figure 3 have been shown to result in harmful radiation burdens over an 11 year period.[13] In a single center study of 246 PAVM patients (mean age, 53 years), the mean cumulative effective dose (CED) over an 11 year period was 51.7mSv, and CED exceeded 100mSv in 26 patients (11%).[13] CT scans accounted for 46% of the

CED, compared to 51% from interventional procedures.[13] A survey with predominantly North American respondents had reported an excess of breast cancer (but no other cancer) in patients with HHT.[87] It therefore seems imperative to reconsider radiation exposure at multiple time points, particularly in younger patients:

Initial PAVM diagnostic investigations

In the HHT Community, there have been major efforts to limit radiation exposure at the point of screening of HHT family members, with contrast echocardiography recommended.[5] If genuinely negative or Grade 1, this can spare individuals with no evidence of shunting from a single thoracic CT scan.

More widely, initial diagnoses often rely on a single thoracic CT scan which in our view is entirely reasonable given the risks associated with PAVMs. However, the initial CT may then be followed by repeat CT scans, and even diagnostic angiography before referral for formal embolization assessments. 'Stop and refer after first CT' seems an appropriate simple paradigm that could be employed.

There seems some confusion about the likelihood of development of PAVMs in an HHT patient with a previously negative CT. In our experience, carefully performed CT scans, if negative, are unlikely to require repeating in adulthood unless clinical circumstances change substantially, thus alternate methods of patient evaluation can be utilised (see below).

Angiographic treatments

Treatment-associated exposures are incorporated in risk-benefit considerations. Careful consideration is given to whether additional embolization treatment of multiple small (<2mm) feeding vessels is likely to carry overall treatment benefit for patients. Where patients appear to be at high risk of complications, for example experiencing recurrent ischemic strokes, surgical resection is considered.

[6,7] Since children are at higher risk from ionising radiation, where possible we avoid CT scans and angiography altogether until after puberty.[6,7,20,22]

Follow up:

Current international guidelines recommend post-embolization CT scans at 6-12 months, then subsequently 3 yearly, with 1-5 yearly CT scans for other patients with CT-evident PAVMs or positive contrast echocardiographic studies.[5] These recommendations were not adopted universally due to radiation concerns,[6,7,20,22,88,89] and in the light of [13], are likely to be revised in the future. Alternate follow up strategies employed include magnetic resonance imaging, noting resolution is currently limiting,[88,89] exercise testing,[90] and SaO_2 plus chest x-ray (Figure 1; further images in[26]). At our institution, CT scans are reserved for patients demonstrating new symptoms, deteriorating SaO_2, or failure to obliterate a PAVM sac which would have been predicted based on angiographic appearances.[6,7]

Medical management of patients with PAVMs

As an adjunct to embolization treatments, a number of relatively simple lifestyle and medical management recommendations may be employed:

Oxygen for hypoxemic patients:

Supplementary oxygen can be prescribed for symptomatic patients, but it is important to recognise that there is no rationale for prophylactic use to prevent hypoxic pulmonary hypertension, as there is no alveolar hypoxia.[26,28,30]

Venesection for polycythemia:

Secondary polycythemia is an adaptive response. Venesection is not without risk, particularly the induction of iron deficiency[76,91] which will increase cardiac demands to maintain tissue oxygen

delivery, and is a strong risk factor for paradoxical embolic stroke in PAVM patients.[20] The pathology most resembling PAVMs is cyanotic congenital heart disease, for which UK polycythemia guidelines[91] only recommend venesection if the patient describes symptoms of hyperviscosity

Lung transplantation:

This has been performed for PAVM patients, but is rarely indicated because of the life expectancy of even severely hypoxemic patients. The three patients in our practice[20] who were referred for lung transplantation assessment in the late 1980s/early 1990s (and elected not to proceed) remain stable 20, 22, and 25 years later. A separate retrospective study of 36 patients with diffuse PAVMs followed up 8.5ys (0.12-26) years later indicated 24 were working or studying full time, but in one, an attempted lung transplant resulted in an operative death.[35]

Pregnancy

To date, it has not been possible to identify women at higher risk of pregnancy-related complications.[31] Unfortunately, maternal deaths and life-threatening pulmonary hemorrhage do occur in previously treated patients.[31] Anglo-French management strategies emphasise the need to inform women of the 1% rate of maternal death pre pregnancy and to manage as high risk pregnancies.[31] Further specific management details are beyond the scope of this text (see [31,32])

Dental

Links between oral bacteria, dental procedures and PAVM-associated cerebral abscess have been recognised for many years and were the reason why antibiotic prophylaxis was recommended for dental and surgical procedures. This was originally based on the endocarditis paradigm, noting the absolute risk for PAVM patients is several orders of magnitude higher, and mechanisms are likely to differ.[92] Antibiotic prophylaxis is still recommended for patients with PAVMs.[92] Judicious dental hygiene is also recommended.[92]

Iron deficiency

Optimisation of iron status is emerging as a core principle for management of patients with PAVMs, particularly those with HHT and substantial iron losses from nosebleeds,[71] when conventional iron-rich diets are insufficient to meet the enhanced iron demands. Iron deficiency restricts hemoglobin synthesis/erythrocytosis, and this is an even greater problem for patients with hypoxemia requiring supranormal hemoglobins to maintain CaO_2,[26] and/or needing to achieve enhanced cardiac outputs.[28,55,56,60] Iron deficiency is also associated with enhanced risks of venous[77] and arterial[20] thromboses in the HHT/PAVM population.

Conclusions

New data offer opportunities for a balanced, informed approach to PAVM risk management. An 'advise and embolize' approach is recommended, weighing up both benefits and risks of specific treatments on an individual basis (Figure 4), before determining a mutually agreed management plan with the patient. Using this approach in our practice, embolization is almost always recommended, together with adjunct medical measures, and radiation-limiting follow-up strategies. Comparative outcome/exposure data, and formal updated management guidance, are urgently required. The terms hypoxemia/hypoxia should not be used interchangeably, as commonly observed in publications and clinical practice.

Acknowledgments:

Dr Shovlin thanks colleagues and students for helpful discussions, and particularly, Dr James Jackson for angiography/embolization insights, and critical manuscript review.

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Table 1: Major physiologic and clinical features of PAVMs

Right-to-left shunting reduce	***Physiologic compensations increase***	***Clinical features****
PaO_2, SaO_2, and CaO_2	Hemoglobin (secondary erythrocytosis)	Cyanosis. Often asymptomatic.
	Cardiac output (stroke volume; heart rate)	Dyspnea, palpitations, cardiac failure
CO_2 clearance	Ventilation (V[dot]E/V[dot]CO_2 slope)	Different ventilation patterns†
Capillary filtration/processing	*Not known*	Paradoxical embolic stroke, MI
		Cerebral and/or peripheral abscesses
		Migraine
		Clubbing
Fragile PAVM walls	*Not known*	Hemoptysis; hemothorax
Endothelial cell changes	*Not known*	*Speculative*

Table highlights primary physiology, identified compensatory mechanisms, and resultant clinical features (references in text). *Vascular bruits may be audible. †Often not appreciated until post embolization. SaO_2, % oxygen saturation of haemoglobin; CaO_2, arterial oxygen content. MI, myocardial infarction,

FIGURE LEGENDS

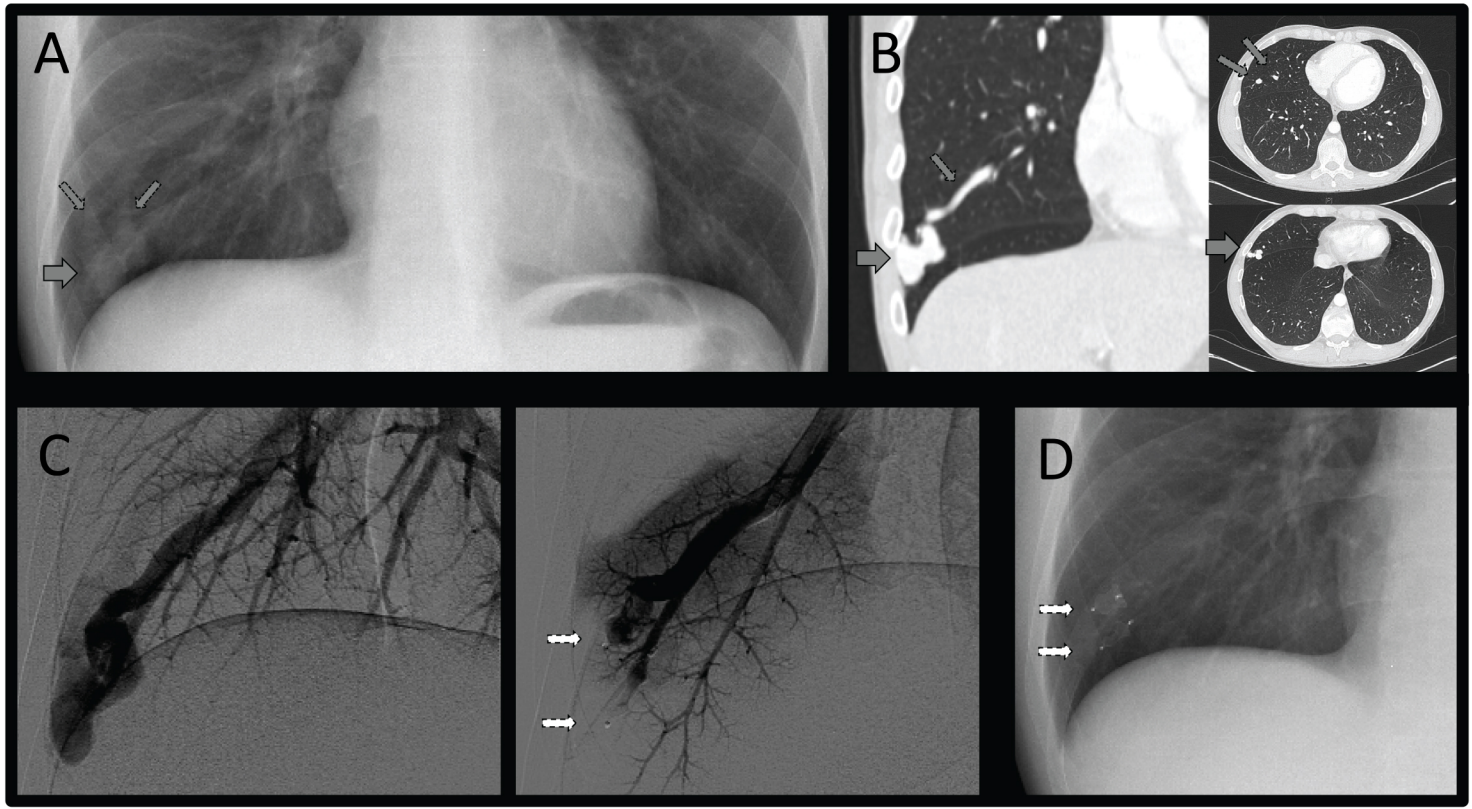
Figure 1:A) Chest x-ray indicating a PAVM (solid line arrow) and the subtle appearances of associated artery and vein (dashed line arrows) in a patient with resting SaO_2 94%. **B)** Thoracic CT scan images. **C)** Angiographic appearances pre (left) and post (right) embolization. Images courtesy of Dr James Jackson, were taken minutes apart. Note that preferential blood flow through the PAVM led to reduced perfusion of non-PAVM associated arteries, and dilatation/early filling of the draining vein. Following embolization (with two Amplatzer plugs (arrowed)), arterial blood flow to normal pulmonary arteries was restored. **D**) Chest radiographs of the same region 8 months post embolization, when the SaO_2 was 97%. Note regression of PAVMs sac, feeding artery and draining vein. The tips and bodies of the Amplatzer plugs are visible.

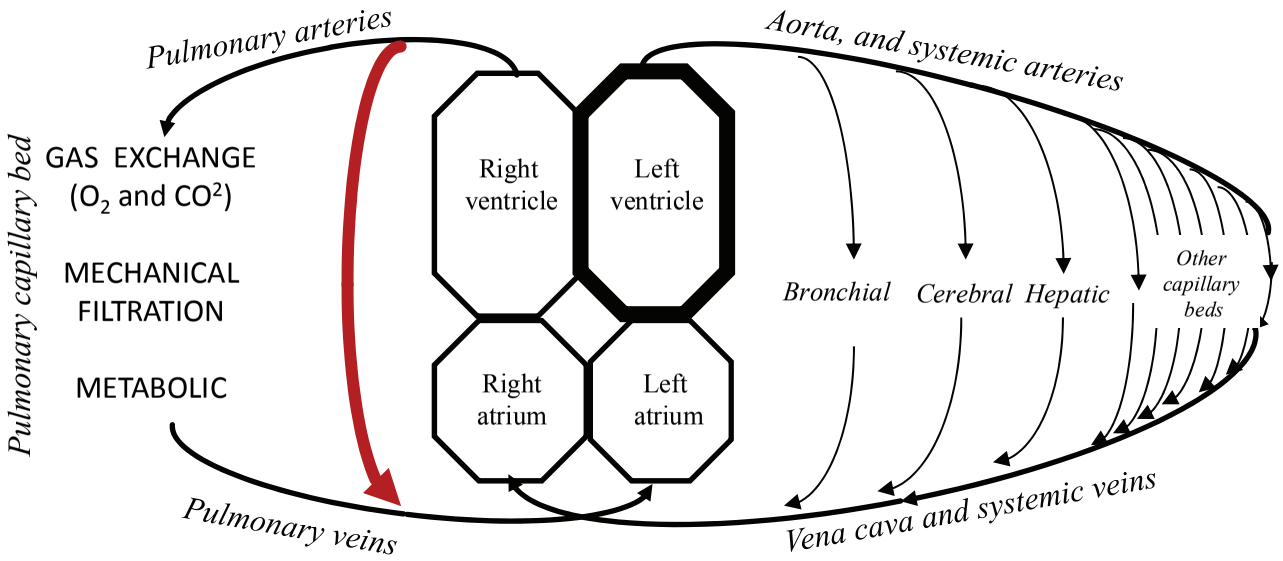
Figure 2: Cartoon indicating the major functions of the pulmonary capillary bed that are bypassed in the setting of PAVMs (red arrows) Adapted from reference[20] with author permission.

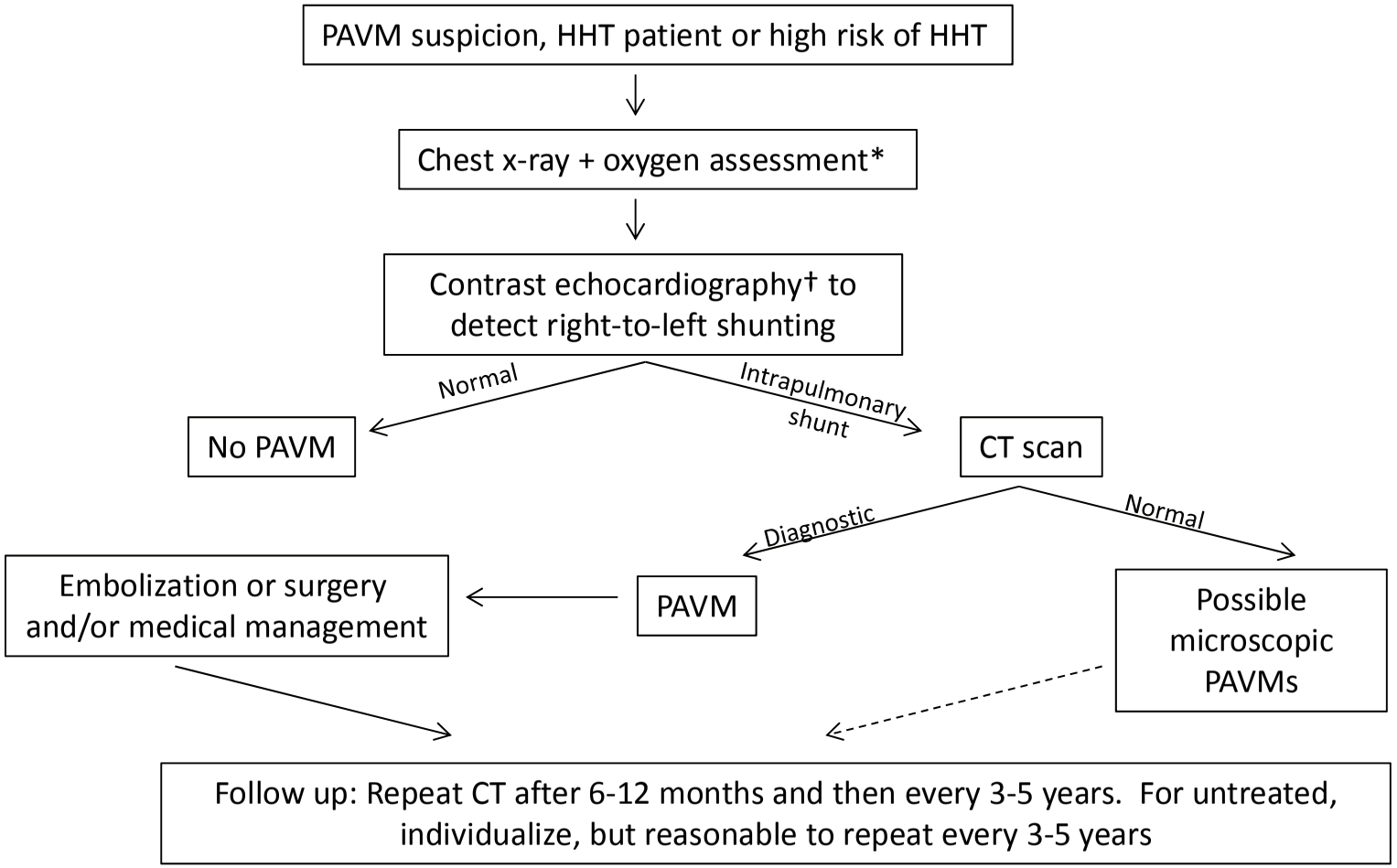
Figure 3 Typical 2013 flow chart: Adapted from reference 8: * indicated to be at rest and on exercise[8]; medical management to include use of supplemental oxygen when needed, prophylactic antibiotics (including for group with possible microscopic PAVMs) and avoidance of SCUBA diving. Dotted arrow: as indicated in international guidelines, reference 5.

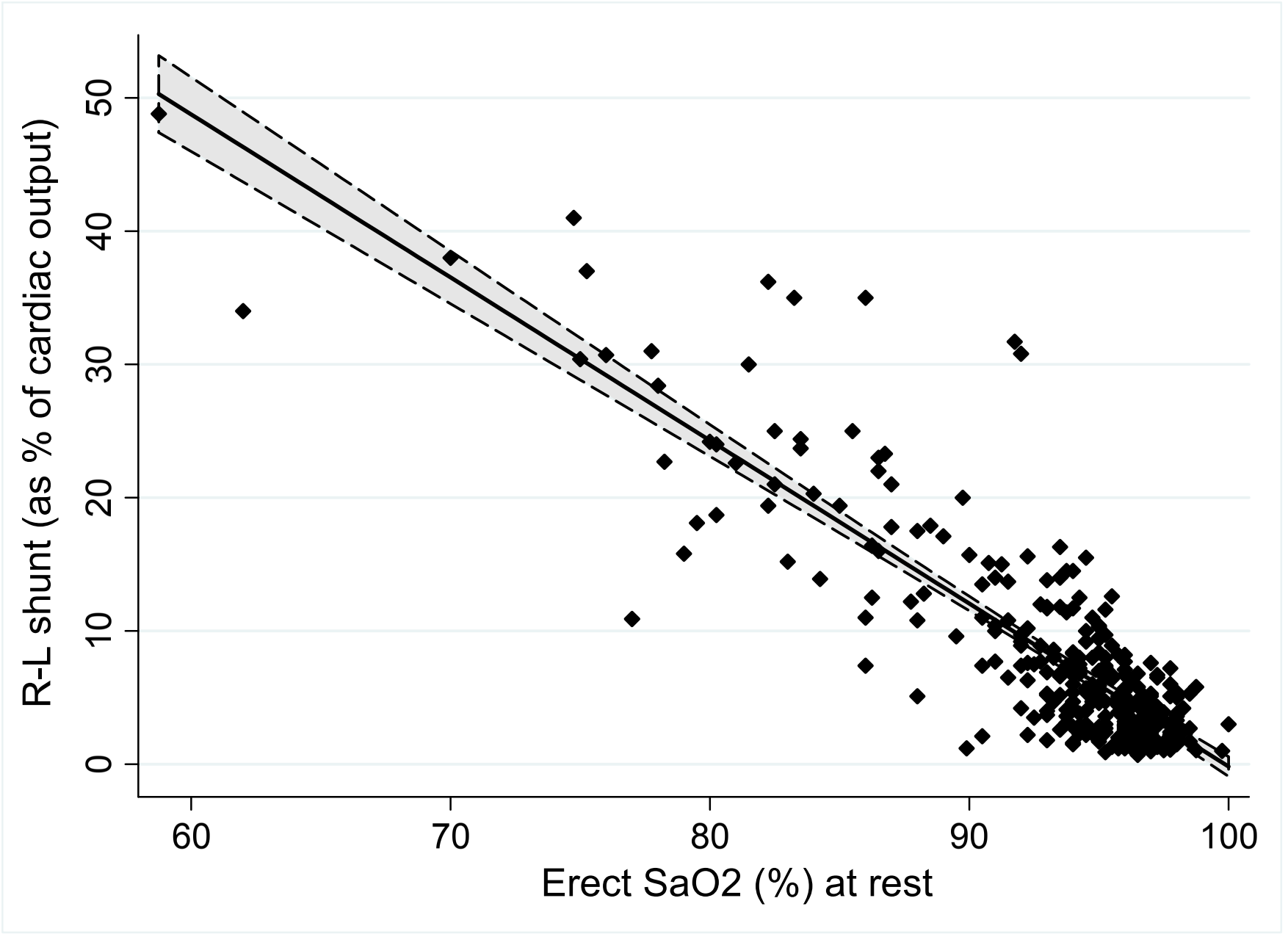
Figure 4: Inverse relationship between right-to-left shunt fraction and oxygen saturation. 309 paired same-day values of right-left shunt (quantified by nuclear medicine perfusion scans using Tc-labelled albumin macroaggregates), and the mean SaO_2 after 7, 8, 9 and 10 minutes standing. Data are from 198 individuals. Regression coefficient -1.22 (95% CI -1.31, -1.14; $p<0.0001$). Adapted from[20] with author permission. Note all would be predicted to have Grade 3 shunts by contrast echocardiography.

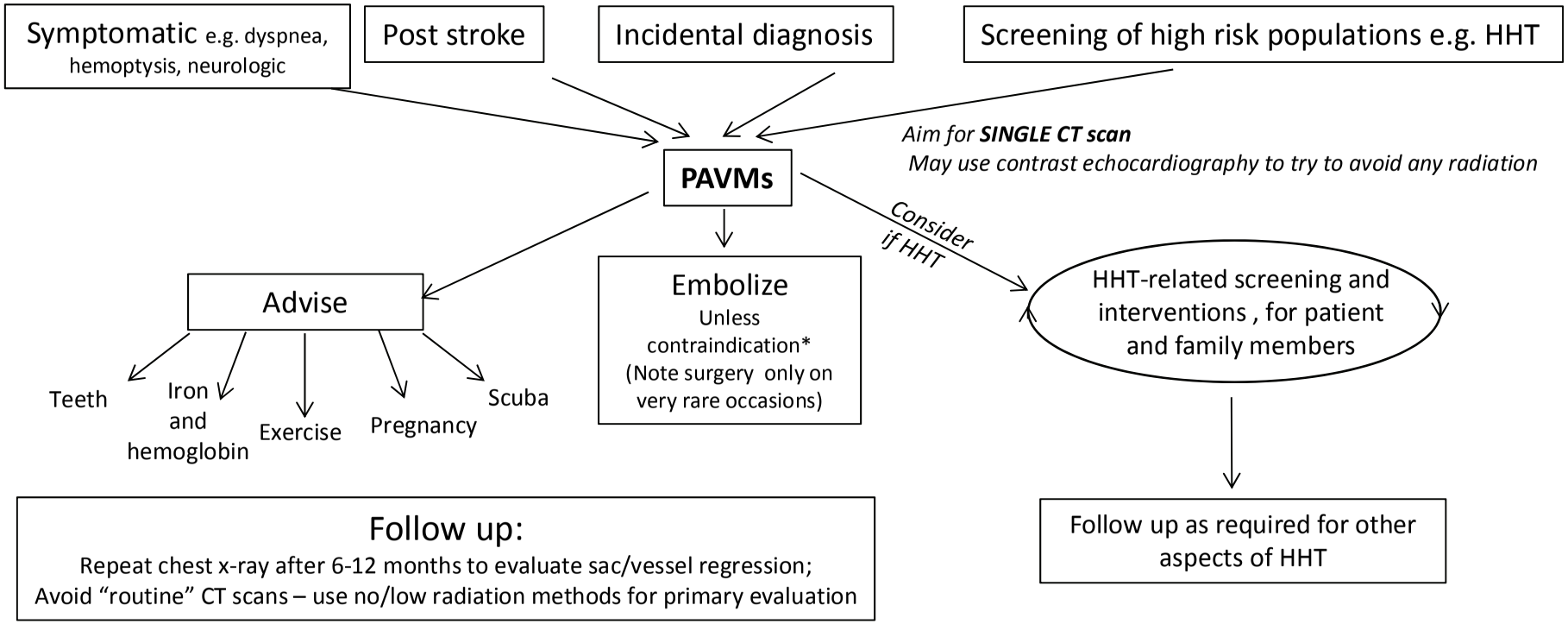
Figure 5: 2014 Proposed management flowchart: Irrespective of why PAVMs identified, all should be considered for embolization if technically feasible, and suitable expertise available. *Caution required if pre-existing severe pulmonary hypertension when risk benefit considerations change (increased risk of procedural related mortality; reduced benefit form prevention of paradoxical embolic strokes[90])


A
B
C
D


Pulmonary arteries
Aorta, and systemic arteries
Pulmonary capillary bed
GAS EXCHANGE
(O_2 and CO^2)
MECHANICAL
FILTRATION
METABOLIC
Right ventricle
Left ventricle
Right atrium
Left atrium
Bronchial
Cerebral
Hepatic
Other capillary beds
Pulmonary veins
Vena cava and systemic veins


PAVM suspicion, HHT patient or high risk of HHT
Chest x-ray + oxygen assessment*
Contrast echocardiography† to detect right-to-left shunting
Normal
Intrapulmonary shunt
No PAVM
CT scan
Diagnostic
Normal
Embolization or surgery and/or medical management
PAVM
Possible microscopic PAVMs
Follow up: Repeat CT after 6-12 months and then every 3-5 years. For untreated, individualize, but reasonable to repeat every 3-5 years


R-L shunt (as % of cardiac output)
0
10
20
30
40
50
60
70
80
90
100
Erect SaO2 (%) at rest


Symptomatic e.g. dyspnea, hemoptysis, neurologic
Post stroke
Incidental diagnosis
Screening of high risk populations e.g. HHT
Aim for SINGLE CT scan
May use contrast echocardiography to try to avoid any radiation
PAVMs
Consider if HHT
Advise
Teeth
Iron and hemoglobin
Exercise
Pregnancy
Scuba
Embolize
Unless contraindication*
(Note surgery only on very rare occasions)
HHT-related screening and interventions , for patient and family members
Follow up:
Repeat chest x-ray after 6-12 months to evaluate sac/vessel regression;
Avoid "routine" CT scans – use no/low radiation methods for primary evaluation
Follow up as required for other aspects of HHT