CASE REPORT

A 58-year-old woman with hypoxia, hypoxaemia, a hole in the heart and a ... herring! Intracardiac or extracardiac shunt? That is the question!

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SUMMARY

We describe a case of a previously healthy 58-year-old woman who presented with gradual onset shortness of breath on exertion, erythrocytosis, hypoxia and hypoxaemia. Initial investigations revealed a normal chest radiography and pulmonary function test, however, there was an isolated reduction in diffusion capacity. She was subsequently found to have a patent foramen ovale (PFO) with intermittent shunting. A contrast echocardiography study hinted towards an extracardiac shunt. No shunt was detected in spite of using advanced imaging techniques. A lung biopsy was ultimately performed and histopathology revealed diffuse microvascular pulmonary arteriovenous malformations. This is one of few cases reported of this rare vascular abnormality and highlights its strong genetic association with hereditary haemorrhagic telangiectasia. The diagnostic challenges and management of this unique condition are reviewed in detail.

BACKGROUND

Diffuse microvascular pulmonary arteriovenous malformation (DMVPAM) is a very rare vascular disease of the lungs. Paradoxically, it presents with the most common of symptoms—shortness of breath on exertion (SOBOE)—and its presence may be suggested by the classic triad of SOBOE, central cyanosis and clubbing.

It was first described in autopsy studies in 1897.¹ It is the result of pulmonary arteriovenous malformations (PAVMs) and has been variously labelled as pulmonary arteriovenous fistula, pulmonary arteriovenous aneurysm, haemangioma of the lungs, cavernous angioma of the lungs and pulmonary telangiectasia.²

These abnormal communications between pulmonary arteries and veins are mostly congenital in nature but they may also be found in a variety of acquired conditions. Extracardiac right-to-left shunting as a result of pathological communications between pulmonary arteries and pulmonary veins has been reported in chronic liver disease, mitral stenosis, trauma, Fanconi's syndrome and metastatic thyroid cancer.^{3–6} Extracardiac left-to-right shunting resulting from abnormal communications between bronchial and pulmonary arteries has been reported in chronic inflammatory conditions such as bronchiectasis.⁷

We present a challenging case of a patient presenting with hypoxia, hypoxaemia and a patent foramen ovale (PFO) with intermittent right-to-left

shunting, and detail the diagnostic work up leading to the rare diagnosis of DMVPAM. The limited literature on this disease will be reviewed and therapeutic modalities discussed including the potential role of lung transplantation.

CASE PRESENTATION

A previously healthy 58-year-old woman was referred to hospital after a 7-month history of progressive SOBOE. Four months prior to admission, she was investigated for fatigue and polycythaemia secondary to ongoing hypoxaemia. The patient was found to have an oxygen saturation of 82% at rest and 72% on mild exertion on room air. She reported becoming short of breath after walking half a mile or ascending 14 steps (modified Medical Research Council dyspnoea scale MMRC 1–2). The patient was previously active and well with no history of coronary artery disease, chronic lung disease, smoking or occupational respiratory exposures. She had no known congenital heart disease or underlying connective tissue disorders. Her family history was significant for pulmonary fibrosis (mother), sarcoidosis (sister) and pancreatic cancer (father).

Preliminary tests were undertaken to investigate the differential diagnoses of interstitial lung disease, pulmonary vascular disease and sleep disordered breathing. Pulmonary function tests (PFTs) revealed a significant isolated significant reduction in the diffusion capacity for carbon dioxide 7.5 mL/mm Hg/min (DLCO 37% of predicted). Spirometry and lung volumes were normal with no evidence of airflow obstruction or bronchodilator response. A polysomnogram did not show any indication of significant obstructive sleep apnoea or hypoventilation. Chest radiography and CT were largely unremarkable with no evidence of interstitial lung disease or thromboembolism.

Reduced exercise capacity and profound hypoxaemia necessitating supplemental oxygen lead to the patient's eventual hospitalisation. She denied any chest pain, cough, sputum production, syncope, paroxysmal nocturnal dyspnoea or orthopnoea. Her vitals were stable. Cardiovascular examination was unremarkable. The lungs were clear to auscultation but central and peripheral cyanosis and mild clubbing were evident. She exhibited no peripheral oedema or abnormalities in her skin and mucosa. Interestingly, only mild nocturnal hypoxaemia was noted requiring only 1 L/min of oxygen to keep oxygen saturation above 90%. Arterial

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blood gases revealed a partial pressure of arterial oxygen (PaO_2) of only 44 mm Hg and partial pressure of arterial carbon dioxide (PaCO_2) of 34 mm Hg with an increased alveolar arterial (A-a) gradient of 63.5 (normal for her age was 23) on room air. Her chest radiography and PFTs remained largely unchanged from studies performed months prior to admission. Blood tests were within normal range revealing normal iron profile and α -1 antitrypsin levels. Autoimmune panel was unremarkable.

INVESTIGATIONS

Echocardiography revealed normal left ventricular systolic function with estimated ejection fraction of 61% and pulmonary artery systolic pressure (PASP) of 43 mm Hg. There were no septal defects but a PFO was visualised across the interatrial septum and a potential right-to-left shunt at this level was considered (figure 1A, B/video 1).

A transoesophageal echocardiography contrast bubble study did not show any significant shunting across the PFO as <5 microbubbles crossed the septum from right to left. However, dense opacification of the left atrium and left ventricle after the third cardiac cycle was observed. Furthermore, microbubbles were clearly seen entering the left atrium from the pulmonary veins and causing dense opacification of the left ventricle (video 2). All pulmonary veins were found to be emptying into the left atrium. This ominous delay in the 'bubbling' of the left atrium and left ventricle was highly suggestive of an extracardiac shunt.

Figure 1 (A) Transoesophageal bubble contrast study showing opacification of the right atrium (RA). Contrast has not yet appeared in the left atrium (LA) and left ventricle (LV). See video 1. (B) Transoesophageal echocardiography showing delayed opacification of the LA and the LV after about 15 s. Arrowhead indicates patent foramen ovale with intermittent shunting. See video 1.

Video 1 Transoesophageal contrast echocardiography showing initial opacification of the right atrium followed by subsequent dense opacification of the left atrium after several cardiac cycles (approximately 15 s). Intermittent shunting across the patent foramen ovale is also observed.

CT angiography was unremarkable. Ventilation-perfusion scintigraphy (technetium-99 m macroaggregated albumin, Tc-99 m MAA) demonstrated no mismatch in the lungs. Furthermore, additional full body Tc-99 m MAA scintigraphy, to define the presence of an occult shunt, did not show any uptake in the kidneys or brain to suggest an intrapulmonary right-to-left shunt.

A diagnostic right and left heart catheterisation was subsequently performed, which included shunt haemodynamic studies. The most prominent finding was a markedly elevated systemic cardiac output of 9.9 L/min, suggestive of a significant right-to-left shunt. The other defining feature of this study was the ratio of pulmonary flow to systemic flow (Qp-Qs ratio), which was found to be 0.9–1.0, implying there was no significant shunting across the PFO. There was also no saturation gradient between the inferior vena cava, superior vena cava, right atrium and pulmonary artery. Coronary angiography showed normal coronary anatomy. Pulmonary angiography did not reveal any vascular malformations but there was delayed opacification of the left atrium after the third cardiac cycle (video 3). Attempts to cannulate the pulmonary veins for saturation studies were unsuccessful. Stress oximetry with supine bicycle exercise resulted in marked oxygen desaturation to 60% with development of severe pulmonary hypertension (mean pulmonary artery pressure 50 mm Hg) and this test was aborted. Shunt study using 100% oxygen inhalation method documented a shunt fraction of 39%.

Video 2 Transoesophageal contrast echocardiography visualising the contrast emerging from the superior pulmonary veins and filling the left atrium after three cardiac cycles, demonstrating the existence of an intrapulmonary shunt.

Video 3 Pulmonary angiogram showing delayed opacification of the left heart after the third cardiac cycle. No arteriovenous malformation is visualised.

A dedicated subsegmental pulmonary angiography study did not reveal any obvious vascular abnormalities.

DIFFERENTIAL DIAGNOSIS

The working diagnosis for our patient's hypoxaemia at this point included a number of extracardiac and intracardiac differentials. Extracardiac causes considered included chronic thromboembolic disease, airways disease, interstitial lung disease, sleep disordered breathing and pulmonary arterial hypertension, and right-to-left shunting arising from PAVMs, platypnoea-orthodeoxia syndrome (POS) and hepatopulmonary syndrome. Intracardiac causes considered included right-to-left shunts such as PFO, atrial septal defects and ventricular septal defects. Congenital heart disease and unroofed coronary sinus were also considered in the differential. Given the reduction in diffusion capacity on PFT, in the absence of any significant airflow obstruction or restriction, the differential diagnosis for her hypoxaemia narrowed to pulmonary arterial hypertension, intrapulmonary or extrapulmonary right-to-left shunt and POS.

Lung biopsy

The patient underwent an uncomplicated video-assisted thoracoscopic wedge biopsy of the left upper lobe. On gross external examination, the pleural surface, though smooth, was mottled in appearance. The tissue appeared healthy with no visible nodules, masses or telangiectasias. The cut surface showed tan pink and spongy parenchyma with small haemorrhagic foci.

Histopathology

Microscopic examination of the H&E stained sections showed lung parenchyma interspersed with large, abnormally dilated vascular structures lined by endothelial cells (figures 2 and 3). These large vessels were located close to the pleural surface, in proximity to the interlobular septa and also deep within the lung parenchyma. It is important to note that, in normal pulmonary anatomy, the size of the vessels and the accompanying airway structures (bronchioles) are of similar diameter. In our case, the distinction between the venous and arterial components of these abnormally large vessels was difficult, though the

Figure 2 Photomicrograph H&E, x4—large, abnormally dilated vessels (arrows), normal artery (arrowhead) and normal small bronchus (star).

smaller channels within the interlobular septa were considered to be veins (figure 4). The thin walled intervening vascular channels imbedded in the interlobular septa were hypothesised to represent the anastomotic channel between the dilated venule and the arteriole indicative of the arteriovenous malformation itself (figure 5). Additional consultation was sought with experts at the Vancouver General Hospital (Vancouver, British Columbia, Canada) and the Mayo Clinic (Scottsdale, Arizona, USA), and their conclusions were in agreement.

The diagnosis of DMVPAVM was confirmed.

TREATMENT

DMVPAVM is a very rare condition that represents an insignificant fraction of all cases with PAVMs. The natural history of cases without obvious radiographic abnormalities that can be targeted for intervention is not entirely clear from the reported literature. In our patient, the malformations remained microscopic in size thus, we believe, significantly reducing the likelihood of embolic complications, which is supported by the absence of scintigraphic evidence of disease. Thus, the outstanding question was, what therapeutic options were available to this patient? The most troubling feature at this point was dyspnoea and dramatic hypoxaemia with exertion. The patient had manifested elevated pulmonary artery pressures on presentation,

Figure 3 Photomicrograph elastin stain, x4—large, dilated vessel. Elastin layer, stained brown in the vessel wall.

Figure 4 Photomicrograph smooth muscle immunohistochemical stain, $\times 4$ —abnormal vessels in the fibrous septa (arrows).

which were likely a consequence of enduring hypoxaemic vasoconstriction. She developed moderate-to-severe pulmonary hypertension with a PASP of 67 mm Hg within a short span. From a physiological point of view, that likely exacerbated the shunting by creating preferential flow through the presumably lower resistance PAVMs, particularly during exercise. The long-term consequences of this can be postulated to result in further dilation of the vessels resulting in further shunting, and potentially resulting in development of macroscopic lesions more typically associated with embolic and bleeding complications associated with PAVMs. It was tempting to consider deliberate interventions to reduce the pulmonary artery pressures (phosphodiesterase 5 inhibitors, endothelin-receptor antagonists) to try and correct this phenomenon but no consensus could be reached by experts.

The patient was referred for PFO closure in an attempt to relieve her of disabling hypoxaemia and intermittent positional desaturation from POS, the prototype for PFO-driven hypoxia. The rationale for percutaneous device closure is supported by the work of Fenster *et al*,⁸ Devendra *et al*,⁹ and El Tahlawi *et al*,¹⁰ who reported significant symptomatic and functional status improvement in their respective cohorts with this therapy. The common denominator in their series was the absence of significant pulmonary hypertension in recipients of percutaneous

Figure 5 Photomicrograph Masson trichrome stain, $\times 4$ —thin vessel representing the anastomotic channel between the dilated venule and the arteriole (arrowheads) indicative of an arteriovenous malformation.

closure devices. Evidence of extracardiac intrapulmonary shunting was also absent in these patients. Our patient was deemed unsuitable for device closure because of marked intrapulmonary shunting as well as pulmonary hypertension in the severe range.

At first glance, one may consider lung transplantation to be the definitive therapy for a patient in this predicament. However, without a clear understanding of the natural history of this condition, decisions regarding indications and timing of transplantation become very challenging. The mean survival of lung transplantation, although improving with time, remains limited. It is worth noting that, in the series of Faughnan *et al*,¹¹ only three deaths occurred, one being of a patient who had undergone lung transplantation and died in the immediate post-transplant period, of multisystem organ failure, after requiring mechanical circulatory support. The average time of follow-up in these cases was 5.4 years. They caution against knee jerk reaction of referring these patients for lung transplantation with the assumption that prognosis is uniformly poor; 2-year survival rate in the medically treated group being better than after lung transplantation (91% vs 63%).¹¹ Reynaud-Gaubert *et al*¹² reported a case of lung transplantation in an adult patient with multiple diffuse PAVMs who had failed repeated, staged embolisation. Their report is limited to 8 months of stable follow-up post-transplant. When considered in the context of the single other case reported, its application to decision-making surrounding a case such as ours is very limited.

Our patient's predominant symptom remains SOB and at rest, with profound hypoxia requiring significant continuous oxygen therapy (17 L/min). We believe the degree of hypoxia and hypoxaemia to be a very accurate clinical marker of disease progression and that it 'enables us to determine the most appropriate timing'¹¹ for lung transplantation. Our patient is currently on an active lung transplantation waiting list.

OUTCOME AND FOLLOW-UP

While awaiting lung transplantation, the patient has become markedly hypoxic at rest and is on high dose continuous oxygen therapy to maintain optimal saturation.

DISCUSSION

The incidence of PAVM is 2–3/100 000 population.¹ The male-to-female ratio ranges from 1:1.5 to 1:1.8, as noted in several series.^{2–4} The majority of cases present in the first three decades, although the age at presentation ranges from the newborn to the elderly.^{4 13 14} PAVMs are caused by abnormal communications between the pulmonary arteries and veins, and are often congenital in nature. The majority, approximately 70%, of PAVMs are associated with hereditary haemorrhagic telangiectasia (HHT).¹⁵

PAVMs may present as single or multiple entities. The incidence of single PAVMs ranges from 42% to 72%.^{13 14 16 17} It has been reported that 53–70% of PAVMs are found in the lower lobes,^{2 13 16 18 19} but their distribution is also dependent on whether they are idiopathic in nature or associated with congenital or acquired conditions.²⁰ In a review of the pathological anatomy of 350 patients with PAVMs, 75% of patients had unilateral disease, 36% had multiple lesions and 50% of those with multiple lesions had bilateral disease.¹⁶ In the same series, PAVMs involved the pleura in 81% and were completely subpleural in 19% of cases.

PAVMs range from 1 to 5 cm in size, occasionally they may exceed 10 cm. PAVMs may be microscopic in size and are then referred to as telangiectases. DMVPAVMs are present in 7–11%

of patients, and may also occur in conjunction with macrovascular, radiologically visible PAVM.¹⁴ The literature reports one case with several hundred plexiform lesions 1–10 mm in diameter that were PAVM of either simple or complex morphology. Up to 90% of PAVMs are of the simple type, characterised by a single feeding segmental artery and a single draining vein.^{21 22} The rest are complex, with two or more feeding arteries or draining veins.²¹ The smaller telangiectases are most commonly of the complex type.²³ They are supplied by pulmonary arteries in about 95% of cases, and by systemic arteries less frequently.¹³ Dual arterial supply has also been reported.²⁴ Drainage is usually to the left atrium, but anomalous drainage to the inferior vena cava or innominate veins has been described in the literature.^{2 25} More colourful (Medusa's head) descriptions of DMVPAVM, spread over both lung surfaces, have also been reported.¹⁶

Contrast echocardiography has added an extra dimension to the non-invasive work-up of shunts, whether intracardiac or extracardiac.²⁶ It involves the injection of agitated saline or dye into a peripheral vein, and observing the appearance and behaviour of these microbubbles as they enter the cardiac chambers. In patients without any shunts, the microbubbles (approximately 10–15 µm in size) will appear rapidly in the right atrium and then gradually dissipate as they become exposed to the anatomic confines of the pulmonary microcirculation.²⁷ They will not appear in the left atrium. In patients with intracardiac shunts, three or more microbubbles should appear in the left atrium within three cardiac cycles of right atrial opacification. This suggests shunting at the level of the atria. Approximate shunt quantification is also possible with a small shunt, defined as the passage of 3–10 bubbles, a medium shunt 10–20 bubbles and a large shunt is suggested by more than 20 bubbles.²⁸ In the presence of extracardiac shunts (ie, PAVMs), the microbubbles will bypass the pulmonary circulation through vascular malformations and reappear in the left atrium typically after several cardiac cycles.

It is quite fortuitous and interesting that our patient presented with both an intracardiac shunt and an extracardiac shunt. The challenge was to establish which was the culprit. Contrast echocardiography answered this vexing but pivotal question beautifully by demonstrating only intermittent right to left shunting across the PFO. The crucial diagnostic finding was that the cardiac output was high (9.9 L/min) in the setting of a normal Qp/Qs, suggesting that very significant shunting was occurring beyond the cardiac chambers.

The technetium-99 m albumin microsphere technique involves the injection of 110 MBq of technetium-99 m spheres via an antecubital vein. In patients without an intrapulmonary shunt, over 90% of technetium 99 m albumin macroaggregated particles (approximately 40 µm) become trapped in the arterioles and capillaries of the lungs (approximately 1–5 µm). Anatomic shunts with dilated pulmonary vessels, however, will allow passage of these particles through the lungs onward to other organs. With whole body imaging, documentation of uptake in the kidneys or brain would suggest an intrapulmonary right-left shunt. This study turned out to be negative in our patient because DMVPAVMs are smaller in diameter (approximately 10 µm) than the radiotracer.

The finding of profound hypoxaemia (PaO₂ of 44 mm Hg) in the setting of a markedly raised A-a gradient without any evidence of V/Q mismatch is highly suggestive of the presence of a shunt. The PaO₂/FiO₂ ratio of 209 was also indicative of a shunt with a grossly estimated shunt ratio of <20%. Furthermore, the marked isolated reduction in the DLCO

supports significant right-to-left shunting and is likely explained by the diffuse nature of the PAVMs. The diagnosis of a right-to-left shunt can also be made by performing a 100% oxygen test. In normal lungs, <5% of cardiac output is shunted through the thebesian system of veins. The shunt fraction is calculated as: % cardiac output = (ideal PaO₂ – actual PaO₂) / 2.66; whereby the ideal PaO₂ is calculated using the following formula: (P_{bar} – 6.27 × FiO₂) – PaCO₂. P_{bar} and FiO₂ represent atmospheric pressure and actual fraction of inspired air, respectively. The patient then breathes 100% oxygen from a Douglas bag for a minimum of 20 min followed by an arterial blood gas sample measuring PaO₂ and SaO₂ values, where SaO₂ represents the measured saturation of arterial oxygen.²⁹ It is the initial recommended method of screening for PAVMs, as it is inexpensive, performed easily and is fairly accurate.¹⁵

Our patient experienced marked oxygen desaturation with supine bicycle exercise during stress oximetry. Exercise-induced or enhanced intrapulmonary arteriovenous shunt (IPAVS) has been described in healthy individuals as well as in pathological conditions with high cardiac output such as severe anaemia, thyrotoxicosis and beriberi heart failure.³⁰ It is postulated that shunts might act as 'release valves' in response to increases in flow and pulmonary vascular resistance and function, to protect the pulmonary vasculature and right heart through the dynamic and adaptive mechanism of inducible IPAVS.³⁰ The profound desaturation observed in our patient could be secondary to this mechanism, which may contribute to the reduction in the efficiency of pulmonary gas exchange that occurs during exercise. Interestingly, exercise-induced IPAVS may also facilitate a pathway for emboli to bypass the rigorous filtering capacity of the pulmonary microcirculation and cause target-organ damage.³⁰

The most common symptoms of PAVMs are epistaxis and dyspnoea with POS.

Persistent right-to-left shunting across the PAVMs, if left untreated, may lead to chronic hypoxaemia, causing high-output heart failure and secondary pulmonary hypertension. Bleeding causing spontaneous haemothorax has also been reported during pregnancy. Given the haemodynamically high output state induced by pregnancy, it is surprising that our patient underwent three successful pregnancies without complications. Spontaneous pulmonary haemorrhage has also been reported.

Khurshid and Downie²⁴ have suggested that PAVMs do not affect cardiovascular haemodynamics. We believe they do, as our patient had a cardiac output of 9.9 L/min, indicating significant right-to-left shunting adversely impacting haemodynamics. If left untreated, high-output heart failure may follow. Moreover, our patient's presentation with mild pulmonary hypertension (PASP 43 mm Hg) leading to pulmonary pressures in the severe range (PASP 67 mm Hg) over a short span of 7 months from symptom onset is unusual and contradicts the reported findings of mostly normal pulmonary pressures in all cohorts; until complications ensue.

By bypassing the rigorous filtering capacity of the pulmonary microcirculation, PAVMs provide a fertile seeding ground for cerebral abscesses through paradoxical embolism. In fact, ischaemic strokes are a major complication of PAVMs. In their retrospective series, Faughnan *et al*³¹ reported an overall incidence of stroke of 30%, brain abscess 10% and pleural or pulmonary haemorrhage of 10% in these patients.²⁴ Neurological complications including stroke, transient ischaemic attacks and cerebral abscesses dominate the clinical picture, and the high prevalence of brain abscess (38%) in this specific subgroup compared to the relatively low prevalence (9%) in the group with discrete PAVM

suggests a mechanism other than paradoxical embolism. The authors suggest that abscess formation may result from bacterial seeding into foci of encephalomalacia caused by microemboli, hypoxia, or sludging with polycythaemia. Our patient did not have a history of stroke or thromboembolism and subsequent neurological imaging was unremarkable.

PAVMs, HHT and POS share an umbilical link and it has been reported that PAVMs occur in up to 50% of patients with HHT.^{11 32} Conversely, up to 70% of all patients with PAVMs have associated HHT. PAVMs have also been reported in patients with polysplenia syndrome.³³

The diagnosis of HHT in patients with PAVM is of prognostic importance because they tend to have worse symptoms due to multiple arteriovenous malformations presenting with rapid disease progression and higher rates of complications.²⁴ POS has also been reported in patients with PAVMs and is the result of positional changes in the flow of blood through the PAVM.³² It is more common in symptomatic patients. Our patient did not have POS on first presentation, but she exhibited significant oxygen desaturation on assuming the upright posture, observed several months after histological diagnosis of her disease and as her symptoms continued to worsen.

CONCLUSION

DMVPAVM is a very rare disease and a diagnostic brain teaser. It remains an elusive diagnosis. It may lurk in the shadow of a PFO and beguile the unwary clinician, ultimately surrendering to histopathology, the gold standard of many a challenging diagnosis.

The unique triad of SOBOE, central cyanosis and clubbing should raise the possibility of this ominous diagnosis. There is an umbilical link between PAVM and HHT that needs further probing, because genetic counselling of patients and first-degree relatives form an important aspect of primary prevention of this disease.

Learning points

- ▶ Diffuse microvascular pulmonary arteriovenous malformation (DMVPAVM) is a very rare clinical entity, classically presenting with the triad of shortness of breath on exertion, and clubbing and central cyanosis, indicative of a right-to-left shunt. Definitive diagnosis rests with histopathology.
- ▶ The bystander patent foramen ovale in this patient was a red herring, and percutaneous closure of the same after the development of severe pulmonary hypertension was unwarranted and potentially harmful.
- ▶ The value of bubble study during contrast echocardiography in diagnosing this rare disease cannot be overemphasised, as it can provide the vital clue to an extracardiac shunt. The small size of microbubbles make them ideal agents to navigate these DMVPAVMs and unmask their presence.
- ▶ Only double-lung transplantation is potentially curative of this rare but disabling disease; there is no effective medical treatment except for bail out oxygen therapy and supportive management of its potentially life-threatening complications.
- ▶ Our case underlines the important message that sophisticated imaging modalities do not diagnose difficult patients; rational clinical thinking, if not thinking outside the box (rather outside the heart!), does.

Non-invasive methodologies, namely, CT, MRI and nuclear imaging techniques, fail to image and define this 'microcosmic' entity, and may expose the patient to unnecessary radiation and potential complications thereof.

Invasive diagnostic strategies with right and left heart catheterisation and pulmonary angiography, while recommended, equally fail to image this vexing vascular anomaly, though cardiac catheterisation with shunt haemodynamics provides the important clue that the shunt is extracardiac. Only double-lung transplantation, a formidable undertaking, holds promise of a cure for this disease entity and may be pursued after diagnosis is confirmed by histopathology.

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REFERENCES

- 1 Churton T. Multiple aneurysms of the pulmonary artery. *Br Med J* 1897;1:1223–5.
- 2 Sloan RD, Cooley RN. Congenital pulmonary arteriovenous aneurysm. *Am J Roentgenol* 1953;70:183–210.
- 3 Lange PA, Stoller JK. The hepatopulmonary syndrome. *Ann Intern Med* 1995;122:521–9.
- 4 Prager RL, Laws KH, Bender HW Jr. Arteriovenous fistula of the lung. *Ann Thorac Surg* 1983;36:231–9.
- 5 Taxman RM, Halloran MJ, Parker BM. Multiple pulmonary arteriovenous malformations in association with Fanconi's syndrome. *Chest* 1973;64:118–20.
- 6 Pierce JA, Reagan WP, Kimball RW. Unusual cases of pulmonary arteriovenous fistulas with a note on thyroid carcinoma as a cause. *N Engl J Med* 1959;260:901–7.
- 7 Liebow AA, Hales MR, Lindskog GE. Enlargement of the bronchial arteries and their anastomoses with the pulmonary arteries in bronchiectasis. *Am J Pathol* 1949;25:211–31.
- 8 Fenster B, Nguyen B, Buckner J, et al. Effectiveness of percutaneous closure of Patent Foramen Ovale for hypoxemia. *Am J Cardiol* 2013;112:1258–62.
- 9 Devendra G, Rane A, Krasuki R. Provoked exercise desaturation in Patent Foramen Ovale and impact of percutaneous closure. *J Am Coll Cardiol Interv* 2012;5:416–19.
- 10 El Tahlawi M, Jop B, Bonello B, et al. Arteriovenous fistula of the lung. *Ann Thorac Surg* 2009;102:755–9.
- 11 Faughnan ME, Lui YW, Wirth JA, et al. Diffuse pulmonary arteriovenous malformations: characteristics and prognosis. *Chest* 2000;117:31–8.
- 12 Reynaud-Gaubert M, Thomas P, Gaubert JY, et al. Pulmonary arteriovenous malformations: lung transplantation as a therapeutic option. *Eur Respir J* 1999;14:1425–8.
- 13 Dines DE, Arms RA, Bernatz PE, et al. Pulmonary arteriovenous fistulas. *Mayo Clin Proc* 1974;49:460–5.
- 14 Dines DE, Seward JB, Bernatz PE. Pulmonary arteriovenous fistula. *Mayo Clin Proc* 1983;58:176–81.
- 15 Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med* 1998;158:643–61.
- 16 Bosher LH Jr, Blake DA, Byrd BR. An analysis of the pathologic anatomy of pulmonary arteriovenous aneurysms with particular reference to the applicability of local excision. *Surgery* 1959;45:91–104.
- 17 Schumaker HB, Waldhausen JA. Pulmonary arteriovenous fistulas in children. *Ann Surg* 1963;158:713–20.
- 18 Yater WM, Finnegan J, Griffin HM. Pulmonary arteriovenous fistula (Varix): review of the literature and report of 2 cases. *J Am Med Assoc* 1949;141:581–9.
- 19 Gossage JR. Role of contrast echocardiography in screening for pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. *Chest* 2010;138:769–71.
- 20 Wong HH, Chan RP, Klatt R, et al. Idiopathic pulmonary arteriovenous malformations: clinical and imaging characteristics. *Eur Respir J* 2011;38:368–75.

- 21 White RI, Mitchell SE, Barth KH, *et al.* Angioarchitecture of pulmonary arteriovenous malformations: an important consideration before embolotherapy. *Am J Roentgenol* 1983;140:681–6.
- 22 White RI Jr, Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. *J Vas Interv Radiol* 1996;7:787–804.
- 23 Hales MR. Multiple small arteriovenous fistulae of the lungs. *Am J Pathol* 1956;32:927–43.
- 24 Khurshid I, Downie GH. Pulmonary arteriovenous malformation. *Postgrad Med J* 2002;78:191–7.
- 25 Anabtawi IN, Ellison RG, Ellison LT. Pulmonary arteriovenous aneurysms and fistulas: anatomical variations, embryology, and classification. *Ann Thorac Surg* 1965;1:277–85.
- 26 Shub C, Tajik AJ, Seward JB, *et al.* Detecting intrapulmonary right-to-left shunt with contrast echocardiography. Observations in a patient with diffuse pulmonary arteriovenous fistulas. *Mayo Clin Proc* 1976;51:81–4.
- 27 Faughnan ME, Palda VA, Garcia-Tsao G, *et al.*, HHT Foundation International—Guidelines Working Group. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet* 2011;48:73–87.
- 28 Stewart MJ. Contrast echocardiography. *Heart* 2003;89:342–8.
- 29 Rodríguez-Roisin R, Krowka J. Hepatopulmonary syndrome—a liver induced lung vascular disorder. *N Engl J Med* 2008;358:2378–87.
- 30 Nakano S, Sujino Y, Tanno J, *et al.* Inducible Intrapulmonary Arteriovenous Shunt in a patient with BeriBeri Heart. *Am J Respir Crit Care Med* 2012;186:332–3.
- 31 Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. *Eur Respir J* 2009;33:1186–94.
- 32 Kumar N, Kraemer RR, Murthy RK, *et al.* Platypnea-orthodeoxia syndrome as a presentation of hereditary hemorrhagic telangiectasia. *Circulation* 2012;126:2645–7.
- 33 Kapur S, Rome J, Chandra RS. Diffuse pulmonary arteriovenous malformation in a child with polysplenia syndrome. *Pediatr Pathol Lab Med* 1995;15:463–8.

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