

Cardiopulmonary exercise testing demonstrates maintenance of exercise capacity in hypoxemic patients with pulmonary arteriovenous malformations

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eTable 1: Descriptive statistics of control group at rest and on exercise**Variables (median (Q1, Q3))****Resting demographics**

Age (yr)	43 (36.5,54)
Gender (% male)	50
Body mass index (kg/m ²)	25.6 (23.6, 27.3)
Resting SaO ₂ (%)	97.5 (96, 99)
FEV1 (L)	3.61 (3.00, 4.88)
FEV1/VC (%)	77.5 (71, 80)
Hemoglobin (g/dl)	14,1 (13,14.65)
Arterial oxygen content (mls/L)	18.3 (16.7, 19.1)
End tidal PCO ₂ (kPa)	4.5 (4.3, 5.2)
Bicarbonate (mmol/L)	24 (23,26)

Exercise demographics

Peak heart rate (min ⁻¹)	175 (167, 184)
Maximum work rate (W)	196 (165, 282)
Maximum work rate as percent of predicted † (%)	128 (116, 162.5)
End-exercise SaO ₂ (%)	97 (96, 98)
End tidal PCO ₂ at maximum exercise (kPa)	4.6 (4.5, 5.2)
Peak $\dot{V}O_2$ (mL O ₂ /min)	2562 (1868, 3565)
Peak $\dot{V}O_2$ as percent of predicted† (%)	118 (110, 128.5)
O ₂ pulse peak (mL O ₂ consumed per heart beat†)	14.85 (11.5, 19.2)
Anerobic threshold (% of predicted peak $\dot{V}O_2$)	0.64 (0.60, 0.75)
End tidal PCO ₂ at anerobic threshold (kPa)	4.5 (4.3, 5.2)
Ventilatory equivalent for CO ₂ (EqCO ₂) at nadir	25.3 (23.7, 27)
$\dot{V}E/\dot{V}CO_2$ slope (l/min/l/min)	24.4 (22.3, 27.1)
Heart rate reserve (%)	1.5 (-2.5, 7)
Breathing reserve (%)	27 (14.5, 39.5)
Respiratory exchange ratio (max RER)	1.21 (1.16, 1.28)

Demographics and key CPET data for the 12 controls most closely age-matched to the PAVM patients. Note that as in other studies,¹ the self-selected volunteer control group was not a suitable control group, because of better pre-test conditioning, evidenced by supranormal anerobic threshold and peak $\dot{V}O_2$ distributions. All 12 stopped because their legs were unable to keep up with the work rate. † Predicted accorded to participants age and gender. Note that 3 of these controls had asthma (well controlled).

eTable2:

	Regression coefficient (95% confidence interval)	p value
Demographics		
Age (yr)	-0.0044 (-0.013, 0.004)	0.27
Gender (% male)	0.01 (-0.23, 0.25)	0.93
Body mass index (kg/m ²)	-0.019 (-0.05, 0.01)	0.23
FEV1/VC (%)	-0.00029 (-0.009, 0.008)	0.95
Resting SaO ₂ (%)	0.17 (-0.007, 0.41)	0.157
Hemoglobin (g/dl)	0.028 (-0.025, 0.08)	0.29
Resting bicarbonate (mmol/l)	-0.009 (-0.044, 0.025)	0.59
Exercise parameters		
End-exercise SaO ₂ (%)	0.009 (-0.01, 0.028)	0.33
Heart rate at maximum exercise (min ⁻¹)	0.008 (0.00061, 0.016)	0.036
O ₂ Pulse at peak exercise (mls/beat)	0.0060 (0.0017, 0.010)	0.009
Peak $\dot{V}O_2$ (ml/min ²)	0.00014 (0.000026, 0.00026)	0.020
Peak $\dot{V}O_2$ (% predicted)	0.0095 (0.006, 0.0130)	0.001
Anerobic threshold (% of peak $\dot{V}O_2$ ³)	1.03 (0.33, 1.72)	0.006
Respiratory exchange ratio	0.03 (-1.18, 1.24)	0.96
End tidal CO ₂ at rest (kPa)	0.13 (-0.045, 0.32)	0.133
End tidal CO ₂ at anaerobic threshold (kPa)	0.10 (0.013, 0.19)	0.027
End tidal CO ₂ at maximum exercise (kPa)	0.097 (-0.007, 0.20)	0.067
Minute ventilation ($\dot{V}E$, % predicted)	-0.0005 (-0.0070, 0.005)	0.88
Breathing reserve (BR max%)	0.00048 (-0.0060, 0.0070)	0.88
$\dot{V}E/\dot{V}CO_2$ slope (l/min/l/min)	-0.012 (-0.023, -0.0010)	0.035
Respiratory compensation point†	-0.013 (-0.024, -0.002)	0.027

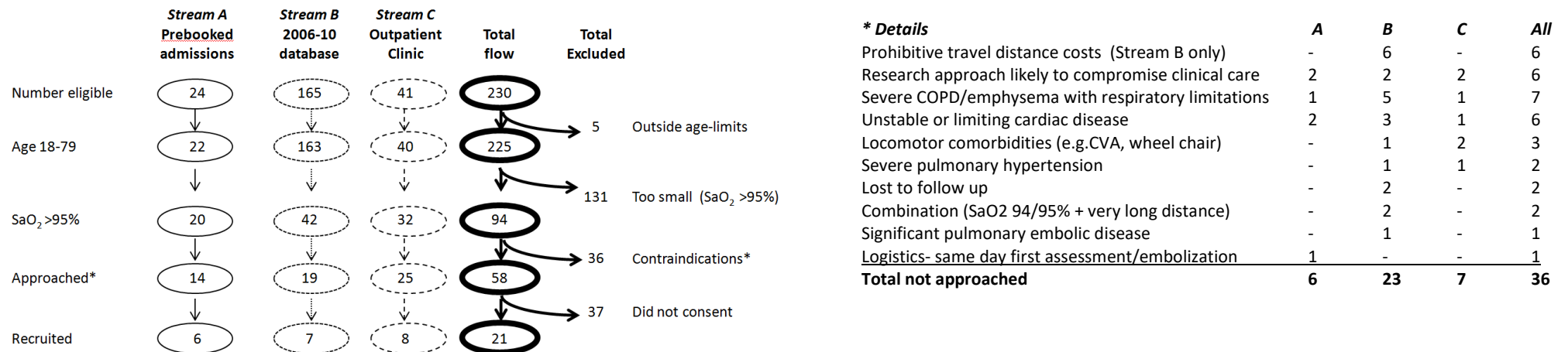
Univariate associations with log transformed (ln) maximum work rate on cardiopulmonary exercise testing in PAVM patients. Log transformed (ln) maximum work rate was used as the dependent variable because the distribution of maximum work rate was skewed, and normalised by log transformation. Presented data are for 14 males, 6 females, p values <0.05 shown in bold. Data exclude one outlier identified by normal quantile plots, but similar results were obtained including the outlier. † Also known as the Ventilatory equivalent for CO₂ at nadir. FEV1, forced expiratory volume in 1 second; VC, vital capacity; SaO₂, oxygen saturation measured by pulse oximetry; O₂ pulse, mL of oxygen consumed per heart beat; Peak $\dot{V}O_2$, peak oxygen consumption; $\dot{V}CO_2$, increase in CO₂ output. See references¹⁻⁴ for further explanations.

eTable 3:

Peak $\dot{V}O_2$ (% predicted)	Regression coefficient (95% confidence interval)	p value
Demographics		
Demographics		
Age (yr)	-0.28 (-1.01, 0.44)	0.43
Gender (% male)	13.9 (-5.9, 33.6)	0.16
Body mass index (kg/m ²)	0.64 (-2.21, 3.49)	0.65
FEV1/VC (%)	0.098 (-0.66, 0.86)	0.78
Resting SaO ₂ (%)	1.83 (-0.18, 3.83)	0.07
Haemoglobin (g/dl)	3.72 (-0.64, 8.07)	0.09
Resting bicarbonate (mmol/l)	-0.24 (-2.74, 2.24)	0.83
Exercise parameters		
End-exercise SaO ₂ (%)	1.36 (-0.22, 2.94)	0.087
Heart rate at maximum exercise (min ⁻¹)	0.29 (-0.049, 0.63)	0.089
O ₂ Pulse at peak exercise (ml/beat)	0.64 (0.32, 0.95)	<0.001
Anaerobic threshold (% $\dot{V}O_2$ peak)	112 (62.7, 162.4)	<0.001
Respiratory exchange ratio	8.15 (-96.6, 112.9)	0.87
End tidal CO ₂ at rest (kPa)	20.1 (6.83, 33.3)	0.005
End tidal CO ₂ (PETCO ₂) at anaerobic threshold	14.1 (8.33, 19.8)	<0.001
End tidal CO ₂ (PETCO ₂) at maximum exercise	13.2 (5.5, 20.78)	0.002
Minute ventilation ($\dot{V}E$, % predicted)	0.21 (-0.76, 0.35)	0.44
Breathing reserve	-0.21 (-0.76, 0.34)	0.44
$\dot{V}E/\dot{V}CO_2$ slope	-1.61 (-2.36, -0.86)	<0.001
Respiratory compensation point†	-0.13 (-0.024, -0.0016)	0.027

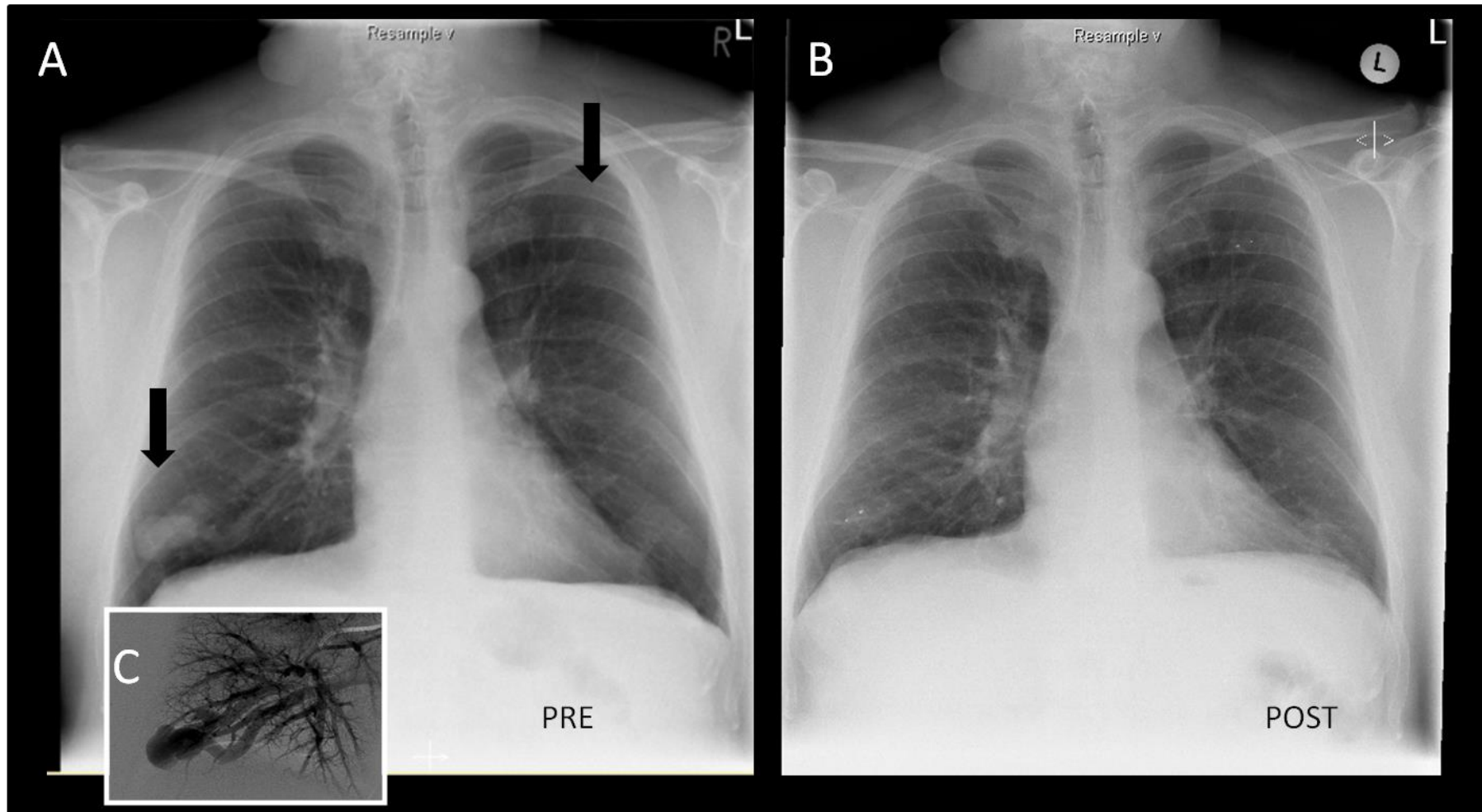
Univariate associations with peak $\dot{V}O_2$ on cardiopulmonary exercise testing in 21 PAVM patients. The distribution of peak $\dot{V}O_2$ was skewed by log transformation. Data presented for all 15 males, 6 females, with p values <0.05 shown in bold. †Also known as the Ventilatory equivalent for CO₂. FEV1, forced expiratory volume in 1 second; VC, vital capacity; SaO₂, oxygen saturation measured by pulse oximetry; O₂ pulse, mL of oxygen consumed per heart beat; Peak $\dot{V}O_2$, peak oxygen consumption; $\dot{V}CO_2$, increase in CO₂ output.

eFigure 1: Study Flow Chart



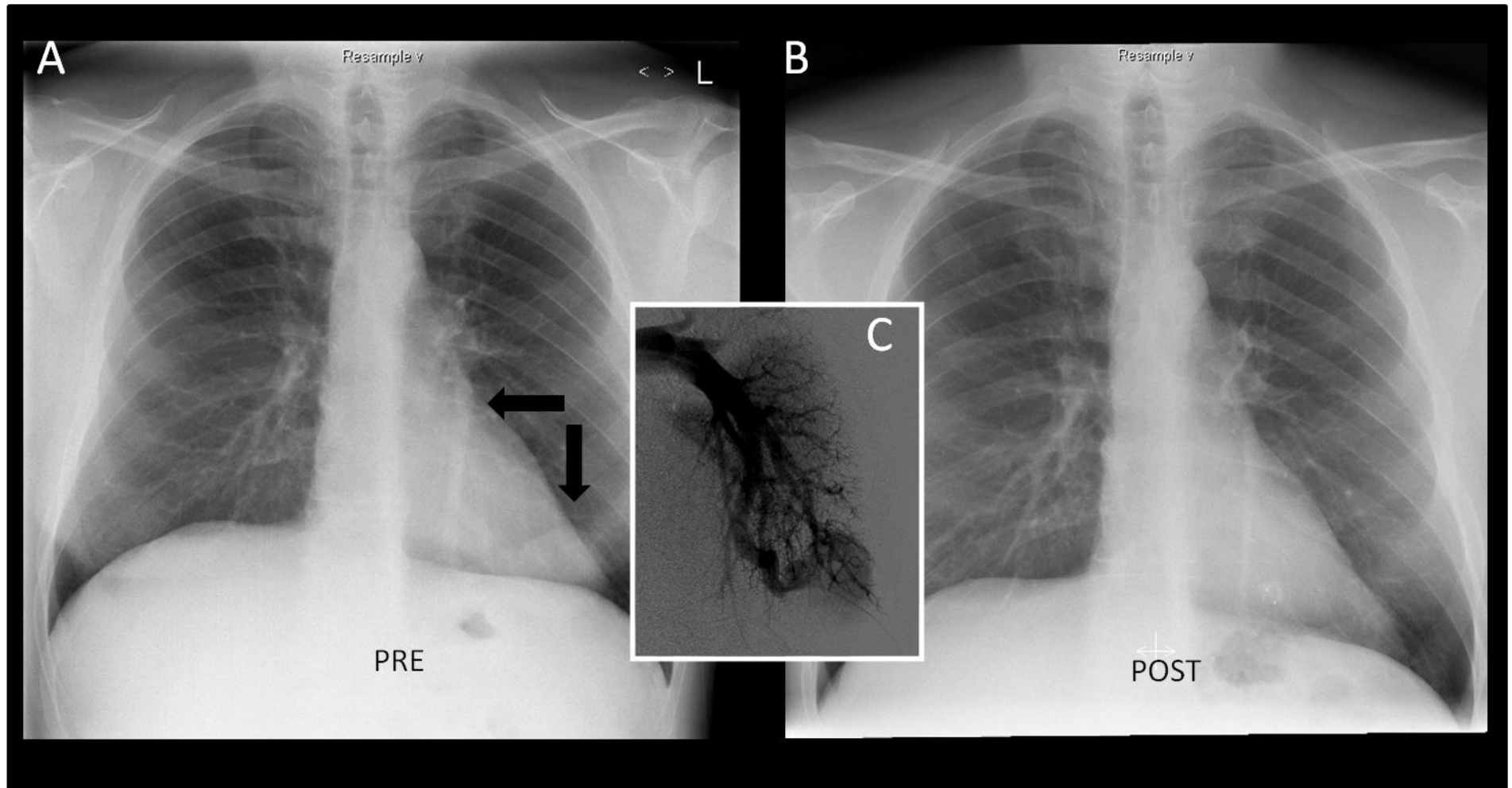
Legend: Subjects were recruited April 2011 to November 2012 through three streams: **Stream A)** Planned admissions for PAVM embolization (recruitment curtailed in November 2011 to allow for follow up). The assessment results of patients scheduled for embolization were reviewed, and appropriate patients approached with the Study information letter. (In keeping with international practice, embolization is recommended to reduce strokes^{5,6} and other PAVM complications⁷). Consenting patients were studied on the day before their embolization procedure, and at the time of their follow up clinic appointment. An unrelated severe illness prevented one individual from performing the planned repeat study post embolization. **Stream B:** The database of all 165 patients in the 2006-2010 PAVM database⁸ was reviewed, and appropriate patients approached with the Study information letter. Consenting patients were studied at their next clinic visit (if scheduled), or on a separate visit offered to patients who lived within England, and within reasonable travel distance of our center. **Stream C:** Evaluation at time of Outpatient visit on days when the Exercise Physiology Suite had capacity. Notes and/or referral letters of patients due to come to clinic were reviewed prior to clinic attendance. Number eligible: Number of patients with PAVMs confirmed by CT scans in the three separate streams. To be considered for the study, patients had to meet the study age requirements, and not have cardiorespiratory, locomotor, or other disease states considered likely to impact on a maximal cardiopulmonary exercise test (see details*). Additionally, patients were only considered for the study if they had evidence of significant right-to-left shunting with their most recently measured SaO₂ (erect) not exceeding 95% on air.⁸ Of the 58 selected patients who were approached, 37 did not consent to the study. The 21 patients recruited were split into tertiles of n=7 for graphical comparisons. These 21 patients included the five who were restudied after embolization.

eFigure2A



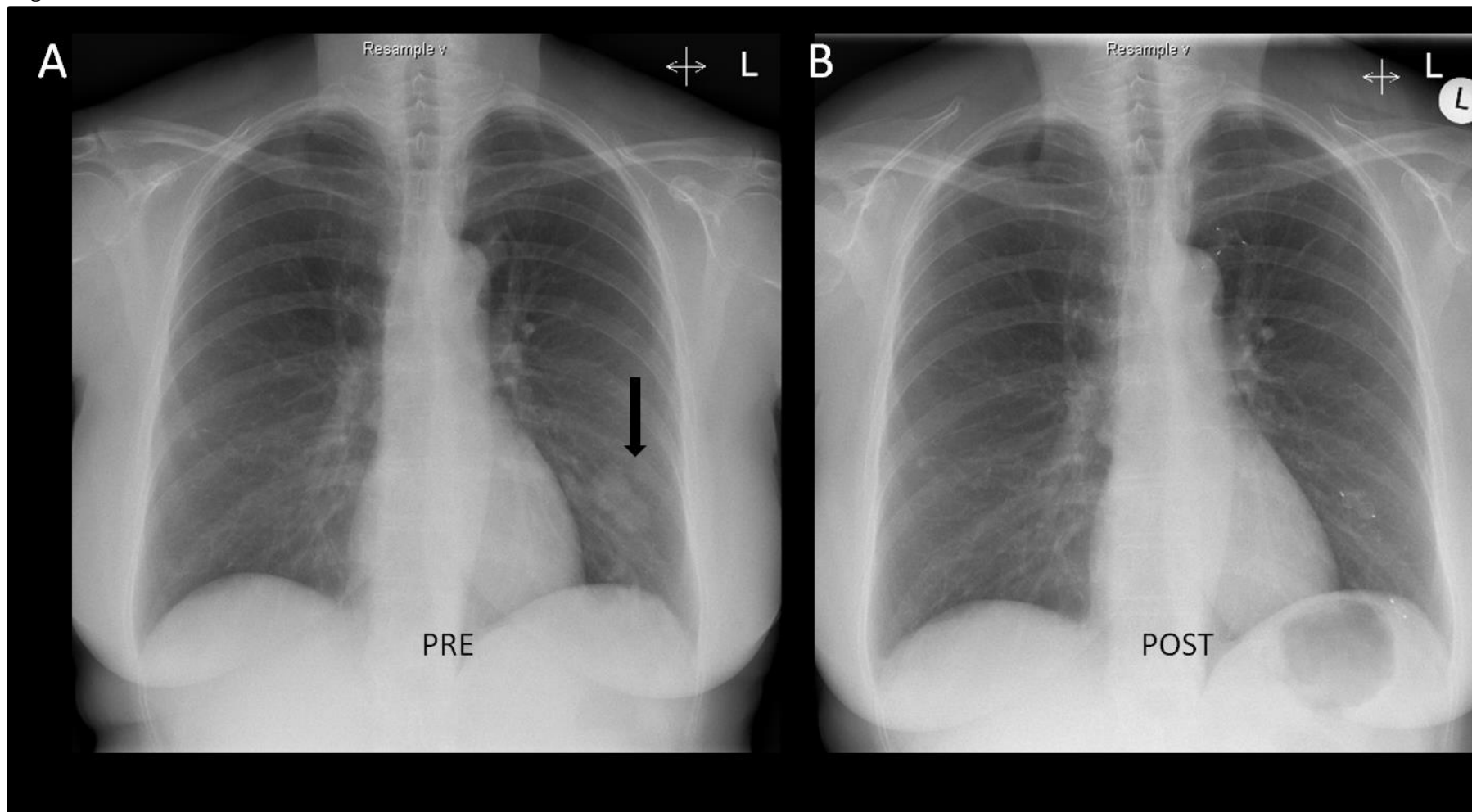
Case #1: Chest radiographs 1 month before (A) and 12 months after (B) embolisation. Original PAVMs arrowed in (A); Inset (C), demonstrates angiographic appearance of largest PAVM prior to embolisation.

eFigure2B



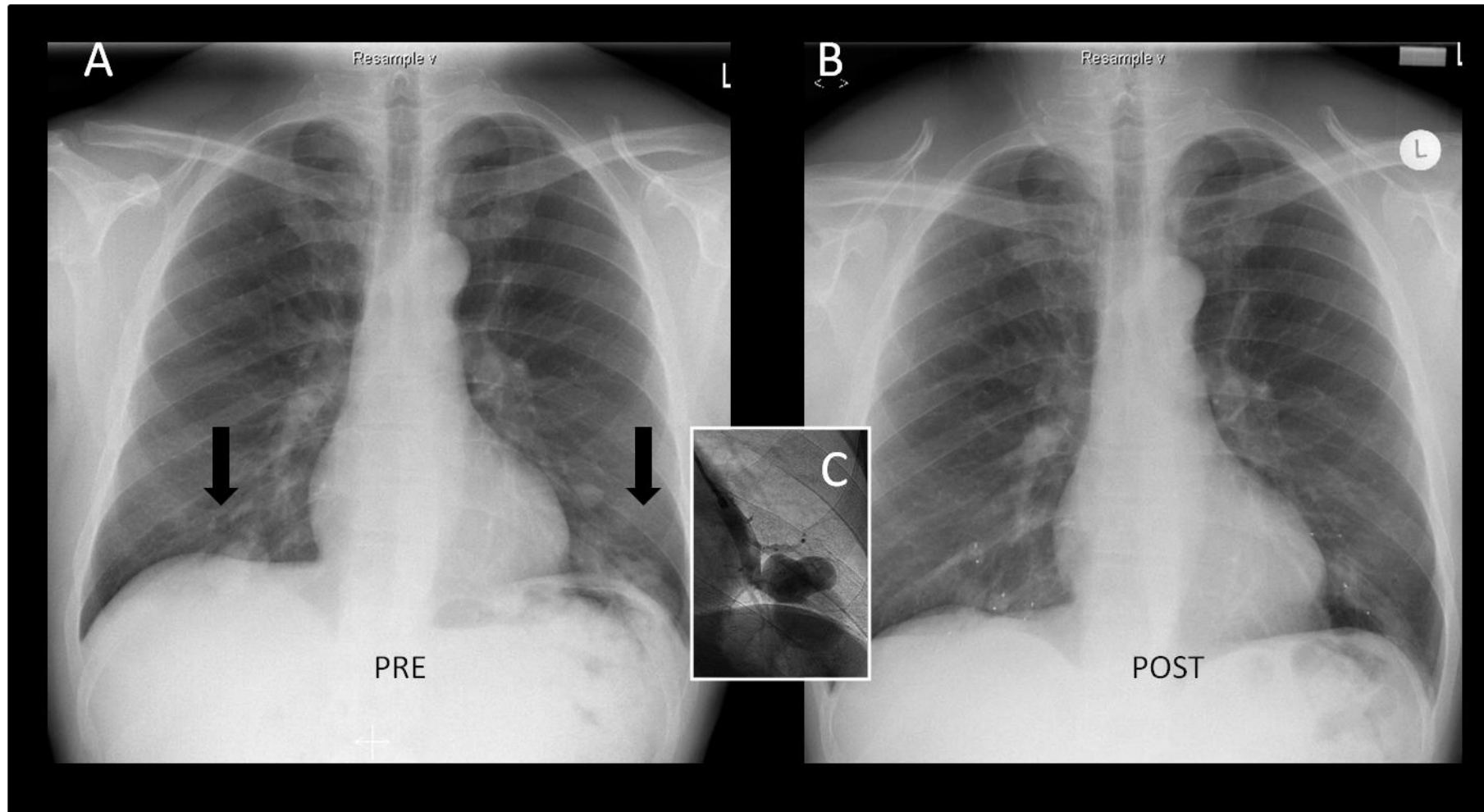
Case #2: Chest radiographs 6 weeks before **(A)** and 7 months after **(B)** embolisation. Original PAVM and large draining vein arrowed in **(A)**; Inset **(C)**, demonstrates angiographic appearance of PAVM prior to embolisation.

eFigure2C



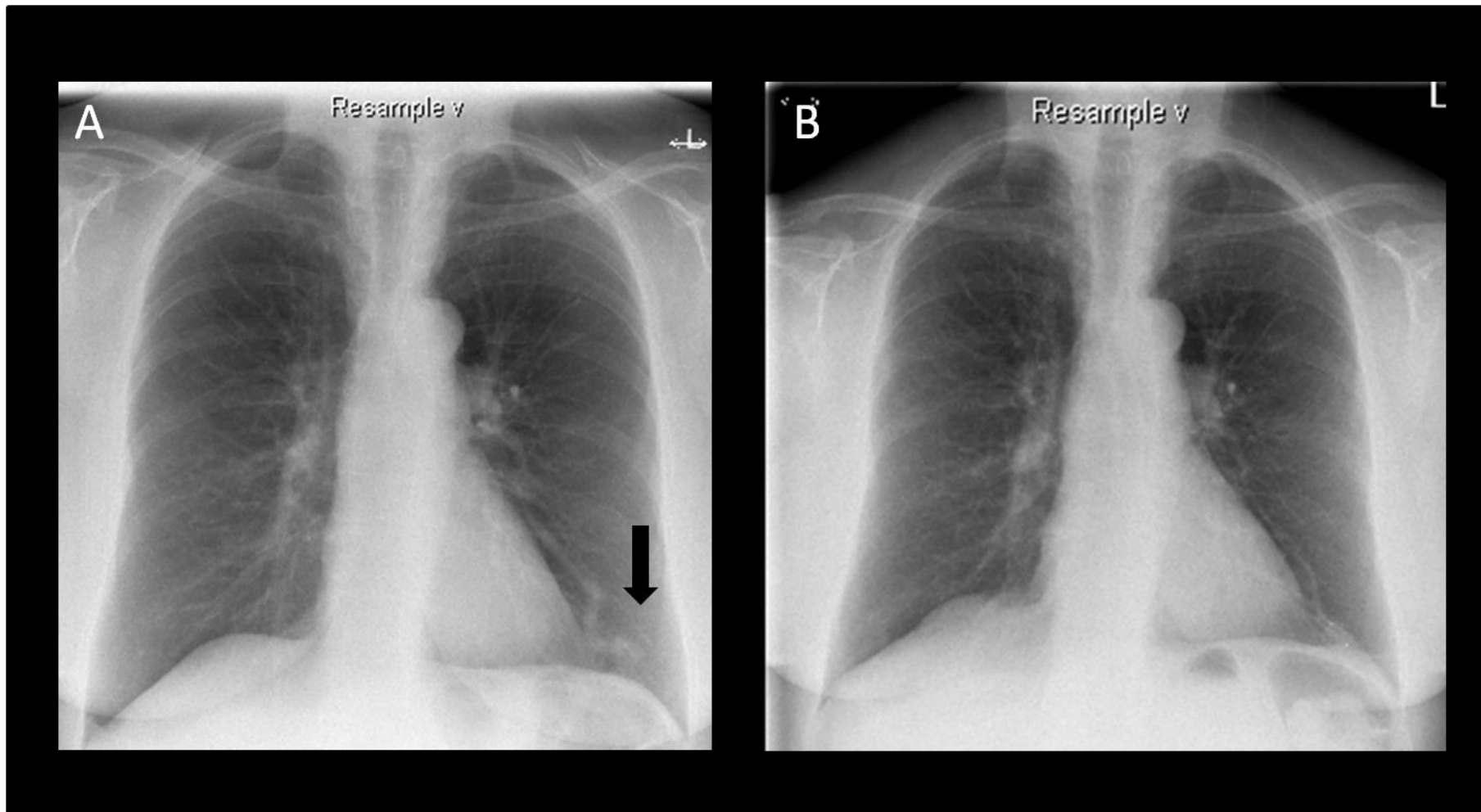
Case #3: Chest radiographs immediately before (A) and 6 months after (B) embolisation. Largest original PAVM vein arrowed in (A).

eFigure2D:



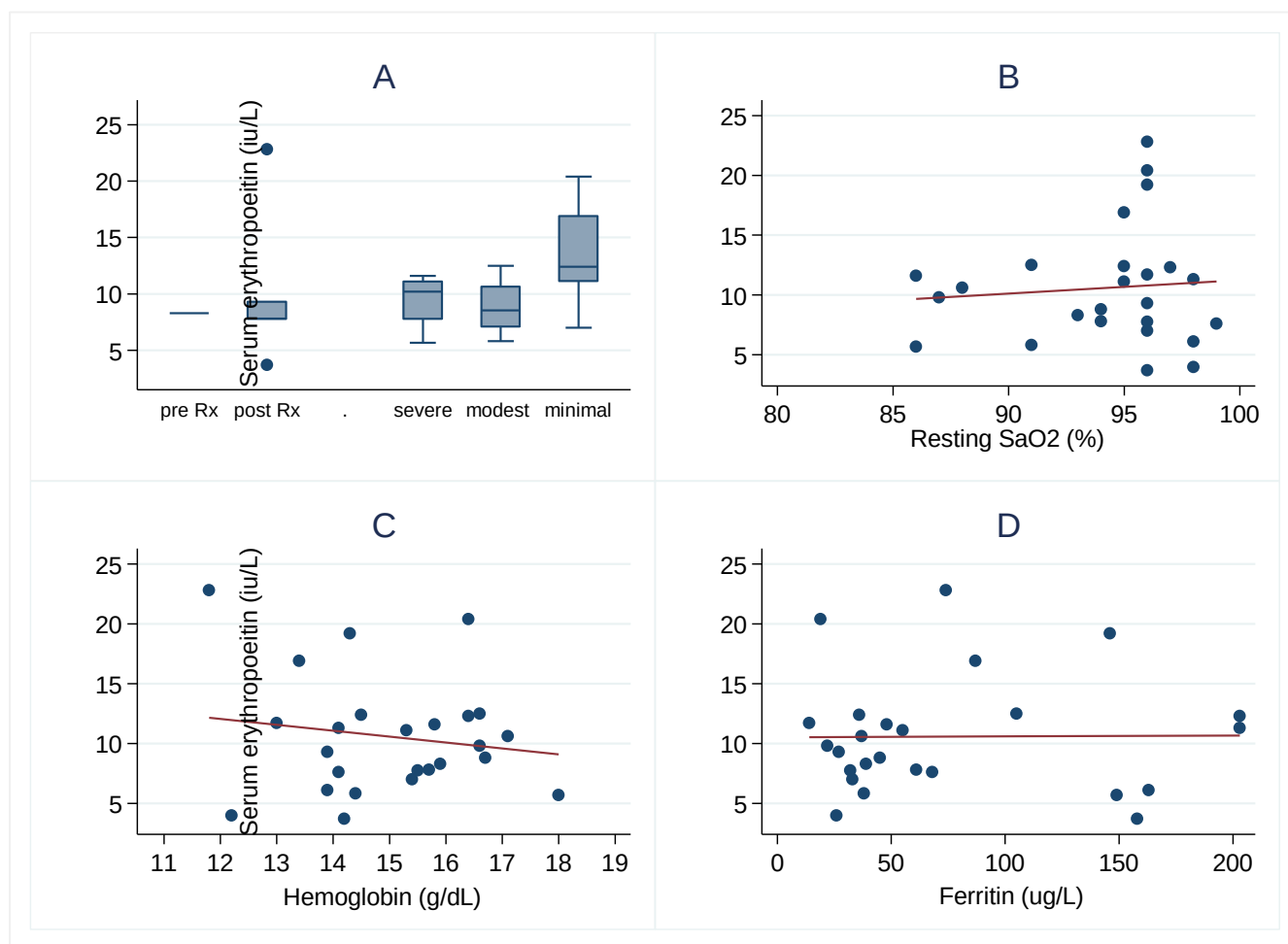
Case #4: Chest radiographs 3 months before **(A)** and 4 months after **(B)** embolisation. Largest PAVMs arrowed in **(A)**; Inset **(C)**, demonstrates angiographic appearance of large left sided PAVM prior to embolisation.

eFigure2E:



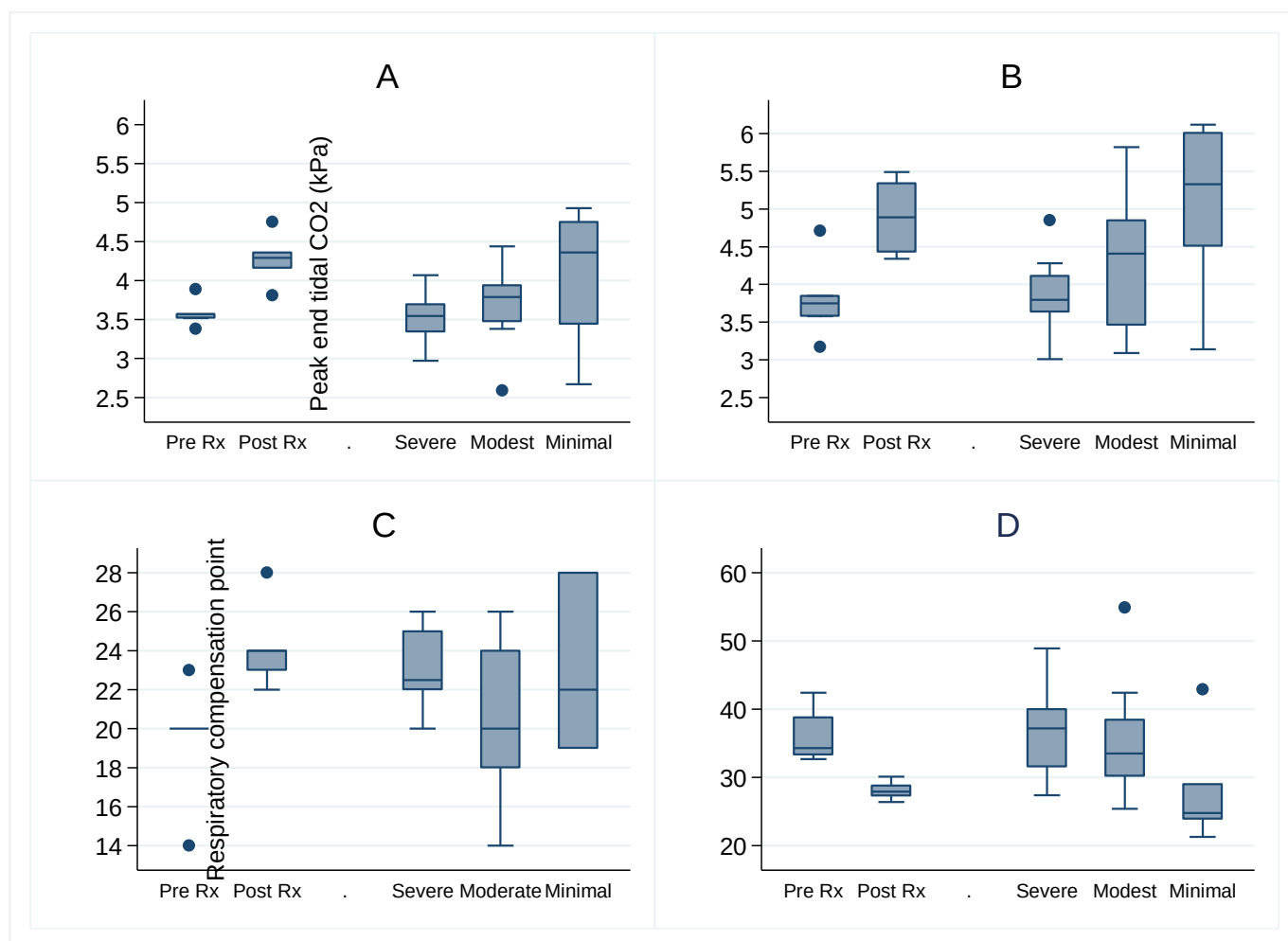
Case #5: Chest radiographs 1 month before (A) and 3 months after (B) embolisation. Large PAVM arrowed in (A).

-Figure 3



Serum erythropoietin: No erythropoietin value exceeded the normal range, and by Spearman correlation and regression analyses, there was no relationship between erythropoietin and SaO₂, (A, B) hemoglobin (C), ferritin (D) or hematinic variables (data not shown). **A)** Box plot comparisons for erythropoietin versus PAVM stratification as in main Figure 1. **B)** Erythropoietin versus resting SaO₂, $r^2=0.0076$, $p=0.68$: note the trend is the opposite to what might be expected. **C)** Erythropoietin versus hemoglobin, $r^2=0.025$, $p=0.46$. **D)** Erythropoietin versus ferritin, $r^2=0.0001$, $p=0.97$.

eFigure 4



In each graph, the left hand two box plots indicate PAVM patients stratified pre and post embolization (Rx); the right hand three box plots indicate PAVM patients stratified into tertiles by severity of resting hypoxemia seated: severe (SaO₂ 80-88%), modest (SaO₂ 90-94%) and minimal (SaO₂ 95-96%). Boxplots indicate median, interquartile range, and two standard deviations for variables, with dots at extremes representing outliers. **A)** Resting end tidal CO₂. **B)** End exercise end tidal CO₂. **C)** Serum bicarbonate. **D)** Respiratory compensation point.

eREFERENCES

1. Neder JA, Nery LE, Castelo A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. *Eur Respir J* 1999; **14**: 1304-1313
2. Mezzani A, Agostoni P, Cohen-Solal A, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2009;**16** :249–67.
3. Koch B, Schäper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. *Eur Respir J*. 2009;**33**: 38997.
4. Hughes JMB. Physiology and Practice of Pulmonary function. ARTP, Boldmere 2009. ISBN 978-0-9536898-5-9
5. Shovlin CL, Jackson JE, Bamford KB, et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. *Thorax* 2008; **63**: 259-66
6. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets *PLoS ONE* 2014 *in press*
7. Shovlin CL, Wilmschurst P, Jackson JE. Pulmonary arteriovenous malformations and other pulmonary aspects of hereditary haemorrhagic telangiectasia. *Eur Respir Mon* 2011; **54**: 218–245
8. Santhirapala V, Williams LC, Tighe H, Jackson JE, Shovlin CL. Arterial oxygen content is precisely maintained by graded erythrocytotic responses in settings of high/normal serum iron levels, and predicts exercise capacity. An observational study of hypoxaemic patients with pulmonary arteriovenous malformations. *PLoS ONE* 2014 *in press*.