

# Intrapulmonary shunts: coils to transplantation



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Intrapulmonary shunts are dilated vascular channels interposed between normal pulmonary arteries and pulmonary veins. These channels replace the normal microvascular network and are inefficient gas exchangers and poor at trapping and removing microthrombi. In practice, there are three main causes:

- hereditary haemorrhagic telangiectasia (75%);
- idiopathic pulmonary arteriovenous malformations (15%); and
- hepatopulmonary syndrome (10%).

## Hereditary haemorrhagic telangiectasia

The association between repeated epistaxes and small mucocutaneous 'angiomas' was reported first by Rendu in the *Gazette des Hôpitaux de Paris* [1]. William Osler drew attention to the hereditary nature of the condition [2], describing two families from his own practice and six others from the medical literature (including the mother and two sons described by Rendu). Parkes Weber also described the hereditary haemorrhagic telangiectasia (HHT) triad in a paper in the *Lancet* [3], the patient (a woman aged 60 years with four out of nine children affected) being shown at the inaugural meeting of the Association of Physicians. The condition was known for years as the Osler-Weber-Rendu (OWR) syndrome, but it is of interest that Osler [2] refers to two descriptions earlier than Rendu's—Legg in 1876 (who considered the diagnosis to be haemophilia) and Chiara in 1887. The more descriptive phrase, hereditary haemorrhagic telangiectasia, is now preferred.

## Diagnosis

HHT is recognised from a history of repeated epistaxes since childhood and a similar history in one or other parent, siblings or children (HHT being an autosomal dominant disorder). Virtually every case has these two features. In 103 three-generation families from the Haut-Jura region [4], an apparently 'skipped generation' was seen in three instances, giving a penetrance of 97%. This means that the diagno-

sis of HHT cannot be completely excluded, even in adult life. Epistaxes were reported in 96% of the 324 cases registered as HHT, occurring before the age of 25 years in 75% [4]. Similar results have been reported for the Hammersmith series by Shovlin *et al* [5]. In 91 affected individuals, clinical symptoms were evident by the age of 12 years in 75%, and by 35 years in 97%. Both studies show that the penetrance of HHT is age related.

To establish a definite diagnosis, telangiectasia should also be present, either on the skin and mucous membranes (75% of subjects affected) or involving the gastrointestinal (25%), pulmonary (15%) [6] or cerebral (4%) circulation. There is some evidence for family clustering in the frequency of visceral involvement [6–8]. Because of our interest at Hammersmith in pulmonary arteriovenous malformations (PAVMs), we have seen many families where the incidence of PAVMs in HHT affected members was greater than 15% (Fig 1). In one large family, Sluiter-Eringa *et al* [7] reported PAVMs in 18/73 (25%) of individuals with HHT.

Mucocutaneous telangiectasia becomes obvious only in the third and fourth decades of life, and the lesions are tiny and sparse in younger subjects. A careful search with a bright light of lower lip, tongue, buccal mucous membrane, palate, face and pulps of the fingers will usually reveal the small reddish-purple blemishes of HHT. Epistaxes usually start in childhood (pre-puberty), but HHT cannot be excluded on clinical grounds until children are 13–16 years old.

## Genetics of HHT

Striking progress has been made in 1993 towards finding the cause of HHT. Two Anglo-American groups have established genetic linkage on the long arm of chromosome 9 [5,9]. Work is now proceeding with candidate genes. The ultrastructural defect is unknown, but in a condition characterised by microvascular dilatation of capillaries and venules, a defect of structural proteins such as collagen seems not unlikely.

## Trigger factors

Although HHT is a genetic disorder, its phenotypic expression is influenced by female sex hormones. The epistaxes worsen in low oestrogen states such as men-

struation and the menopause, and improve during pregnancy (as do the spider naevi of cirrhosis). Oestrogen and progestogen therapy improves the epistaxes and the gastrointestinal bleeding in HHT. In the absence of pulmonary telangiectasia, the spontaneous abortion rate was normal and pregnancies uncomplicated, but in the presence of pulmonary shunts, there were eight serious complications in 15 pregnancies: three cerebrovascular accidents, two fatal pulmonary haemorrhages and an increase in the pulmonary shunt in three cases (CL Shoulin, personal communication).

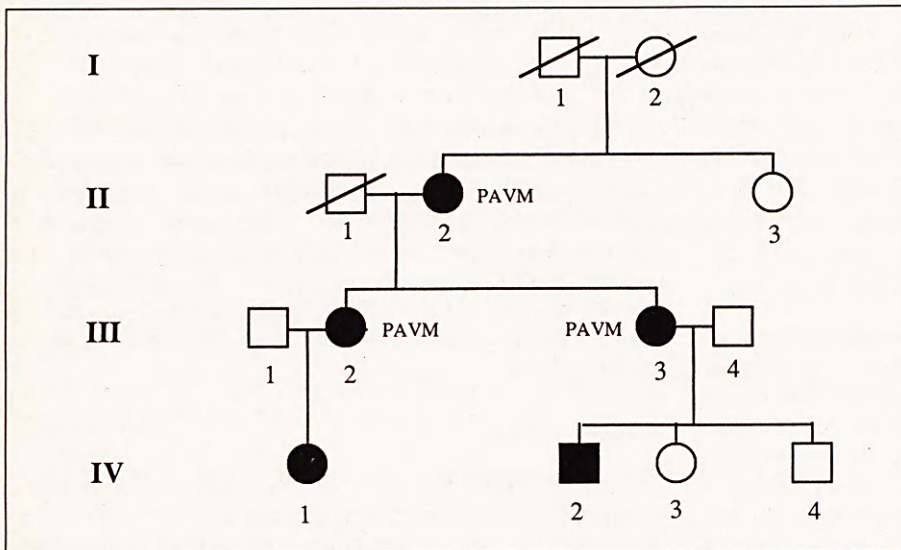
*HHT and PAVMs*

In the Hammersmith series of HHT with PAVMs ( $n = 46$ ), the average age was 43.4 years (range 9–78). In more than half the patients, PAVMs were recognised between the ages of 20 and 50 years, with 28% at over 50 years and 19% under 20 years. There is an interesting and unexplained female sex preponderance (F:M ratio 1.6:1), which has also been found in two other series (reviewed in [10]). For HHT itself, there is no gender bias: in the 324 cases of HHT reported by Plauchu *et al* [4], the F:M ratio was 1.04:1.

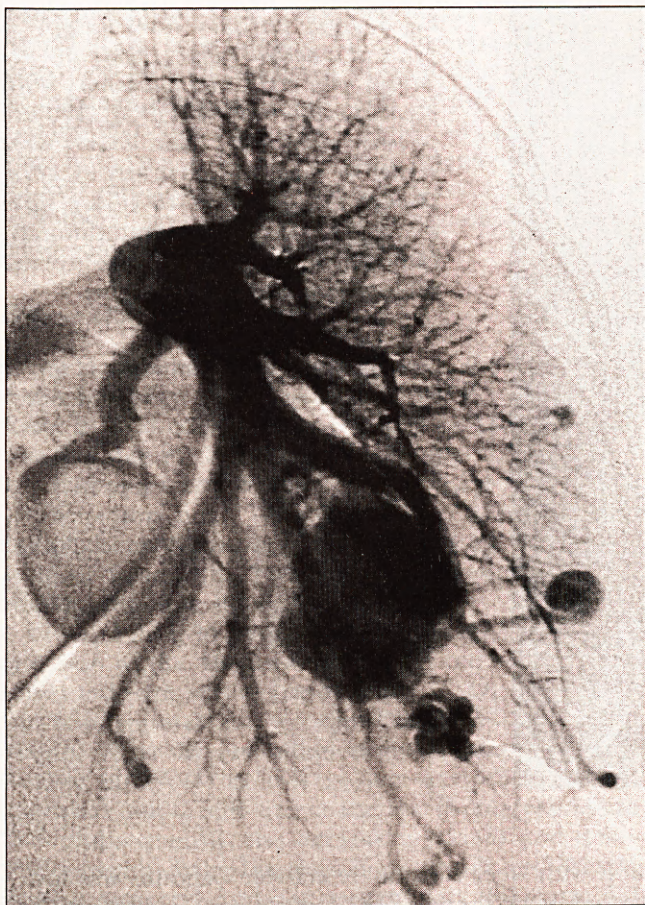
In an analysis of 26 patients with HHT and PAVMs [11], 11 (42%) presented with respiratory symptoms, with exertional dyspnoea or cyanosis (noted by the patient or relatives). Four were asymptomatic despite arterial oxygen saturations ( $\text{SaO}_2$ ) averaging 89%. They were brought to medical attention only as a result of an abnormal chest radiograph. Most importantly, nine cases (35%) presented with neurological complications due to paradoxical embolism. In another series of 27 patients with PAVMs [7], 24 (89%) had not consulted their doctor for symptoms attributable to PAVMs, including neurological symptoms. Eleven (41%) were picked up on mass miniature x-ray sur-

veys. On questioning, 40% admitted to exertional dyspnoea and 67% to central nervous system (CNS) symptoms, presumably related to paradoxical embolism rather than to cerebral AVMs. Clubbing of fingers occurred in 54% and a pulmonary bruit in 67% [7]. Haemoptysis is a relatively uncommon symptom in PAVMs, with a frequency of 13% in two series [7,12]. Polycythaemia ( $\text{Hb} > 16 \text{ g/dl}$ ) was present in 45%, but iron deficiency anaemia ( $\text{Hb}, 12.5 \text{ gdl}$ ) was seen in 20% of 46 patients. Exercise tolerance may be remarkably well preserved [13] in spite of deep cyanosis which gets deeper on exertion. Functional compensations for hypoxaemia include polycythaemia and a high cardiac output at rest and on exercise [14]. It is interesting that the cardiac output exceeds normal by an amount equal to the flow through the PAVMs [14], helped by the *low* pulmonary vascular resistance.

The telangiectactic lesions in the pulmonary circulation are much larger than the pin-head sized mucocutaneous lesions. On a pulmonary angiogram, large and small sacs (5–50mm diameter) are seen replacing the normal microvascular bed, with enlarged feeding arteries and draining veins (Fig 2). The vascular resistance through PAVMs is lower than in surrounding normal lung, so there is a steal effect. The enlargement of the artery and vein is 'physiological' (due to high flow). The term 'arteriovenous malformation' refers to an abnormal communication between arteries and veins through loss of the intervening capillary bed and not necessarily to any structural abnormality of these larger channels. An interesting feature is that 95% of PAVMs are caudally (basally) placed in the lungs, probably linked to the higher vascular pressures there, especially when sitting or standing. High microvascular pressures cannot be the only explanation, however, because telangiectases are much less common on the feet than on the hands.



**Fig 1.** Family tree in hereditary haemorrhagic telangiectasia showing 'clustering' with respect to pulmonary arteriovenous malformations (PAVMs). IV1 and IV2 are less than 14 years old and PAVMs cannot be excluded yet; II2 is featured in Table 2.



**Fig 2.** Digital subtraction pulmonary angiogram of left lung (arterial phase) showing one very large sac and multiple small sacs, corresponding to arteriovenous malformations. A second large sac (poorly outlined) is visible on the left side. Later, both large sacs and the two bigger of the smaller sacs were embolised with a total of 27 coils. (Courtesy of Dr JE Jackson, Department of Radiology, Hammersmith Hospital.)

#### Paradoxical embolism

The seriousness of PAVMs lies not so much in the hypoxaemia (except in the severest cases) but in the frequency of paradoxical embolisation (Table 1). In the Hammersmith series of 46 patients with HHT and PAVMs, the neurological complication rate was 40%. In the largest North American series [12], ischaemic lesions were present in 21 (36%) of 59 patients who had computerised tomography (CT) brain scans. The neurological complication rate was 64%, and the incidence of cerebral abscess 9% (less than our 20%). The organisms found in cerebral abscesses are usually anaerobes or actinomyces species. This suggests an origin in the mouth and the importance of antibiotic prophylaxis for all dental work should be stressed. In a survey of the neurological literature [15], 61% of CNS

**Table 1.** Neurological complications of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia caused by paradoxical embolism.

Neurological complication	No. cases	%
<b>Hammersmith series (n = 46)</b>		
Cerebral abscess	9	20
Cerebrovascular accident	3	7
Transient ischaemic attack	6	13
<i>Total</i>		<i>40</i>
<b>Baltimore series (12) (n = 76)</b>		
Cerebral abscess	7	9
Cerebrovascular accident	14	18
Transient ischaemic attack	28	37
<i>Total</i>		<i>64</i>

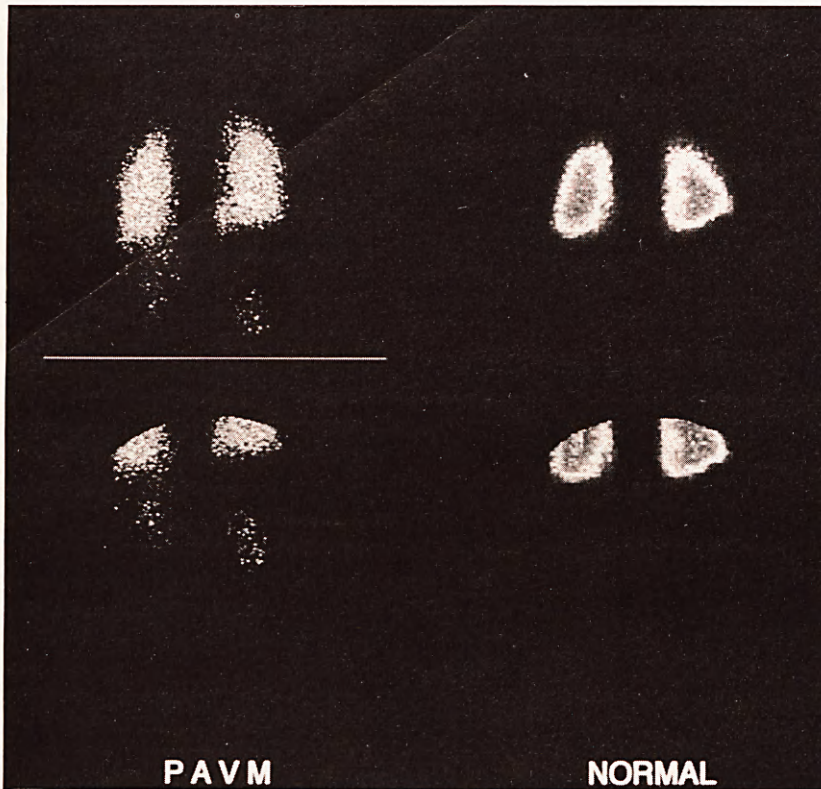
lesions in HHT were secondary to paradoxical embolism from PAVMs, and 36% were attributable to AVMs of the brain or spinal cord.

#### Measurement of the right-to-left shunt

Quantification of the intrapulmonary shunt is important in gauging the success of treatment and in detecting re-emergence of shunts during long term follow-up. In the classical measurement of an anatomic shunt [16] the subject breathes 100% oxygen through a mouthpiece with a noseclip for 15 minutes; arterial blood is then sampled for PaO<sub>2</sub> (Hb must also be measured). This method is quite demanding for the patient and requires good technique. The principle of the lung perfusion scan for the diagnosis of pulmonary embolism is that macroaggregated human albumin particles (20–60 µm diameter tagged with radioactivity (<sup>99m</sup>Tc-MAA)) after intravenous injection impact in the pulmonary arteries wherever there is blood flow. In the presence of an anatomic shunt (in the heart or lungs), a fraction of the particles (proportional to the shunt flow) will escape into the systemic circulation where they can be detected by a gamma camera placed over the kidneys (Fig 3). This method was shown to be in good agreement with the 100% oxygen technique [11,17]. It has the advantage of being less invasive and can be used on exercise [11]. Pulse oximetry is a useful screening test but is not specific for anatomic shunting. The <sup>99m</sup>Tc-MAA technique is more sensitive.

#### Screening for PAVMs

All patients with HHT should be screened for the presence of PAVMs because of the serious consequences of paradoxical embolisation. A physician dealing with an HHT patient should also remind the proband of the importance of his/her relatives being screened for



**Fig 3.** Lung perfusion scans using  $^{99m}\text{Tc}$ -MAA in a normal subject (right) and in a patient with HHT and pulmonary arteriovenous malformations (PAVM) (left) with posterior views (top), coned down (bottom right) to show radioactivity escaping through the lungs into left kidney, spleen and right kidney. No extrapulmonary radioactivity is visible in the normal subject (top and bottom right).

HHT and PAVMs. The following screening tests are used at Hammersmith:

- $\text{SaO}_2\%$  (pulse oximeter) in the standing and lying positions;
- chest radiograph; and
- lung perfusion scan using  $^{99m}\text{Tc}$ -MAA.

To reach a steady state, the pulse oximetry readings should be taken at one-minute intervals for 10 minutes in each posture.  $\text{SaO}_2$  less than 95% in both postures and/or a fall on standing greater than 2% compared to supine supports a diagnosis of PAVMs. A few patients with limited disease (1–2 abnormal channels) will pass this test but their chest x-ray will be abnormal. A lung perfusion scan should be ordered if either  $\text{SaO}_2$  or radiography is abnormal, or if there is a history of transient ischaemic attacks, migraine or other neurological events *even if  $\text{SaO}_2$  etc are normal*. Other useful investigations would be Hb estimation and  $\text{SaO}_2$  on exercise (there is usually a pronounced fall). PAVMs show well on a thoracic CT scan, but pulmonary angiography remains the definitive procedure.

#### *Treatment of PAVMs*

Successful excision of a PAVM was first reported in 1942 [18], and surgery remained the treatment of choice until the 1980s. Surgery was never the ideal solution when PAVMs were multiple (as they frequently are in HHT). Percutaneous trans-catheter embolisa-

tion with steel coils or detachable balloons was introduced in 1978 [19]. For practical purposes, the radiologist has now replaced the surgeon [20]. Considerable skill is required to place the tip of the pulmonary artery catheter close to the neck of the AVM sac—too proximal placement means sacrificing normal lung, and too peripheral risks losing the coil into the sac and passing into the left atrium. In over 100 embolisations at Hammersmith Hospital (DJ Allison, JE Jackson; personal communication) the morbidity of the procedure has been less than 10% and there have been no long term complications.

Illustrative examples are given in Table 2. The family history in case 1 (Fig 1) shows unusual clustering of PAVMs (father, proband and her two daughters; sister of the proband unaffected with HHT). The cerebral complications in father and proband are obvious. The right to left shunt (supine) was quite small (9%) but increased to approximately 28% in the erect posture (not shown in Table 2). The PAVM channels were all in the lower zones. Coil embolisation completely obliterated the shunt. The hemiparesis following the embolisation is our only recorded example; the patient recovered fully within 48 hours and there have been no sequelae.

Case 2 was unusual in lacking any family history of epistaxes or telangiectasia in siblings or parents. PAVMs were recognised at the age of 16 years (at the same age as his eldest daughter), and surgery was carried out at age 16 and 27 years. Multiple PAVMs

remained, giving him a large shunt (39%, supine) at age 39 years. Nevertheless, his exercise capacity (150 watts) was 80% of predicted normal despite an SaO<sub>2</sub> on maximal exercise of only 66% (at this time he was milking 300 cows each day!). Repeated embolisations were undertaken (over 100 coils inserted) with substantial improvement in SaO<sub>2</sub> and reduction in the right-to-left shunt, but without noticeable increase in his already excellent exercise capacity.

*Efficacy of coil embolisation*

In the Hammersmith series of 46 cases, the right-to-left shunt has been eliminated in 28 (61%) (eg case 1, Table 2) and considerably reduced in 13 (28%) (eg case 2, Table 2). It has been unaffected in five (11%) who had more than 20 small PAVMs whose feeding vessels were too small (less than 3 mm diameter) for embolisation. All patients are followed up for a minimum of 24 months. Enlargement of residual lesions after treatment is unusual.

Deterioration in oxygenation has been observed in only one of the 46 cases—a 24 year old woman who presented with severe hypoxaemia (SaO<sub>2</sub>, 74% erect and 85% supine) and a large shunt (41% of cardiac output). After five embolisation sessions and the occlusion of 20 PAVM channels, her oxygenation had improved (SaO<sub>2</sub>, 80% erect) and the shunt declined to 21%. Subsequently, she became pregnant and delivered a healthy baby, but then her cyanosis and breathlessness returned, and her oxygenation and shunt fell to the original presentation values. Pulmonary angiography at this time showed multiple small PAVMs, none of which was large enough to embolise. Swinburne *et al* [21] have reported a case of HHT with PAVMs whose PaO<sub>2</sub> and right-to-left shunt deteriorated markedly during pregnancy. Patients with extensive PAVMs should be warned of the hazards of pregnancy.

**Idiopathic PAVMs (non-HHT)**

Twenty per cent of PAVMs seen on angiography are not associated with HHT, although the angiographic appearances are identical. These patients have no family history, no telangiectasia and no recurrent epistaxes. They are more likely to have polycythaemia because they are not bleeding from the nose or the gastrointestinal tract. They usually have less than five abnormal vascular channels, all of which are amenable to embolisation. Typically, they are not left with any residual shunt.

**Hepatopulmonary syndrome**

The hepatopulmonary syndrome affects up to one-third of patients with liver failure [22]. It has also been reported in pre-hepatic portal hypertension with normal liver function [23]. The pulmonary features have recently been reviewed [24]. The cardinal features are:

**Table 2.** Case histories of hereditary haemorrhagic telangiectasia and intrapulmonary shunting.

<b>Case 1</b>	
Female:	age 53
Family history:	father died age 34 (cerebral abscess); two daughters with HHT and PAVMs
On examination:	epistaxes, telangiectasia on tongue
Past history:	TIAs, brain CT showed cerebellar infarcts
Pulmonary function:	normal
Pre-embolisation:	SaO <sub>2</sub> %: 88 (erect), 95 (supine); right-to-left shunt %: 9 (supine)
Embolisation:	five PAVMs with 17 coils
Post-embolisation:	left hemiparesis lasting 24 hours; SaO <sub>2</sub> %: 97 (erect), 97 (supine); right-to-left shunt %: nil
<b>Case 2</b>	
Male:	age 44, herdsman
Family history:	nil in parents or siblings, but eldest daughter affected
Past history:	epistaxes, clubbing, telangiectasia, polycythaemia, haemoptysis; segmental resections in 1965 and 1976
Pulmonary function:	normal spirometry, low diffusion (62%)
Pre-embolisation:	SaO <sub>2</sub> %: 71 (erect), 84 (supine), 66 (maximum exercise, 150 watts); right-to-left shunt %: 39 (supine)
Embolisation:	seven sessions with occlusion of 42 AVMs with 110 coils
Post-embolisation:	SaO <sub>2</sub> %: 82 (erect), 96 (supine), 86 (maximum exercise, 150 watts); right-to-left shunt %: 11 (supine)

- AVM = arteriovenous malformation
- CT = computerised tomography
- HHT = hereditary haemorrhagic telangiectasia
- PAVM = pulmonary arteriovenous malformation
- SaO<sub>2</sub> = arterial oxygen saturation
- TIA = transient ischaemic attack

- severe hypoxaemia (PaO<sub>2</sub> less than 8 kPa (60 mmHg)), incompletely corrected by breathing 100% oxygen;
- low diffusing capacity (D<sub>L</sub>CO and D<sub>L</sub>CO/V<sub>A</sub> less than 50%);
- normal pulmonary angiogram; and
- <sup>99m</sup>Tc-MAA lung perfusion scan shows radioactivity in the kidneys.

Radioactive albumin particles escape into the systemic circulation, just as happens in PAVMs (Fig 3), but the ultrastructure is quite different from PAVMs. The microvasculature is not replaced by a sac; instead,

**Table 3.** Reversal of lung shunts with liver transplantation.

Authors	No. of cases	Diagnosis	<sup>99m</sup> Tc-MAA	PaO <sub>2</sub> (mmHg) (pre/post)	Shunt (%) (pre/post)
Stoller [35]	1	PBC	Yes	67/89	18/5.2 (100% O <sub>2</sub> )
Dimand [23]	3	Cirrhosis (2) Pre-hepatic PHT*	Yes	50/86	<sup>99m</sup> Tc-MAA improved
Schwarzenburg [36]	1	α <sub>1</sub> -antitrypsin deficiency	Yes	69/561 (100% O <sub>2</sub> )	<sup>99m</sup> Tc-MAA large/nil
Eriksson [37]	6	PBC or PSC or CAH	No	79/90	11.8/0.6** (100% O <sub>2</sub> )

\* Normal liver function

\*\* Pulmonary artery pressure (pre/post) = 13/18 mmHg

\*\* Pulmonary vascular resistance (pre/post) = 0.7/1.6 mmHg min/l

CAH = chronic active hepatitis

MAA = Macroaggregated albumin

PaO<sub>2</sub> = arterial partial pressure of oxygen

PBC = primary biliary cirrhosis

PHT = portal hypertension

PSC = primary sclerosing cholangitis

many of the capillaries in the alveolar septa are grossly dilated, with internal diameters up to 100 µm [25].

#### *Pathogenesis of the hypoxaemia*

The low PaO<sub>2</sub> is an example of a true diffusion defect. The anatomic shunt, calculated from the <sup>99m</sup>Tc-MAA scan, is about 30% in the more severe cases. When breathing air, the oxygen shunt is at the same level, but when breathing 100% oxygen, it averages 15% [26]. The <sup>99m</sup>Tc-MAA shunt does not change with 100% oxygen. Diffusion distances from alveolar gas to the centre of the dilated capillaries are too long, and transit times too short (because of the low resistance) for alveolar end-capillary oxygen equilibrium to occur. Increasing the oxygen driving pressure 6–7 fold by inspiring 100% oxygen partially eliminates the diffusion block. Other workers, using similar [27] or different [28,29,30], techniques have come to the same conclusion.

#### *Mechanism of the vascular dilatation*

The stimulus for capillary remodelling in this syndrome is unknown. The anatomic shunt is not affected by indomethacin (inhibition of vasodilator prostaglandins) [31], propranolol (which reduces flow through gastro-oesophageal collateral channels) [32], somatostatin infusion [33] or a selective pulmonary vasoconstrictor (almitrine) [34].

#### *Treatment*

The hypoxaemia can be reversed by liver transplantation [23,35–37] (Table 3). There are also two single

case reports of a reduction in anatomic shunt either following medical therapy with corticosteroids and cyclophosphamide [38] or spontaneously [39]. In several instances, pulmonary haemodynamics were measured before and after treatment [37,38]. Reduction in the anatomic shunt was accompanied by an increase in pulmonary artery pressure and pulmonary vascular resistance, as expected. Therefore, severe hypoxaemia should not be a contraindication to liver transplantation if investigations reveal intrapulmonary shunting.

#### **Conclusions**

- The commonest causes of intrapulmonary shunting are HHT and the hepatopulmonary syndrome.
- Coil embolisation is a safe and effective therapy for discrete lung shunts with feeding vessels over 3 mm in diameter.
- In HHT, the PAVMs can be completely eliminated in 60% of patients, but 10% of patients will be left with many small unoccludable vessels and a large right-to-left shunt.
- The pathogenesis of the hepatopulmonary syndrome is not known. The most effective treatment for the lung shunts is liver transplantation.

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