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Embolisation of pulmonary arteriovenous malformations: no consistent effect on pulmonary artery pressure

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ABSTRACT: Increasing evidence supports the use of embolisation to treat pulmonary arteriovenous malformations (AVMs). Most pulmonary AVM patients have hereditary haemorrhagic telangiectasia (HHT), a condition that may be associated with pulmonary hypertension.

The current authors tested whether pulmonary AVM embolisation increases pulmonary artery pressure (P_{pa}) in patients without baseline severe pulmonary hypertension. P_{pa} was measured at the time of pulmonary AVM embolisation in 143 individuals, 131 (92%) of whom had underlying HHT. Angiography/embolisation was not performed in four individuals with severe pulmonary hypertension, whose systemic arterial oxygen saturation exceeded levels usually associated with dyspnoea in pulmonary AVM patients.

In 143 patients undergoing pulmonary AVM embolisation, P_{pa} was significantly correlated with age, with the most significant increase occurring in the upper quartile (aged >58 yrs). In 43 patients with repeated measurements, there was no significant increase in P_{pa} as a result of embolisation. In half, embolisation led to a fall in P_{pa}. The maximum rise in mean P_{pa} was 8 mmHg: balloon test occlusion was performed in one of these individuals, and did not predict the subsequent rise in P_{pa} following definitive embolisation of the pulmonary AVMs.

In the present series of patients, which excluded those with severe pulmonary hypertension, pulmonary artery pressure was not increased significantly by pulmonary arteriovenous malformation embolisation.

KEYWORDS: Brain abscess, hypoxaemia, nosebleeds, oxygen saturation, right-to-left shunt, stroke

Does embolisation of pulmonary arteriovenous malformations (AVMs) precipitate pulmonary hypertension (PH)? The reason this question is important is that for individuals with pulmonary AVMs, embolisation is an effective means of reducing lifetime risks of paradoxical embolic stroke and brain abscess [1, 2], improving oxygenation [3–17] and treating pulmonary AVM-related haemoptysis [18, 19]. Conversely, embolisation may be expected to elevate pulmonary artery pressure (P_{pa}), since pulmonary AVMs are abnormal dilated vessels between pulmonary arteries and veins that provide low resistance pathways for pulmonary blood flow [20].

The question of whether pulmonary AVM embolisation increases P_{pa} is particularly pertinent, since most individuals with pulmonary AVMs have underlying hereditary haemorrhagic telangiectasia (HHT). Typically recognised by nosebleeds, mucocutaneous telangiectasia and visceral AVMs [21], HHT may be associated with PH [9, 22–30]. The secondary causes of PH in HHT are diverse, as they are in the normal population [31], but PH particularly occurs either as a true pulmonary arterial hypertension (PAH) phenotype [9, 22, 28–30] or in the context of high output cardiac failure secondary to hepatic AVMs, when PH may be reversible after hepatic AVM treatment [32]. The frequencies of PAH and hepatic AVMs differ with HHT genotype: HHT is caused by mutations in at least five genes, including *endoglin* (HHT type 1) and *ALK-1* (HHT type 2), with pulmonary AVMs most common in HHT type 1 [33]. PAH phenotypes are more common in HHT type 2 [22, 28, 29] than HHT type 1 [30]. Hepatic AVMs are also more frequent in HHT type 2 [33].

For editorial comments see page 15.

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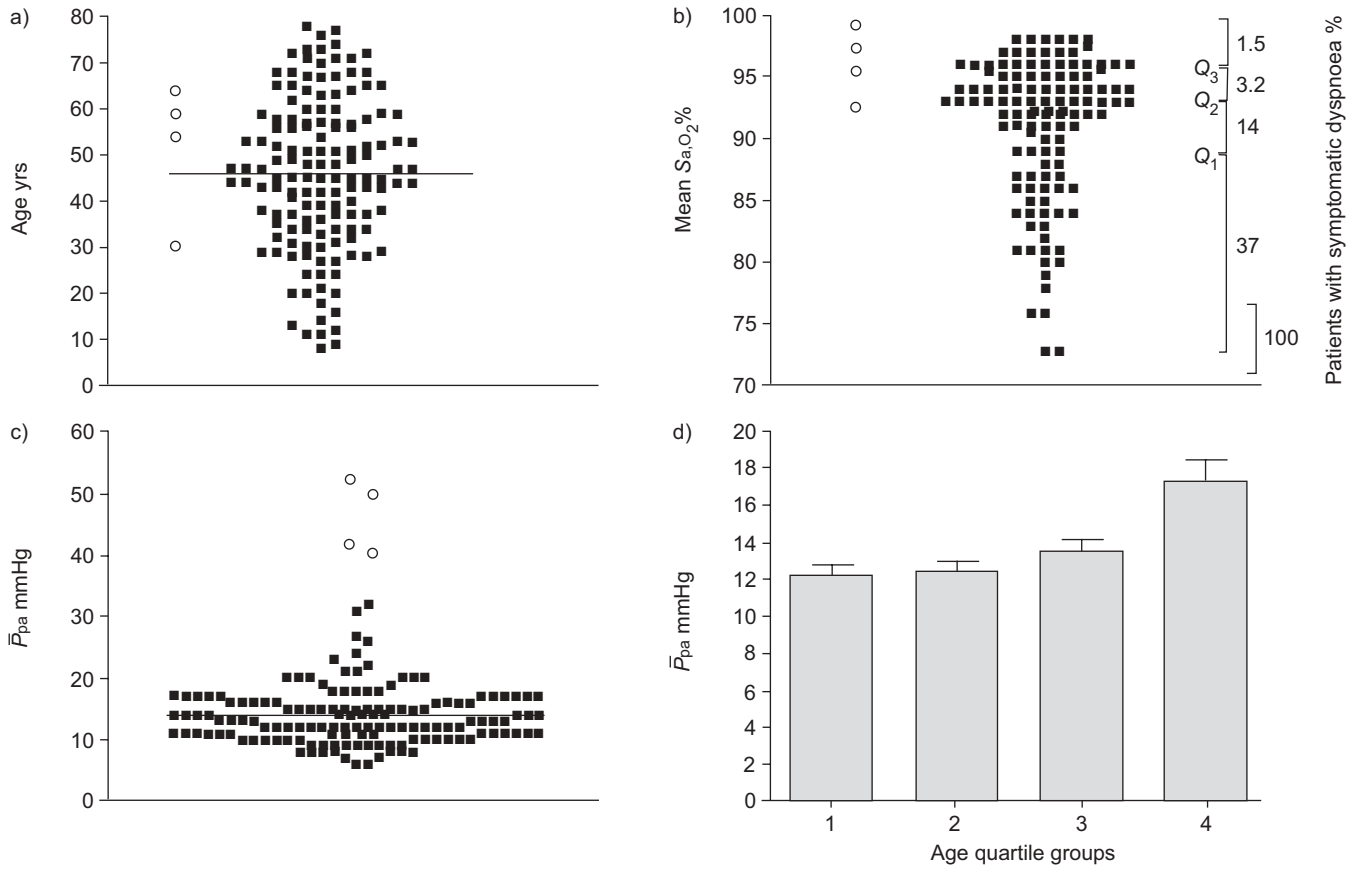

FIGURE 1. Baseline characteristics of study population. Comparison of a) age, b) baseline erect arterial oxygen saturation (S_{a,O_2}), and c) mean pulmonary artery pressure ($\bar{P}_{pa}$) for the 143 patients undergoing embolisation (■) and the four patients not offered embolisation (○). For b), quartile groups are as previously reported for 219 pulmonary arteriovenous malformation (AVM) patients [2]. d) Age-dependent increase in $\bar{P}_{pa}$ in 143 patients with pulmonary AVMs; quartile boundaries are 34, 45 and 58 yrs.

Out of >700 reported pulmonary AVM embolisations [1–18, 34–42], data on P_{pa} measurements pre- and post-embolisation are scarce [9, 11, 17, 32]. In three out of the four reported cases [9, 17, 32], each selected from larger series, P_{pa} increased post-embolisation, while in the fourth it was unchanged [11]. There is also a report of worsening PH after surgical resection of a pulmonary AVM [43].

The current authors have previously reported that in a population of pulmonary AVM patients, 92% of whom had HHT, the overall prevalence of PH is low [44]. It was hypothesised that, in contrast to the limited data in the literature, pulmonary AVM embolisation would not increase P_{pa}. Presented herein are results of a retrospective study in the series of pulmonary AVM patients reported recently [2], performed to determine whether pulmonary AVM embolisation affected P_{pa}, and whether it may be safe to extend this embolisation practice to individuals with severe PH.

METHODS

Study population

All studies were ethically approved by the Hammersmith, Queen Charlotte's, Chelsea and Acton Hospital Research Ethics Committee (LREC 00/5764; London, UK), and performed as part of routine clinical management of individuals with pulmonary AVMs.

Arterial oxygen saturation (S_{a,O_2}) was measured as described previously [2, 4, 45]. For S_{a,O_2} values reported in the present study, recordings were made every 60 s for 10 min standing, since S_{a,O_2} in the erect posture correlates better with right-to-left shunt [45]. All patients with pulmonary AVMs of a size amenable to embolisation treatment underwent pulmonary angiography with a view to embolisation, unless there was a major medical contraindication. In view of theoretical concerns, angiography/embolisation was not considered for four females referred to the service with severe PH and well-preserved oxygen saturations. Pulmonary angiography was

TABLE 1 Pulmonary haemodynamic variables in 143 pulmonary arteriovenous malformation patients undergoing embolisation

	Median (IQR)	Mean (range)	Normal range#
Systolic *Ppa* mmHg	23 (19–27)	23.6 (13–60)	13–26
Diastolic *Ppa* mmHg	7 (5–9)	7.2 (0–30)	6–16
$\bar{P}_{pa}$ mmHg	13 (11–16)	13.5 (6–45)	7–19

IQR: interquartile range; P_{pa}: pulmonary arterial pressure. $\bar{P}_{pa}$: mean pulmonary arterial pressure; #: data obtained from [50].

TABLE 2 Pulmonary haemodynamic variables in four pulmonary hypertension (PH) patients not undergoing pulmonary arteriovenous malformation (AVM) embolisation

Case	Age yrs	Erect $S_{a,O2}$ %	P_{ra} mmHg	P_{rved} mmHg	Systolic P_{pa} mmHg	Diastolic P_{pa} mmHg	$\bar{P}_{pa}$ mmHg	P_{cwp}[#] mmHg	CO L·min^{-1}	CI L·min^{-1}·m^{-2}	PVR[¶] dyn·s·cm^{-5}
144	64	100	12	10	74	21	41	17	7.0	4.0	272
145	30	95	0	8	80	30	50	2	3.3	2.3	1160
146	59	97.5	23	9	70	40	52	25	3.1	1.7	396
147	53	92	12	9	55	38	40	18	7.8	4.6	274

S_{a,O_2}: arterial oxygen saturation; P_{ra}: right atrial pressure; P_{rved}: right ventricular end diastolic pressure; P_{pa}: pulmonary arterial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{cwp}: pulmonary capillary wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance. #: normal range 5–13 mmHg [50]; ¶: normal range 11–99 dyn·s·cm^{-5} [50]. Note the variety of PH phenotypes in this population: case 144 has post-capillary PH; case 145 has a pulmonary arterial hypertension profile; and the other two cases display a mixed profile. High-output cardiac failure secondary to hepatic AVMs was present in cases 144 and 146.

performed as described previously [4] in conscious patients who had not been pre-medicated or fluid-restricted before the procedure. Systolic and diastolic P_{pa} and mean P_{pa} ($\bar{P}_{pa}$) were recorded routinely prior to contrast injection *via* a multi-sidehole catheter (Grollman pigtail catheter; William Cook Europe, Bjaeverskov, Denmark). Measurements were repeated immediately after embolisation in the subgroup of individuals with higher P_{pa}. In the majority of patients, only a single angiography/embolisation session was required [2].

Statistics

For S_{a,O_2}, the last 4 min readings for erect postures were entered as replicate data for each of the pre- and post-embolisation data. Quartile group data were incorporated from the full series of 219 pulmonary AVM patients, as reported previously [2].

Age was expected to influence P_{pa}, since catheterisation data at rest in two groups of healthy individuals (17 aged 16–28 yrs [46]; 15 aged 61–83 yrs [47]) demonstrated significantly higher systolic P_{pa} (mean 24.47 *versus* 19.94 mmHg; p=0.003, Mann–Whitney) and $\bar{P}_{pa}$ (mean 16.13 *versus* 13.65 mmHg; p=0.026) in the older group. This has also been supported by more recent echocardiography data [48]. In the present patient series, associations of P_{pa} measurements with age were performed using Spearman rank analyses and linear regression. The patients were also stratified into age quartile groups, and interquartile differences analysed by ANOVA with post-test correction for linear trend.

In order to test whether P_{pa} was elevated following embolisation of pulmonary AVMs, P_{pa} measurements recorded pre-embolisation were studied in all patients with at least two P_{pa} measurements. A total of 39 pairs of consecutive P_{pa} measurements recorded at the outset of at least two embolisation sessions were available from 35 patients. In addition, nine pairs of P_{pa} measurements recorded pre- and post-embolisation in the same session were available for eight patients with pre-existing mild to moderate PH, in whom the repeat measurements during the same procedure had been justified as part of their clinical management. To test the null hypothesis that embolisation of pulmonary AVMs does not increase P_{pa}, measurements pre- and post-embolisation, and pre-embolisation and age-adjusted post-embolisation measurements, were analysed by two-tailed paired t-test and significance assessed at a false discovery rate level of 0.05 [49].

RESULTS

Patient populations

Patient ages ranged 8–78 yrs at the time of embolisation (fig. 1a). In patients undergoing embolisation, baseline erect S_{a,O_2} ranged 73–98%, with a median value of 93% in the full population, as reported previously (fig. 1b) [2]. For the four individuals who did not undergo embolisation due to severe pre-existing PH, erect S_{a,O_2} was in the upper two quartiles of the full pulmonary AVM population, at levels for which the majority of individuals did not experience dyspnoea (fig. 1b) [2].

Baseline *P*pa measurements (systolic, diastolic and mean) varied widely, as illustrated in table 1 and figure 1c. The distribution of the embolised patients was skewed (fig. 1c), but nevertheless, the four patients who were not offered

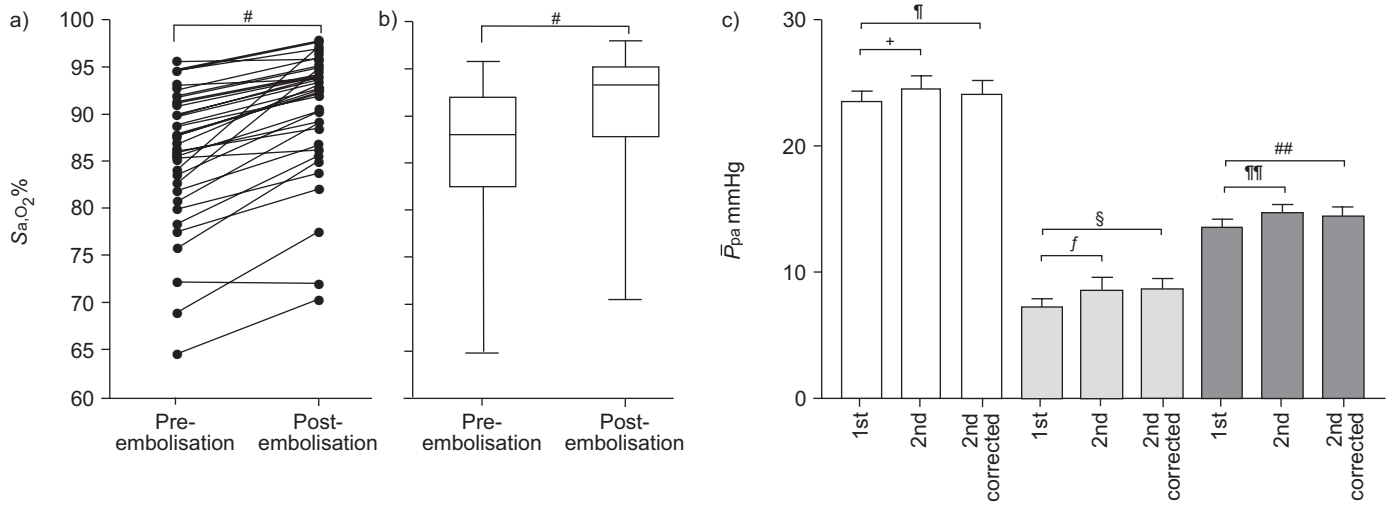

FIGURE 2. Effects of pulmonary arteriovenous malformation embolisation. a and b) Erect arterial oxygen saturation (Sa,O_2) and c) mean pulmonary arterial pressure ($\bar{P}pa$) recorded at consecutive embolisation sessions (□: systolic Ppa; ▫: diastolic Ppa; ■: $\bar{P}$pa) in 35 patients. In c), age-adjusted figures were calculated by $\bar{P}pa=9.88+(0.107\times age)$ as defined in the population (see text), and in contrast to Sa,O_2, overall p-values did not reach significance at false discovery rate level of 0.05 [49]. #: p<0.0001; ¶: p=0.25; +: p=0.15; §: p=0.14; *f*: p=0.12; ##: p=0.08; ¶¶: p=0.05.

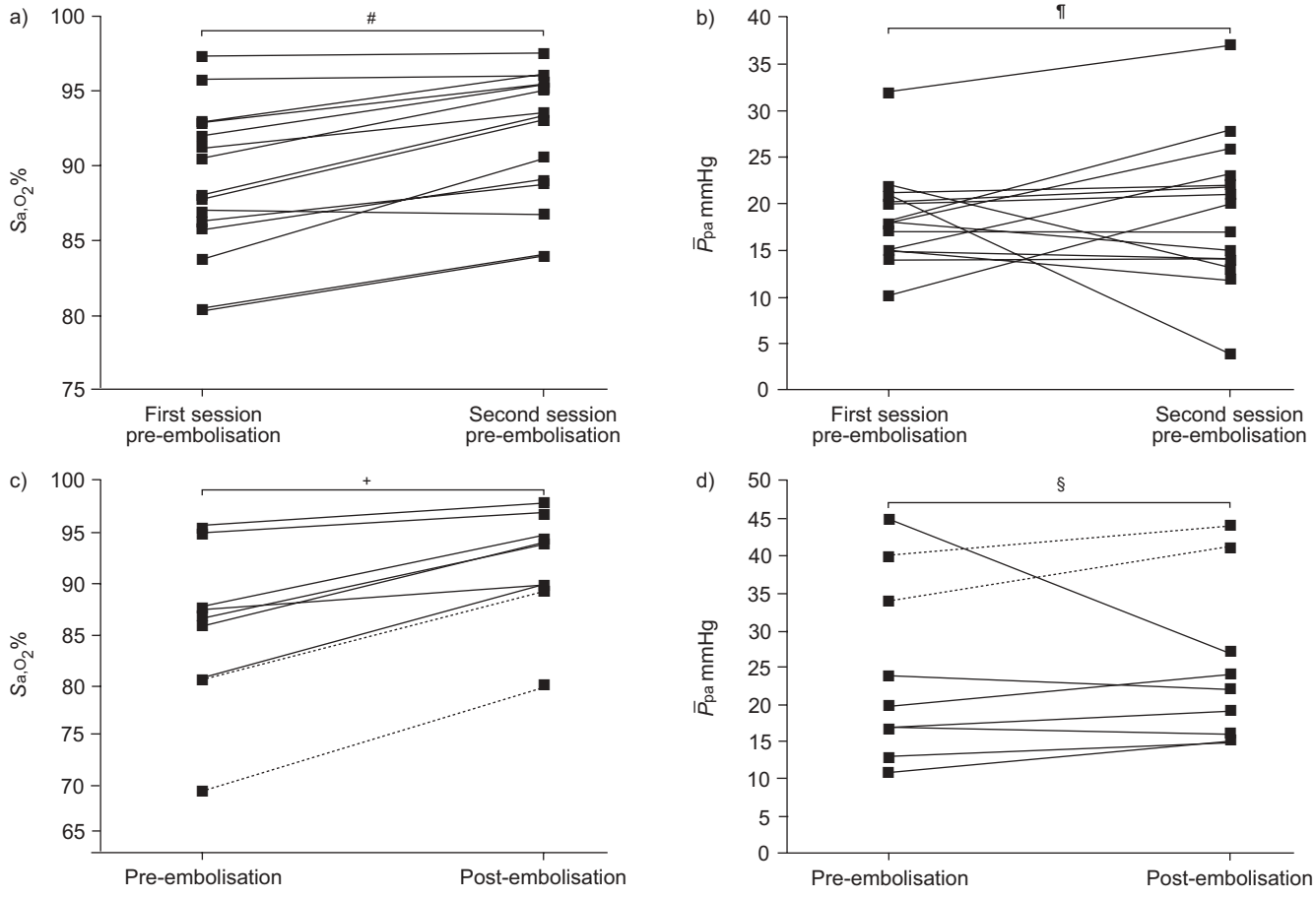

FIGURE 3. Individual patient details. a) Erect arterial oxygen saturation (Sa,O_2) and b) mean pulmonary arterial pressure ($\bar{P}pa$) recorded pre-embolisation at consecutive embolisation sessions in a subgroup of 15 patients with pre-existing elevated $\bar{P}$pa (⩾16 mmHg). c) Sa,O_2 (erect) and d) $\bar{P}$pa recorded pre- and post-embolisation at the same session in eight patients with pre-existing elevated $\bar{P}$pa (⩾16 mmHg). The two measurements for the patient with balloon test occlusion reported in table 2 are illustrated by dotted lines. #: p<0.0001; ¶: p=0.76; +: p=0.0039; §: p=0.93.

TABLE 3 Comparison of balloon test occlusion and pulmonary arteriovenous malformation (AVM) embolisation

	Day 0		Day 8		Day 169		Change post-balloon	Change after complete embolisation
	Pre-balloon	Post-balloon	Pre-embolisation	Post-embolisation	Pre-embolisation	Post-embolisation		
Sa,O_2 %	67	85	69	80	81	89	+18	+22
Systolic *Ppa* mmHg	47	50	54	60	57	63	+3	+16
Diastolic *Ppa* mmHg	0	0	24	32	27	35	0	+35
Mean *Ppa* mmHg	22	25	34	41	36	44	+3	+22

Sa,O_2: arterial oxygen saturation; *Ppa*: pulmonary arterial pressure. Test occlusion (stable for 5 min) and subsequent data following two separate pulmonary AVM embolisation sessions in a 65-yr-old male with pulmonary hypertension secondary to left ventricular disease. The embolisation sessions reduced the right-to-left shunt from 18% to 13.3% (session 1), then to undetectable levels (session 2). In session 1, embolisation was curtailed due to the rise in *Ppa*.

embolisation represented significant outliers. Further details of their haemodynamic variables are presented in table 2.

Univariate analysis of first recorded P_{pa} measurements in the 143 embolised patients indicated that all three P_{pa} measurements were influenced by age. For age and $\bar{P}_{pa}$, the Spearman r correlation was 0.33 (95% confidence interval 0.17–0.47; $p<0.0001$), and $\bar{P}_{pa}$ could be described by the expression $9.88+(0.107 \times \text{age})$; $r^2=12.33\%$, $p<0.0001$. ANOVA indicated significant differences in P_{pa} between age quartile groups (fig. 1d). Post-test analysis confirmed a linear trend ($p<0.0001$), with significant increases occurring between the third (45–58 yr) and upper (>58 yr) age quartiles (fig. 1d).

Effect of embolisation

In order to test whether P_{pa} was elevated following embolisation of pulmonary AVMs, P_{pa} measurements recorded pre-embolisation were studied in all 43 patients for whom post-embolisation measurements were also available, either from consecutive sessions (35 patients), or from the same embolisation session (eight patients).

For the 35 patients in whom measurements were made prior to consecutive embolisation sessions, S_{a,O_2} increased in all except one of the patients following embolisation ($p<0.0001$; fig. 2a). In contrast, there was no significant change in P_{pa} as a result of embolisation (fig. 2b). There was a trend towards higher P_{pa} post-embolisation, but this was in part accounted for by increased patient age, as measurements were recorded at a mean interval of 19.9 (range 2–121) months.

Recognising that the pooled groups may have masked individual changes, individual P_{pa} responses were examined in a subgroup of 15 patients with mean P_{pa} in the upper quartile. In this small group, embolisation resulted in a highly significant improvement in S_{a,O_2} ($p<0.0001$; fig. 3a). In contrast, P_{pa} measurements recorded at a mean interval of 26 (range 13–80) months demonstrated no consistent trend, and no significant difference between pre- and post-embolisation measurements ($p=0.76$; fig. 3b). Comparable findings were observed with systolic and diastolic P_{pa} (data not shown).

These measurements addressed whether embolisation led to a sustained change in P_{pa}. In order to explore whether there were any acute changes in P_{pa}, nine pairs of P_{pa} measurements recorded pre- and post-embolisation in the same session were examined. Embolisation resulted in a consistent and highly significant improvement in S_{a,O_2} ($p=0.0039$; fig. 3c). Again P_{pa} responses to pulmonary AVM embolisation varied between individuals. In half of all patients, post-embolisation $\bar{P}_{pa}$ was lower than prior to embolisation and, overall, there was no significant difference as a result of embolisation ($p=0.93$; fig. 3d). Comparable findings were observed for systolic and diastolic P_{pa} (data not shown).

While overall there were no significant increase in P_{pa} as a result of embolisation, within both groups there were occasional individuals in whom P_{pa} did increase, by up to 8 mmHg between consecutive sessions, and up to 4 mmHg during the same session. It may be helpful to be able to identify these rare individuals prior to embolisation. Others have suggested test occlusion of the pulmonary AVM before definite embolisation [32]. This technique was attempted for

one patient early in the series. Balloon occlusion increased S_{a,O_2} to a similar degree as eventual complete embolisation (table 3). This test occlusion did not significantly increase P_{pa}, whereas P_{pa} was significantly higher following maximal embolisation.

DISCUSSION

The key finding of the present study was that embolisation of pulmonary AVMs did not lead to a consistent increase in resting P_{pa} in a series which excluded individuals with severe PAH.

The strengths of the study included the relatively large patient group, correction for age, which could have been an important confounding variable in assessments over consecutive embolisation sessions, and strong evidence of embolisation efficacy. Weaknesses include the retrospective nature of the study, and the reliance on measurements performed for clinical purposes such that pulmonary vascular resistance measurements and same-session repeat measurements following embolisation were not available for the majority of patients. In addition, the study was only powered to address consistent changes pre- and post-embolisation.

Within the study limitations, in the present patient series embolisation of pulmonary AVMs did not generally increase P_{pa}, even in the setting of mild to moderate pre-existing PH. No patient in the present study developed clinical PAH (*i.e.* right heart failure) after embolisation.

The current authors were surprised by the significant fall in P_{pa} in one patient with pre-existing PH attributed to left ventricular disease, and also initially surprised to see that embolisation did not lead to a consistent increase in P_{pa} in other patients, since effective embolisation occludes vessels that provide a lower resistance to flow than the rest of the pulmonary vasculature [20]. None of the patients illustrated in figure 3 were known to have hepatic AVMs, and this may explain the differences between the results of the present study and those of others. Importantly, however, noting that embolisation leads to a reduction in cardiac output [11, 17], the present data suggest that the fall in cardiac output can have a greater effect on pulmonary vascular resistance than occlusion of individual pulmonary AVMs.

While the data indicate that pulmonary AVM embolisation does not necessarily lead to elevated P_{pa}, P_{pa} did rise in some individuals; rises which, in this study, were not predicted by balloon test occlusion pre-embolisation. It is important to recognise that in the setting of severe PAH and HHT-associated hepatic AVMs, there are reports that embolisation of pulmonary AVMs may precipitate a fatal increase in P_{pa} [32]. Furthermore, in addition to previously reported cases, clinical PAH developed in another patient in the present series [2] in the years following pulmonary AVM resection and embolisation at another institution.

The current authors' interpretation of these considerations, and of observations from the series reported herein and elsewhere [2], is that for patients with pre-existing severe PAH, the risks of pulmonary AVM embolisation outweigh the potential benefits. The main indications for pulmonary AVM embolisation are to reduce the risk of paradoxical embolic stroke and, for individuals with hypoxaemia, to improve dyspnoea and exercise tolerance. The present authors have recently shown that the risk of paradoxical embolic stroke is substantially lower in individuals with higher P_{pa} [2]. Furthermore, the present data serve as a reminder that pulmonary AVMs generally result in symptomatic dyspnoea only when resting S_{a,O_2} is $<80\%$, perhaps suggesting that symptomatic relief should not be expected for patients with PH and S_{a,O_2} $>90\%$, as was the case in all four excluded patients in the study. In the current authors' experience, the most difficult judgements relate to individuals with elevated P_{pa} and major haemoptysis, a consideration that was not required for the four individuals with PH in this series.

In summary, the data are a useful adjunct to case reports indicating increased pulmonary artery pressure post-embolisation, and indicate that embolisation may be undertaken with caution in the presence of pre-existing mild to moderate pulmonary hypertension in selected individuals.

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