Exercise capacity reflects airflow limitation rather than hypoxaemia in patients with pulmonary arteriovenous malformations

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ABSTRACT

BACKGROUND: Pulmonary arteriovenous malformations (PAVMs) generate a right-to-left shunt. Impaired gas exchange results in hypoxemia and impaired CO_2 clearance. Most patients compensate effectively but a proportion are dyspneic, and these are rarely the most hypoxaemic.

AIM: To test degrees of concurrent pathology influencing exercise capacity

DESIGN: Replicate, sequential single centre, prospective studies.

METHODS: Cardiopulmonary exercise tests (CPET) were performed in 26 patients with PAVMs, including individuals with and without known airflow obstruction. To replicate, relationships were tested prospectively in an independent cohort where self-reported exercise capacity evaluated by the Veterans Specific Activity Questionnaire (VSAQ) was used to calculate metabolic equivalents at peak exercise (METS N=71). Additional measurements included oxygen saturation (SpO_2), forced expiratory volume in 1 second (FEV1), vital capacity (VC), exhaled nitric oxide (FeNO), haemoglobin and iron indices.

RESULTS: By CPET, the peak work-rate was only minimally associated with low SpO_2 or low arterial oxygen content (CaO_2=*1.34 x SpO_2 x haemoglobin*), but was reduced in patients with low FEV1 or VC. Supranormal work-rates were seen in patients with severe right-to-left shunting and SpO_2 <90%, but only if FEV1 was >80% predicted. VSAQ-calculated METS also demonstrated little relationship with SpO_2, and in crude and CaO_2-adjusted regression, were lower in patients with lower FEV1 or VC. Bronchodilation increased airflow even where spirometry was in the normal range: exhaled nitric oxide measurements were normal in 80% of cases, and unrelated to any PAVM-specific variable.

CONCLUSIONS: Exercise capacity is reduced by relatively mild airflow limitation (obstructive or restrictive) in the setting of PAVMs.

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Introduction

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that provide a direct communication between pulmonary arteries and veins.[1] PAVMs may affect as many as 1 in 2,600 individuals,[2] though there is evidence that the unusual pathophysiology demonstrated by patients is under-appreciated.[3] PAVMs usually occur in association with the more general vascular dysplasia, hereditary haemorrhagic telangiectasia (HHT), a condition commonly recognized by the presence of familial nosebleeds (epistaxis), mucocutaneous telangiectasia, and iron deficiency anaemia.[4]

PAVMs result in an anatomic right-to-left shunt.[1,5,6] The proportion of the right ventricular stroke volume (cardiac output) transiting PAVMs is termed the "shunt fraction". The shunt fraction determines the degree of hypoxaemia as defined by low PaO_2 and low SpO_2.[8-10] However, arterial oxygen content (CaO_2) is usually preserved by secondary erythrocytosis[11] with values stable across decades and PAVM treatments.[8,10] Right-to-left shunting also leads to exuberant ventilation,[12,13] high cardiac outputs,[14] and paradoxical emboli resulting in ischaemic strokes and brain abscess[4,9,15-19]. All of these features improve following treatment of PAVMs, which is usually by transcatheter embolization.[5,7] However, due to untreatable small PAVMs, many patients are left with significant right-to-left shunting after maximal embolization,[7,10,18,] posing challenges for general and respiratory physicians.[20]

When reviewing an asymptomatic patient with PAVMs, clinicians are frequently surprised by the degree of hypoxaemia present. In 165 consecutive patients with SpO_2 ranging from 78.5-99% (median 95%), Medical Research Council (MRC) dyspnoea grades did not exceed 3 unless there was significant co-existing cardiopulmonary disease.[21] Patients with SpO_2 <85% are able to pursue sporting activities to a very high level,[8,21] and 86/98 (87.8%) consecutive patients reported no improvement in dyspnoea/exercise capacity after embolization had corrected their hypoxemia.[8] Formal cardiopulmonary exercise tests (CPET) of 21 PAVM patients with SpO_2 80%-96%, demonstrated that Borg scale dyspnoea, maximal work-rates and peak oxygen consumption (V[dot]O_2) did not differ according to hypoxaemia severity.[13] Furthermore, in five

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patients where embolization increased median SpO_2 from 90% to 96% and normalized what had been exuberant ventilation for the degree of CO_2 production (the "V[dot]EV[dot]CO_2 slope"), serial CPET studies demonstrated no difference in peak work-rate or peak V[dot]O_2.[13] All of these findings emphasize that in the chronically adapted state, patients with PAVMs can maintain arterial oxygen content and oxygen delivery.[8,10]

That said, a small proportion of patients do develop dyspnoea, and 12/98 (12.2%) did report substantial improvement in respiratory symptoms after embolization of PAVMs.[8] precipitating the current study.

METHODS

Study population assessments:

Between May 1999 and May 2018, study subjects were evaluated using established clinic methodologies,[9,17] (*LREC 2000/5764).* Spirometric measurements included forced expiratory volume in 1 second (FEV1) and non-forced ("slow") vital capacity (VC)) for new clinic patients, and where clinically indicated in follow up[30,31]. SpO_2 was measured by pulse oximetry (Ohmeda Biox 3900, Boulder, Colorado) while breathing room air and the mean SpO_2 calculated in the erect posture across minutes 7 to 10. We have shown this measure can be used as a surrogate for right-to-left shunt severity.[9,10] As described elsewhere[9,17], patients had same-day blood tests which included full blood counts and iron indices.

CPET cohort:

CPET studies recruited between May 2011 and September 2012 (NRES *11/H0803/9:* significant cardiorespiratory disease an exclusion criteria), and May 2015-April 2017 (*15/LO/0598*: significant airflow obstruction not an exclusion criterion). Studies were performed in the clinical service exercise physiology suite

on a Masterscreen CPX exercise system (Carefusion, Germany) as previously described.[13] Briefly, subjects underwent a progressive incremental test seated on a cycle ergometer breathing room air, with encouragement to achieve their perceived maximum.

Replication cohort:

The replication cohort assessed patients between March 2017 and May 2018. They completed the Veterans Specific Activity Questionnaire (VSAQ), a validated, self-reported, 13 point scale that permits calculation of the achieved metabolic equivalents (METs) where one MET is equal to the consumption of 3.5 ml O_2 per kilogram of body weight.[23,24] Minor UK-modifications were made to the text to facilitate patient familiarity [25].

Fractional exhaled nitric oxide (FeNO) has emerged as a point-of-care tool in managing allergic asthma,[26,27] and was introduced into PAVM clinic assessments in March 2017. FeNO has high positive and negative predictive value in identifying steroid-responsive airway inflammation,[28,29] and is better at predicting responses to inhaled corticosteroids than peak flow, spirometry or bronchodilation.[29] Measurements were made on a Bedfont NObreath® (Bedfont Scientific Ltd, Maidstone, Kent) .

Data Analysis

Arterial oxygen content CaO_2 in mls/dL was calculated by $SpO_2 \times hemoglobin \times 1.34/100$ where SpO_2 was expressed as a percent, and 1.34mls is the empirically determined amount of oxygen carried per gram of hemoglobin at sea level breathing room air.[11] Metabolic equivalents at peak exercise (METs) in kcal/kg/hour were calculated by $4.7+0.97(VSAQ)-0.06(age)$,[23] and for graphical illustrations, categorised by quintililes.

Incidental iron deficiency limits secondary erythrocytotic compensatory responses: as in [8], iron deficiency was assigned as absent (‘‘0’’) if serum ferritin, serum iron and transferrin saturation index (T*f*SI) were clearly normal (ferritin>20 mg/L; serum iron>11 mmol/L; T*f*SI>20%); present (‘‘1’’) if same-day ferritin was <15

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mg/L; and also assigned for individuals with both iron and T*f*SI clearly subnormal (<7 mmol/L and <20% respectively).[8]

STATA IC version 15.1 (Statacorp, Texas), was used to calculate distributions of participant-specific variables, to compare groups (using Mann Whitney, or Wilcoxon matched pairs signed rank test for pre-post bronchodilator measurements), for graphs, and for linear regression of biologically plausible associations in crude regression, and after adjustment for recognised confounders (peak-work rate for FEV1 and VC associations; anaerobic threshold for associations with V[dot]O_2peak and V[dot]EV[dot]CO_2 slope [13]).

RESULTS:

Overview of PAVM Cohort

Our serial adult databases included 611 PAVM patients in whom spirometry had been measured with a mean of 2.18 measurements per patient when aged 16-89 (median 47) years. 391 (64.4%) were female, and at least 503 (82%) had confirmed hereditary haemorrhagic telangiectasia (HHT). In this cohort, SpO_2 ranged from 50.75% to 100% (median 94.8%, interquartile range 91%-96%). As in previously published subgroups [8,10,25], arterial oxygen content (CaO_2) was generally maintained by secondary erythrocytosis and polycythaemia, but not in the presence of iron deficiency (***Figure 1*****).** The median vital capacity (VC) was 99% predicted (interquartile range 88%-110%), median FEV1 93% predicted (interquartile range 80%-103%), and median FEV1/VC ratio 93.8% (interquartile range 84.6, 1.00).

CPET Cohort

26 patients underwent CPET. The median age was 57ys (IQR 42, 66) years. 16 (61.6%) were female. Full demographics are provided in ***Supplementary Table 1*****,** emphasising often substantial right-to-left shunting resulting in SpO_2 of 79-99 (median 92%) at rest, and 72-99 (median 91)% at peak exercise. Haemoglobin

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ranged from 108g/L to 183g/L (median 156 g/L) reflecting both compensatory polycythaemia and iron deficiency Spirometric measurements are not usually made for pulmonary AVM cohorts where specific pathology is limited to the pulmonary vasculature, but these also varied substantially, with FEV1 55-120% predicted (median 98.5%), and VC 65-158% predicted (median 108%).

We have previously shown by CPET that normal oxygen delivery can be maintained in hypoxaemic patients with PAVMs[13]. In the current cohort, there was also no clear relationship between peak work rate and any oxygenation parameter.(***Table 1***). However, patients with lower FEV1, or lower VC achieved lower peak work rates (***Table 1***). Further, we showed that once adjusted for peak work rate, lower FEV1 and VC were associated with lower minute ventilation (V[dot]E), and lower breathing reserve at peak exercise, indicative of ventilatory-limited exercise capacity (***Supplementary Table 2***).

Step wise evaluations detailed in the Appendix (***Supplementary Tables 3,4***) indicated why low FEV1 or low VC, but not hypoxaemia were associated with exercise limitation. Briefly, ventilation per unit of CO_2 production is known to be greater in patients with more severe right-to-left shunts, resulting in a steeper V[dot]EV[dot]CO_2 slope.[13] However, the V[dot]EV[dot]CO_2slope displayed no relationship with FEV1 or VC in crude or anaerobic threshold-adjusted regression. We concluded that reduced FEV1 and VC were associated with reduced work rate, in the setting of, but not via, steeper V[dot]EV[dot]CO_2 slopes.

Contour plot analyses (***Figure 2***) suggested that patterns with work rate differed at approximately 80% predicted FEV1, and below 100% predicted VC. Below these thresholds, patients were not likely to achieve high normal predicted work-rates, and there seemed to be a stronger association between low SpO_2 and low work rates. Conversely, while supranormal work rates were feasible for patients with SpO_2 <90%, this appeared to only be the case for patients with FEV1 >100% predicted (***Figure 2a***) Similar findings were observed for vital capacity - again, supranormal V[dot]O_2 peak appeared to be feasible for patients with SpO_2 <90% only in the setting of a normal to high VC (***Figure 2b***).

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183 **Replication data in clinical practice**

184 The cohort of 71 patients with PAVMs completing the VSAQ were aged 20-85 (median 52) years. As presented
185 in[25], there was broad representation of exercise limitation across the 13 point activity scale resulting in METs
186 of 1.33-15.55 kcal/kg/hour. The very modest association between METs and oxygen saturation (SpO_2[25])
187 reflected a handful of individuals with the lowest exercise capacity (***Figure 3a***). As expected, arterial oxygen
188 content (CaO_2) was higher in patients with greater exercise capacity [8,13,25], and this primarily resulted from
189 differences in haemoglobin (***Figure 3b***).

190 Importantly, in crude regression, as for the CPET-measured indices, VSAQ-calculated METs were lower for
191 patients with lower FEV1, and this persisted after adjustment for CaO_2 (***Table 2***, ***Figure 3c)***. Once adjusted for
192 CaO_2, METS were also associated with VC, but not lower FEV1/VC ratio, and associations were maintained
193 using same-day or nearest values measurements (***Table 2, Figure 3d*)**.

194 There were further similarities between peak work rate by CPET and the VSAQ-calculated METs when 3-way
195 relationships were examined. Contour plots suggested that hypoxaemic patients only achieved high-normal
196 METs with FEV1 at least 70% of predicted (***Supplementary Figure 1***).

197

198 **Relevance to clinical management**

199 To test if the study cohorts had been unusual subgroups, we re-examined our serial databases of 1,329
200 spirometric measurements in 611 PAVM patients. In the 93 same-day bronchodilator responses, the mean
201 change in % predicted FEV1 and VC were 6.5% 5.0% respectively (***Figure 4a/b***). For every 1% predicted
202 increase in FEV1 there was a 0.47% (95% CI 0.26, 0.67)% predicted increase in VC, with similar increments
203 irrespective of the FEV1/VC ratio (***Figure 4c***), or original FEV1 (data not shown). The modest changes (***Figure***

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4d), would nevertheless equate to clinically meaningful increases of approximately 5% of predicted CPET work-rate, and ≥0.5 VSAQ score (≥9 kcal/kg/hour METS).

FeNO measurements identify patients in whom corticosteroid therapy may be beneficial. It was not clear this test could be applied to the PAVM population, due to potentially abnormal NO production from pulmonary vascular endothelial cells, particularly for those with HHT. However, in the tested cohort of 115 measurements, FeNO measurements were reproducible, and normal (<25ppb) in over 80% of cases (***Table 3***). Neither FeNO, nor natural log-transformed FeNO (that better fitted a Gaussian distribution), differed in relation to age, PAVM status, PAVM embolization, HHT status, SaO_2, FEV1, VC, or the FEV1/VC ratio (data not shown).

DISCUSSION

We have demonstrated that the achievable workload and exercise capacity of patients with PAVMs is strongly associated with the degree of airflow limitation, and not with hypoxaemia. Where there was work-rate limitation, this was usually ventilatory-limited, in contrast to expectations of cardiovascular limitations for hypoxaemic patients. Relationships with CPET-derived outcome measures were mirrored by metabolic equivalents calculated from the simple 13 point, patient-completed VSAQ which is suitable for all patients, whatever their perceived exercise capacity. In the replicate series, small (<10%) increments in FEV1 and VC were associated with clinically significant increases in exercise capacity. Conventional bronchodilator and fractional exhaled nitric oxide (FeNO) assessments provided clinically useful tools to optimize airflow management.

The strength of the study is the number of patients studied in replicate cohorts for a rare disease. The study builds on 30 years of published physiological data and observational studies to help solve the question of why patients with PAVMs and dyspnoea are rarely the most hypoxaemic. Study limitations include the "real life" nature of the series, resulting in absence of arterial blood gases (to ensure patient compliance, these have not been used in clinical or research practice since before 1999). Additionally we were not able to explore possible

contributions from pH, temperature or 2,3 DPG effects. On the other hand, this allowed us to formally demonstrate the suitability of VSAQ (introduced to enable measurement of finer granularities of "normal"[25]), exhaled nitric oxide measurements, and conventional spirometry/reversibility assessments performed in a single clinic visit.

Prior to this study, having demonstrated the lack of relationship between exercise capacity and hypoxaemia,[8,13,21] we had hypothesized that the main driver to exercise limitation would be cardiovascular, most likely higher pulmonary artery pressures.[8] While measurements were only available in the subgroup undergoing embolization, and values were within the normal range, we were still surprised that there was no relationship with exercise capacity or V[dot]O_2 peak. Instead, the stimulus for dyspnoea appears to relate to factors that impede the necessary increased minute ventilation required to clear CO_2 in the setting of a right-to-left shunt, and possible overshoots in correction.[13]

One quarter of the cohort had a vital capacity (VC) >120% predicted. It was not possible to evaluate in this study why some patients with PAVMs had supra-normal VC or FEV1, and whether this was due to chance, a result of athletic training in earlier life, or a physiological response to maturation in the setting of a steep V[dot]E/V[dot]CO_2 slope (PAVM development is usually complete soon after puberty). In adult life, vital capacity is thought to only be "increased" by limiting reductions due to pathologies or surgery. For FEV_1, bronchodilators clearly offer the possibility of an increase in the setting of airflow obstruction, but we were also able to demonstrate helpful increments in VC, and that both occurred in the settings of minimal airflow limitation or restriction.

Exhaled nitric oxide measurements supplement spirometric evaluations to guide on likely responses to inhaled corticosteroids: American Thoracic Society 2011 guidelines suggest that in adults, FeNO <25ppb and >50 ppb are strong indicators of likely steroid non-responsiveness and responsiveness respectively.[27] FeNO is a direct output of the Th2-mediated, pro-inflammatory cytokine cascade which underlies the pathophysiology of allergic airway inflammation- Th2 induced interleukin (IL)-4 and IL-13 upregulate inducible nitric oxide synthase

(iNOS) expression in bronchial epithelial cells via STAT-6, in a process which is corticosteroid sensitive.[33,34] However, NO is also produced by vascular endothelial cells in the respiratory tract, and there have been reports that FeNO is higher in patients with HHT.[35] Fortunately the reported mean increase was only 1.5ppb[35], not impacting on the clinically distinguishing 25ppb scale units.[27]

In summary, these data emphasize again that despite the highly abnormal values often observed in PAVM patients, SpO_2 is of minimal value in explaining dyspnoea in isolation. However, relatively mild airflow limitation, whether restrictive or obstructive, is associated with reduced exercise capacity in patients with PAVMs, likely by limiting the exuberant minute ventilation required to exhale CO_2. For patients with large right-to-left shunts, even normal ventilatory capacity may be suboptimal, and if symptomatic, a trial of bronchodilation appears to us to be appropriate. Standard spirometric assessments, supplemented by FeNO and a VSAQ questionnaire, provide sufficient information to direct PAVM patients towards clinically relevant bronchodilator therapy, and facilitate objective follow-up.

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Contributions:

Conception and design: FG, TS, VS, JB, LH, CLS. Analysis and interpretation: FG, TS, AA, ST, JM, JB, LH, HT CLS; Drafting the manuscript for important intellectual content: CLS. *In detail:* FG generated the 2017-2018 database, introduced the VSAQ and FeNO PAVM clinic assessments, performed literature studies, generated the observational database and drafted manuscript sections. TS performed literature studies, assisted in obtaining ethical approvals to recruit patients with airflow obstruction, added to the PAVM CPET database, performed initial PAP analyses, and drafted manuscript sections. AA identified the work rate and peak VO_2 associations with FEV1 and drafted manuscript sections. JP and HT co-supervised AA and ST and performed and interpreted data measurements; ST performed literature studies and added to the PAVM CPET database; AR contributed to generation of the observational PAVM database; JEJ reviewed patients, performed PAVM embolizations from 1988 and contributed to data interpretation; VS performed literature studies, contributed to generation of the observational PAVM database, assisted in obtaining initial ethical approvals to recruit patients without airflow obstruction, and initiated the PAVM CPET database; JM generated the VSAQ, advised on physiological concepts, and contributed to data interpretation; JB introduced FeNO methodologies to the pulmonary function laboratory, contributed to data interpretation, and drafted manuscript sections; LH co-

supervised VS, ran the CPET laboratory, and contributed to data interpretation; HT instituted data measurements, ran the Lung Function laboratory, co-supervised AA and ST, and contributed to data collection and interpretation. CLS devised the study; supervised all students, reviewed all patients, performed literature searches, analysed and interpreted data, performed all presented data analyses, generated the Tables and Figures, and wrote the final manuscript. All authors contributed to and approved the final version of this manuscript.

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***Table 1*: Key relationships with work rate at peak exercise**

	N	Linear Regression coefficient (95% confidence intervals)	adjusted r^2	p-value
SpO_2 rest, %	26	0.20 (-0.007, 0.046)	0.05	0.14[1]
SpO_2 peak exercise, %	26	0.011 (-0.007, 0.029)	0.01	0.23[1]
Haemoglobin	26	0.018 (-0.046, 0.082)	-0.027	0.56[2]
CaO_2 (mls/L)	26	0.031 (-0.012, 0.073)	0.04	0.16[3]
FEV1, % predicted	**26**	**0.0088 (0.0018, 0.016)**	**0.19**	**0.016[4]**
VC, % predicted	**26**	**0.0064 (0.001, 0.012)**	**0.17**	**0.021[5]**
FEV1/VC, %	26	-0.0035 (-0.017, 0.0094)	-0.028	0.58[1]
Peak V[dot]O_2, mls/min/kg	**26**	**0.019 (0.008, 0.031)**	**0.29**	**0.002**
Peak V[dot]O_2, % predicted	**26**	**0.012 (0.009, 0.014)**	**0.79**	**<0.0001**
V[dot]EV[dot]CO_2 slope	**26**	**-0.17 (-0.28, -0.005)**	**0.25**	**0.0056[6]**
Anaerobic threshold	**26**	**0.016 (0.0088, 0.022)**	**0.47**	**0.0001[7]**
Minute ventilation (L/min)	26	0.004 (-0.0027, 0.012)	0.027	0.21
Peak end tidal PCO_2 (kPa)	**26**	**0.13 (0.0029, 0.26)**	**0.12**	**0.045**
Heart rate reserve (%)	**26**	**-0.013 (-0.021, -0.005)**	**0.31**	**0.002**
Breathing reserve (%)	26	-0.0045 (-0.012, 0.003)	0.03	0.21
Respiratory exchange ratio (RER)	26	0.20 (-1.27, 1.68)	-0.038	0.78
PAP mean (mmHg) *	19	-1.36 (-5.1, 2.37)	0.02	0.45
PAP systolic (mmHg) *	19	-0.71 (-2.61, 1.19)	-0.02	0.44
PAP diastolic (mmHg) *	19	-0.61 (-5.25, 4.03)	-0.05	0.78

FEV1 and VC were recorded using a Zan 100 spirometer (Zan Messergäte GmbH, Germany): predicted values were calculated from ERS/ECCS 1993 reference equations.[32]. The participants had continuous electrocardiogram and pulse oximetry monitoring ; breath-by-breath measurements of ventilatory and metabolic variables (recorded for this manuscript at start and end only); and intermittent automated blood pressure recordings (Masterscreen CPX exercise system (Carefusion, Germany). The load on the bicycle (work rate) was increased as a continuous ramp, at a ramp rate estimated to result in a work phase of 8-12 minutes. Natural log-transformation of work-rate resulted in a more Gaussian distribution, and hence it was used as the as outcome variable in the above models. Quadratic regression p values were broadly similar ([1] >0.40; [2] 0.15; [3] 0.12; [4] 0.021, [5] 0.29; [6] 0.008; [7] 0.001). FEV1 and VC were strongly associated (Spearman rho 0.79, p<0.0001), and multiple regression did not suggest which, if either, was more strongly associated with work rate. Relationships with p-value <0.05 shown in bold
* Reported pulmonary artery pressures (PAP) were measured in 19/26 (73.1%) patients undergoing embolization, recorded by a centrally-placed catheter prior to contrast medium injection.[5,22] The interval between embolization/CPET measurements was 0-122 (mean 10) months.

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Table 2: Replicate cohort exercise capacity associations

			Crude regression				Same day CaO_2 adjusted regression	
METs via VSAQ†	**N**	**Regression coefficient**	**adjusted r^2**	**p-value**	**N**	**Regression coefficient**	**adjusted r^2**	**p-value**
Same day FEV1	**55**	**0.086 (0.032, 0.14)**	**0.17**	**0.002**	**48**	**0.00086 (0.00033, 0.0014)**	**0.32**	**0.002**
Same day VC	55	0.041 (-0.011, 0.092)	0.026	0.12	**48**	**0.00097 (0.00042, 0.0015)**	**0.23**	**0.001**
Same day FEV1/VC ratio	55	7.6 (-1.57, 16.8)	0.032	0.10	48	4.41 (-5.2, 14.0)	0.17	0.36
Nearest FEV1	**62**	**0.070 (0.017, 0.123)**	**0.086**	**0.011**	**54**	**0.00091 (0.00044, 0.0014)**	**0.34**	**0.002**
Nearest VC	62	0.047 (-0.0022, 0.098)	0.05	0.060	**54**	**0.00098 (0.00048, 0.0015)**	**0.26**	**0.035**
Nearest FEV1/VC ratio	62	6.99 (-2.04, 16.01)	0.023	0.13	54	2.65 (-6.35, 11.65)	0.19	0.56

METS, metabolic equivalents calculated from the self-reported VSAQ score by 4.7+0.97(VSAQ)−0.06(age),[24], † using UK-modified scale.[25]

Relationships with p-value <0.05 shown in bold

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Table 3 : Exhaled nitric oxide (FeNO) measurement reproducibility in PAVM patients

	Overall	***<25ppb***	***25-50ppb***	***>50ppb***
Usual interpretation		No ICS	Borderline	ICS Rx
Number of datasets	202	165 (81.6%)	28 (13.9%)	9 (4.5%)
FeNO (ppb): mean (SD)	18.2 (14.7)	12.7 (5.8)	34.2 (6.6)	69.3 (17.55)
SD of 3 FeNO replicates: mean (SD)	2.78 (2.7)	2.15 (1.7))	4.14 (2.7)	10.1 (5.4)

Legend: Exhaled nitric oxide (FeNO) values were measured on 3 consecutive occasions on the same day. To illustrate reproducibility across all severities of FeNO, datasets were divided into clinically used categories. SD, standard deviation; ppb, parts per billion.

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Figure 1: Relationship between arterial oxygen content and oxygen saturation (SpO_2) in full PAVM cohort

CaO_2 across all degrees of hypoxaemia was calculated by SpO_2 x haemoglobin x 1.34/100, where SpO_2 was expressed as a %, and 1.34mls is the amount of oxygen carried per gram of haemoglobin.[20] The bold black line represents the regression line for all patients, irrespective of iron status (p=0.87). Grey circles/dotted line/shaded 95% confidence interval represent patients without iron deficiency (p=0.27). Red diamonds/dotted line/shaded 95% confidence interval represent patients with iron deficiency (p=0.27). Iron deficiency was usually a result of HHT-related blood losses, particularly nosebleeds.

Figure 2: Three-way relationships between peak work rate, airflow and SpO_2

Contour plot representing 3-way relationship between SpO_2, spirometric values, and CPET-derived work rate illustrated by colour-defined, linear scales: 80-100% predicted work rate indicated by greens, >100% predicted by yellows to reds, and <80% predicted by increasingly deeper blue colours. **a)** Forced expiratory volume in 1 second (FEV1), oxygen saturation measured by pulse oximetry after 7-10 minutes standing (SpO_2), and work rate**. b)** Vital capacity (VC), SpO_2 and work rate. The lowest peak work rates are seen in the lower left corner and no yellow/red colours are seen at <80% predicted FEV1, or <100% predicted VC. Supranormal work rates are seen for SpO_2 of ~80% but only on the far right where FEV1/VC are >100% predicted.

Figure 3: Graphical illustrations of associations with METS

Same-day measurements categorised by METS quintile boundaries at 5, 7, 10, and 12.5 kcal/kg/hour. **a)** oxygen saturation measured by pulse oximetry after 7-10 minutes standing (SpO_2), **b)** Calculated arterial oxygen content (CaO_2), **c)** forced expiratory volume in 1 second (FEV1), **d)** Vital capacity (VC).

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Figure 4. Same-day bronchodilator responses in 72 PAVM patients studied due to same-day evidence of possible airflow obstruction

Reversibility assessments were performed where clinically indicated (most commonly reduced FEV1, reduced FEV1/FVC ratio or curvature on the expiratory limb of the flow volume loop suggesting airflow obstruction). The post bronchodilator measurements were made 20-30 minutes following inhaled or nebulized salbutamol according to clinical protocols at the time, usually within 2 hours of the pre-bronchodilator measurements. **A)** FEV1 and **B)** VC using only one measurement per patient (72 datapoints). **C)** Change in FEV1 (as % of predicted value) by FEV1/VC in all data (93 datapoints). **D)** Change in FEV1 and VC (as % of predicted value), all 93 datapoints. Error bars indicate mean and standard deviations**.**

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