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# Cardiopulmonary Exercise Testing Demonstrates Maintenance of Exercise Capacity in Patients With Hypoxemia and Pulmonary Arteriovenous Malformations

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**BACKGROUND:** Patients with pulmonary arteriovenous malformations (PAVMs) are unusual because hypoxemia results from right-to-left shunting and not airway or alveolar disease. Their surprisingly well-preserved exercise capacity is not generally appreciated.

**METHODS:** To examine why exercise tolerance is preserved, cardiopulmonary exercise tests were performed while breathing room air in 21 patients with radiologically proven PAVMs, including five restudied 3 to 12 months after embolization when their PAVMs had regressed. Where physiologic matching was demonstrable, comparisons were made with 12 healthy control subjects.

**RESULTS:** The majority of patients achieved their predicted work rate despite a resting arterial oxygen saturation ($Sao_2$) of 80% to 96%. Peak work rate and oxygen consumption ($\dot{V}o_2$) were no lower in patients with more hypoxemia. Despite higher $Sao_2$ following embolization (median, 96% and 90%; $P = .009$), patients achieved similar work rates and similar peak $\dot{V}o_2$. Strikingly, treated patients reset to virtually identical peak oxygen pulses (ie, $\dot{V}o_2$ per heart beat) and in many cases to the same point on the peak oxygen pulse/work rate plot. The 21 patients had increased minute ventilation ($\dot{V}e$) for given increases in $CO_2$ production ($\dot{V}e/\dot{V}co_2$ slope), but perceived dyspnea was no greater than in the 12 control subjects or in the same patients before compared to after embolization comparison. Overall, work rate and peak $\dot{V}o_2$ were associated not with oxygenation parameters but with $\dot{V}e/\dot{V}co_2$ slope, BMI, and anaerobic threshold.

**CONCLUSIONS:** Patients with hypoxemia and PAVMs can maintain normal oxygen delivery/$\dot{V}o_2$ during peak exercise. Following improvement of $Sao_2$ by embolization, patients appeared to reset compensatory mechanisms and, as a result, achieved similar peak $\dot{V}o_2$ per heart beat and peak work rates.

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**ABBREVIATIONS:** CPET = cardiopulmonary exercise testing; IQR = interquartile range; $O_2$ = oxygen; PAVM = pulmonary arteriovenous malformation; $Sao_2$ = arterial oxygen saturation; VAS = visual analog scale; $\dot{V}co_2$ = $CO_2$ production; $\dot{V}e$ = minute ventilation; $\dot{V}o_2$ = oxygen consumption

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Pulmonary arteriovenous malformations (PAVMs) are aberrant communications between pulmonary arteries and veins[1] and may affect one in 2,600 individuals.[2] The fraction of pulmonary arterial blood flow passing through these right-to-left shunts determines the severity of hypoxemia, which may be profound.[3-9] Patients with PAVMs rarely present with dyspnea or respiratory symptoms, however,[1,10-13] and often do not receive a diagnosis for decades until detection by incidental[2] or screening[1] studies. Exercise studies performed > 20 years ago provide insights into why patients with PAVMs differ from patients with hypoxemia and other respiratory conditions.[3,6,7] Although the concepts are recognized in highly specialized circles, they do not seem to have been incorporated into general pulmonary practice. For example, currently, none of the 2,700 records retrieved through PubMed searches using the terms "oxygen" and "guidelines" is retrieved when "pulmonary arteriovenous malformation" or equivalent terms are added.

This is important because in airway or alveolar disease states that more commonly result in hypoxemia (eg, COPD, asthma), a separate set of circulatory changes operate. Alveolar hypoxia triggers hypoxic pulmonary vasoconstriction, leading to elevation of pulmonary vascular resistance, increased right ventricular afterload, and reduced stroke volume on exercise.[14-16] In contrast, for patients with PAVMs, the absence of alveolar hypoxia or hypoxic pulmonary vasoconstriction, and PAVM-related structural alterations in the pulmonary vessels means that pulmonary vascular resistance at rest is low in those with severe hypoxemia.[3,6,7] The majority of patients with PAVMs have underlying hereditary hemorrhagic telangiectasia,[17,18] but overall, pulmonary hypertension is uncommon in patients with PAVMs due to hereditary hemorrhagic telangiectasia.[12] When pulmonary hypertension does occur,[19,20] it results not from hypoxia but from other pathophysiologic processes, particularly pulmonary arterial hypertension[12,21-24] and pulmonary venous hypertension associated with hepatic arteriovenous malformations and high output states.[12,25-27]

We hypothesized that in the presence of hypoxemia but absence of pulmonary hypertension, exercise capacity can be maintained by cardiovascular and hematologic[28] adaptations. The goal of the current study was to draw attention to the clinical differences between patients with hypoxemia and PAVMs and other more common conditions by further elucidating the mechanisms behind the generally good exercise tolerance in patients with PAVMs.

## Materials and Methods

This study was conducted in accordance with the amended Declaration of Helsinki. The South West London REC3 Research Ethics Committee (11/H0803/9) approved the protocol. All participants provided written informed consent.

### *Study Population*

Patients with PAVMs and significant hypoxemia were recruited between May 2011 and September 2012. Concurrent disease states likely to affect exercise tolerance were contraindications to study enrollment (e-Fig 1). Priority was given to new patients due to undergo PAVM embolization (recommended to reduce stroke risk[11,29] and other complications). Fifteen were recruited through postal invitations to previously reviewed patients or by invitation during a clinic visit on a day when space was available in the exercise physiology suite (e-Fig 1). Blood tests were done on the day of the exercise test; pulmonary artery pressure measurements were done at the time of PAVM embolization. Control subjects were recruited from staff and student volunteers (e-Table 1).

Cardiopulmonary exercise testing (CPET) was performed in the clinical service exercise physiology suite, which performs > 500 tests per year. Participants underwent a progressive incremental test while seated on a cycle ergometer (MasterScreen CPX; Jaeger) and breathing room air, with encouragement given to achieve their perceived maximum effort. At the start of the study, participants were familiarized with the equipment, including a participant-operated sliding rheostat scale, with feedback given through a light level to indicate their perceived level of dyspnea each minute. This visual analog scale (VAS) was operated linearly in keeping with the 0 to 10 Borg scale[30] to which participants were given verbal reference anchors for 0 and 10. The participants underwent continuous ECG and pulse oximetry monitoring, breath-by-breath measurements of ventilatory and metabolic variables, and intermittent automated BP recordings. The load on the bicycle (work rate) was increased as a continuous ramp at a rate estimated to result in a work phase of 8 to 12 min based on predicted values.[31]

Prior to statistical analyses, the relationship between minute ventilation ($\dot{V}_E$) and rate of $CO_2$ production ($\dot{V}CO_2$) was assessed from cycling onset to the respiratory compensation point. Anaerobic threshold was determined from the inflection point in the $\dot{V}CO_2$/oxygen consumption ($\dot{V}O_2$) relationship or the point when the ventilatory equivalent for oxygen ($O_2$) increased against time, whichever was clearer.[32] Reference ranges were derived from published values.[31-33] Biochemical tests on blood samples included venous bicarbonate (measured by an ARCHITECT ci16000 analyzer [Abbott Laboratories]) and

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erythropoeitin measured by enzyme-linked immunosorbent assay (R&D Systems, Inc). Also before statistical analyses and with investigators blinded to other physiologic variables, all VAS rheostat voltage readings on a scale of 1 to 6 were converted to Borg scale scores[30] of 0 to 10 by the equation Borg = 2 × (VAS − 1). Arterial oxygen content in milliliters per deciliter was calculated by the equation (hemoglobin × $Sao_2$ × 1.34)/100, where hemoglobin was measured in grams per deciliter, and 1.34 mL is the empirically determined amount of oxygen carried per gram of hemoglobin.[34] From the Fick equation, the oxygen pulse is the product of the stroke volume and tissue oxygen extraction (the arteriovenous oxygen content difference).[15,34] In the current study, the peak oxygen pulse was calculated by peak $\dot{V}o_2$/heart rate at peak exercise.

### *Statistical Analyses*

Data from all 21 patients with PAVMs undergoing CPET are reported. Stata/IC 11 and 12 (StataCorp LP) were used to calculate distributions of participant-specific variables; compare groups (using the Mann-Whitney *U* test); generate graphs; and perform linear, logistic, and quantile regressions. For multiple regression analyses, 26 variables, including all in Table 1, were first tested independently. The most significant variables were selected for base models, and the remaining variables were retested against the strongest preceding set of models, with *P* values calculated by postestimation likelihood ratio tests. Final models were selected where the adjusted $r^2$ explained the highest proportion of total variance.

Eighteen control subjects were recruited and were, on average, younger and fitter than the patients with PAVMs. Raw data from six control subjects aged < 24 years were excluded to keep age matching as close as possible. The maximum work rate remained a supernormal 128% predicted vs a normal 94% predicted for patients with PAVMs. Direct comparisons (control vs PAVM) were therefore applied with caution and restricted to special situations as discussed later.

## Results

### *Participant Demographics*

Resting $Sao_2$ in the 21 patients with PAVMs ranged from 80% to 96% (median, 91%) (Fig 1A, right boxes). Resting $Sao_2$ of the highest tertile was slightly lower than that of the 12 control subjects (95%-96% vs 96%-99%, respectively). Five patients with PAVM acted as their own controls by performing a second study 3 to 12 months (median, 6 months) postembolization when chest radiographs demonstrated PAVM sac obliteration and reduced caliber of draining veins (e-Fig 2). The second exercise study was performed with higher resting $Sao_2$ (median, 96%; range, 94%-96%) compared with preembolization (median, 90%; range, 88%-94%; *P* = .009) (Fig 1A, left boxes).

### *Exercise Demographics*

Twelve of the patients with PAVMs stopped exercising because their legs were unable to keep up as the work ramp increased, a normal response at peak exercise.[31-33] Four stopped due to shortness of breath, two due to general exhaustion (one with a headache), and two were stopped because of hypertension. There was, however, no discernible difference in general or study demographics between patients with PAVMs stopping because of their legs and those stopping for other reasons (data not shown).

At peak exercise, heart rate was 153/min (interquartile range [IQR], 125-163/min), representing 92% (IQR, 80%-100%) of the predicted maximum. At peak exercise, the ventilatory rate was 33/min (IQR, 27-41/min). End-exercise $Sao_2$ was on average 1% lower than resting values (*P* = .0017) (Fig 1B).

### *Work Rate and Peak $\dot{V}o_2$*

The majority of patients with PAVMs achieved their predicted work rate (median, 94%; IQR, 73%-103%). Overall, work rate was no lower in patients with more hypoxemia (Fig 1C, right boxes). Furthermore, the maximum work rate achieved by the patients in the postembolization group was very similar to their preembolization work rate (median, 113 W vs 119 W, respectively) (Fig 1C, left boxes).

The majority of patients with PAVMs also achieved their predicted $\dot{V}O_2$ at peak exercise (Table 1). Peak $\dot{V}O_2$ was similar in patients with PAVMs stratified by severity of hypoxemia (Fig 1D, right boxes) and in the same patients studied preembolization and postembolization (median, 1.69 L/min vs 1.72 L/min, respectively) (Fig 1D, left boxes). We next examined how they were able to achieve this.

### *Preserved Arterial Oxygen Content/Oxygen Pulse*

Oxygen delivery depends on both oxygen content per unit blood volume and cardiac output (which is the product of stroke volume and heart rate). As demonstrated in a wider series of 165 patients with PAVMs,[28] patients with more hypoxemia had evidence of polycythemia, and overall hemoglobin concentrations were higher in the PAVM group than in the control group (median, 15.9 g/dL vs 13.1 g/dL, respectively; *P* = .0074). As a result, arterial oxygen content per unit blood volume was maintained at rest (Table 1). Erythropoietin concentrations were normal in the more hypoxemic groups (e-Fig 3) in keeping with an established compensatory process.

At peak exercise, arterial oxygen content (Fig 2A) and heart rates (Fig 2B) were also similar in patients with PAVMs stratified by severity of hypoxemia as well as in the group studied preembolization and postembolization. The relationship between work rate and oxygen pulse (a composite measure of stroke volume

**TABLE 1** ] Descriptive Statistics of Cardiopulmonary Exercise Tests in 21 Patients With PAVMs

| Variable | All Patients (N = 21) | Preembolization (n = 5) | Postembolization (n = 5) | *P* Value |
|---|---|---|---|---|
| Resting demographics | | | | |
| Age, y | 57 (46-67) | 59 (57-62) | 59 (57-62) | .83 |
| Male sex, % | 71.4 | 60 | 60 | 1.00 |
| BMI, kg/m$^2$ | 25.1 (22.7-27.7) | 27 (25.8-31.2) | 27 (26.4-30.2) | .67 |
| Resting $Sao_2$, % | 91.0 (88-94) | 90 (88-93) | 96 (96-96) | .0092[a] |
| $FEV_1$, L | 3.35 (2.46-3.74) | 2.7 (2.46-3.35) | 2.6 (2.29-3.25) | .92 |
| $FEV_1$/FVC, % | 76 (66-81) | 77 (67-81) | 79.5 (72-82.5) | .62 |
| Hemoglobin, g/dL | 15.9 (14.5-16.6) | 14.9 (13.9-15.9) | 14.2 (13.9-15.5) | .68 |
| $Cao_2$, mL/dL | 19.5 (17.6-20.4) | 18.8 (16.4-19.8) | 18.2 (17.9-19.7) | .92 |
| End-tidal $Pco_2$ at rest, kPa | 3.7 (3.4-4.0) | 3.6 (3.5-3.6) | 4.29 (4.2-4.4) | .016[a] |
| Resting bicarbonate, mmol/L | 22 (20-24.5) | 20 (20-20) | 24 (23-24) | .019[a] |
| Mean PAP,[b] mm Hg | 15.5 (12.3-16.8) | 17 (15.5-18) | … | … |
| Exercise demographics | | | | |
| Peak heart rate, beats/min | 153 (125-163)[c] | 158 (155-163) | 158 (154-171) | .92 |
| Maximum work rate, W | 139 (87-169) | 119 (87-148) | 113 (88-168) | .92 |
| Maximum work rate,[d] % predicted | 94 (73-103) | 79 (68-94) | 87 (86-98) | .60 |
| End-exercise $Sao_2$, % | 90 (84-93) | 90 (88-91) | 95 (94-96) | .013[a] |
| End-tidal $Pco_2$ at maximum exercise, kPa | 4.3 (3.7-4.9) | 3.75 (3.58-3.85) | 4.9 (4.4-5.3) | .028[a] |
| Peak $\dot{V}o_2$, mL/min | 1,903 (1,361-2,432) | 1,692 (1,372-1,903) | 1,721 (1,417-2,061) | .60 |
| Peak $\dot{V}o_2$ % predicted[d] | 88 (81-104) | 82 (75-104) | 87 (82-108) | .40 |
| $O_2$ pulse peak,[d] mL/beat | 12 (9.2-16.2) | 11 (10.4-12) | 11.2 (10.9-12.1) | .60 |
| Anaerobic threshold, % predicted peak $\dot{V}o_2$ | 0.50 (0.45-0.64) | 0.49 (0.45-0.71) | 0.54 (0.41-0.64) | .54 |
| End-tidal $Pco_2$ at anaerobic threshold, kPa | 4.5 (3.8-5.2) | 4.3 (4.1-4.4) | 5.4 (5.4-5.6) | .009[a] |
| $Eqco_2$ at nadir | 33.3 (27.7-38.8) | 34.3 (33.3-38.8) | 27.9 (27.3-28.9) | .009[a] |
| $\dot{V}E/\dot{V}co_2$ slope, L/min/L/min | 32.2 (26.5-37.5) | 35.9 (30.3-36) | 27 (27-27.3) | .028[a] |
| Heart rate reserve, % | 8 (0-18) | 2 (−1-3) | 2 (−3-3) | .60 |
| Breathing reserve, % | 28 (19-39) | 20 (12-27) | 29 (26-33) | .47 |
| Respiratory exchange ratio | 1.08 (1.03-1.14) | 1.12 (1.06-1.14) | 1.19 (1.14-1.24) | .14 |

Data are presented as median (IQR) unless otherwise indicated. Demographics and key cardiopulmonary exercise test data for the 21 patients with PAVMs (15 men and six women). *P* values calculated by Mann-Whitney *U* test comparing the paired preembolization and postembolization values. $Cao_2$ = oxygen content, arterial; $Eqco_2$ = ventilatory equivalent for $CO_2$; IQR = interquartile range; PAP = pulmonary artery pressure; PAVM = pulmonary arteriovenous malformation; $Sao_2$ = arterial oxygen saturation (seated); $\dot{V}co_2$ = $CO_2$ production; $\dot{V}E$ = minute ventilation; $\dot{V}o_2$ = oxygen consumption.

[a]Significant at $P < .05$.

[b]PAP measurements available in 20 of 21 patients with PAVM (median interval, 10 mo; IQR, 0-35 mo from the cardiopulmonary exercise tests) and in all five patients treated with embolization. Comorbidities were present in 10 patients and included mild and well-controlled hypertension (n = 4), asthma/COPD (n = 2), type 2 diabetes mellitus (n = 2), benign prostatic hypertrophy (n = 2), previous ischemic stroke/transient ischemic attack (n = 2), venous thromboemboli (n = 1), atrial fibrillation (n = 1), sleep apnea (n = 1), hypercholesterolemia (n = 1), and depression (n = 1).

[c]At peak exercise.

[d]Data include one individual taking β-blockers with peak heart rate of 88/min and work rate of 64% predicted.

and tissue oxygen extraction, expressed as milliliters of oxygen consumed per heart beat[15,34]) was similar at peak exercise for participants in both the control and the PAVM groups (Fig 2C). Strikingly, after embolization and correction of $Sao_2$, patients reset to almost identical peak oxygen pulse values and, in three, to almost identical points on the peak oxygen pulse/peak work rate plot (Fig 2D).

### *Ventilatory Abnormalities and Dyspnea*

Previous small studies demonstrated abnormally high ventilatory drives in patients with hypoxemia and

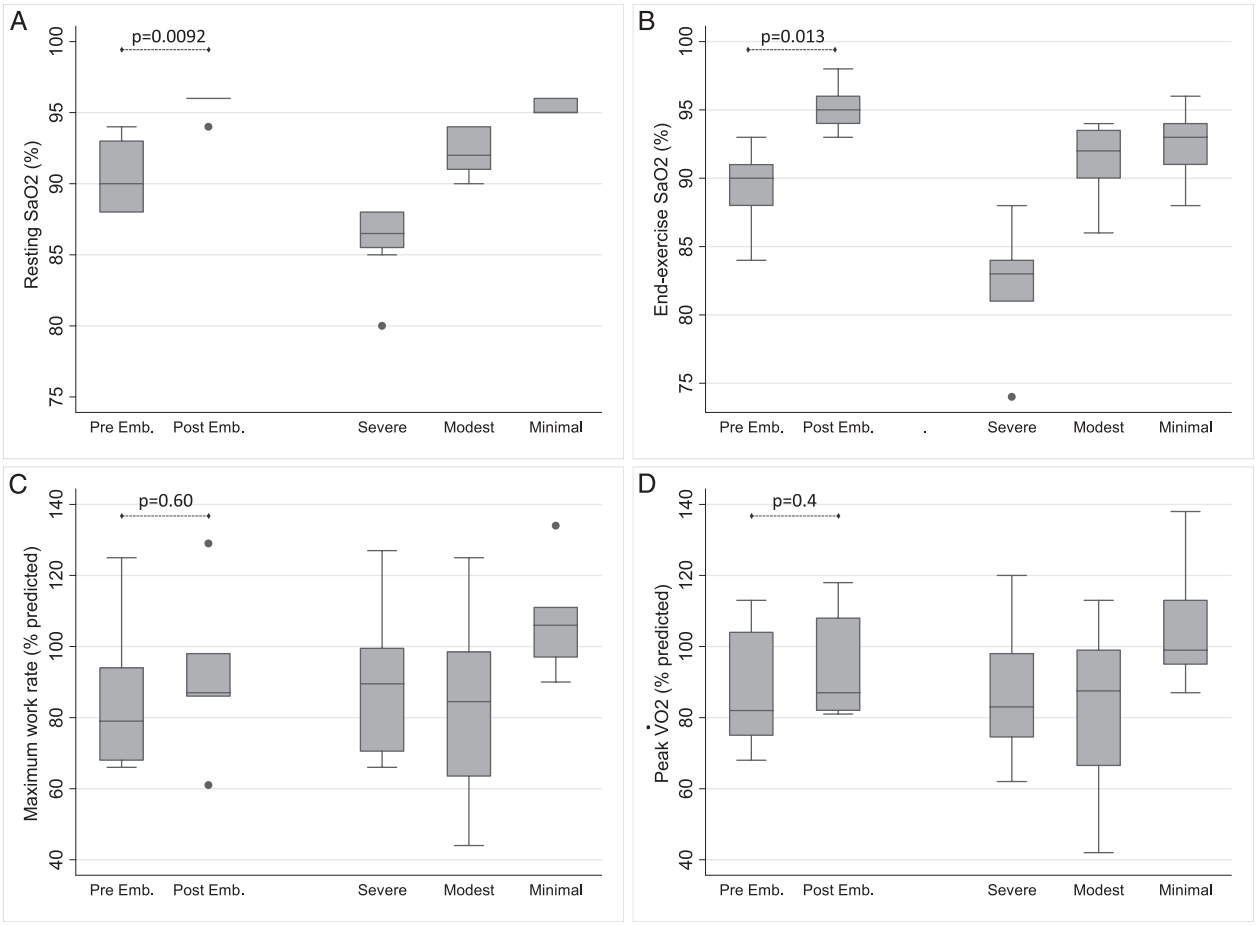


Figure 1 – *Exercise demographics in patients with pulmonary arteriovenous malformations (PAVMs). Each graph shows two box plots indicating the patients with PAVMs studied both preembolization and postembolization (left) and three indicating all 21 patients with PAVMs stratified into three tertiles (n = 7 each) by severity of resting hypoxemia while seated (right): severe (SaO2, 80%-89%), modest (SaO2, 90%-94%), and minimal (SaO2, 95%-96%). Box plots indicate median, interquartile range, and 2 SDs for variables, with dots at extremes representing outliers. A, Resting SaO2. B, End-exercise SaO2. C, Maximum work rate (% predicted). D, Peak V̇O2 (% predicted). Emb = pulmonary arteriovenous malformation embolization treatment; SaO2 = arterial oxygen saturation; V̇O2 = oxygen consumption.*

PAVMs,[3,6,7] and these were observed in the current study (Table 1). Lower end-tidal $P_{CO_2}$ was confirmed as resulting from the right-to-left shunt because in the subgroup restudied after embolization, resting and end-exercise expired $CO_2$ normalized (Table 1). Venous bicarbonate level and the ventilatory equivalent for $CO_2$ at nadir also normalized after embolization (Table 1). Graphic illustrations of patients stratified by severity of hypoxemia, and preembolization and postembolization, are presented in e-Figure 4.

During exercise, patients with PAVMs increased $\dot{V}_E$ more than control subjects for a given increase in $CO_2$ production (Fig 3A). The $\dot{V}_E/\dot{V}_{CO_2}$ slope is predicted to be steeper with enhanced right-to-left shunting, and this was supported in the patients with PAVMs by a significant relationship between a steeper $\dot{V}_E/\dot{V}_{CO_2}$ slope and lower $Sa_{O_2}$ (resting $Sa_{O_2}$, $P = .049$; end-exercise $Sa_{O_2}$, $P = .065$). Postembolization, the $\dot{V}_E/\dot{V}_{CO_2}$ slopes normalized (Fig 3B).

We postulated that the increased ventilation might be sensed by patients as dyspnea, which would improve after PAVM embolization. Surprisingly however, at equivalent percentages of maximum work rates achieved during CPET (by in-test Borg scale scores), the level of perceived dyspnea was no higher in patients with PAVMs than in control subjects (Fig 3C). Similarly, there was no difference in reported Borg scale dyspnea in the five patients restudied after embolization had essentially corrected ventilatory abnormalities (Fig 3D).

### *Predictors of Exercise Capacity*

To explore which factors predicted exercise capacity in patients with PAVMs, univariate (e-Tables 2, 3) and

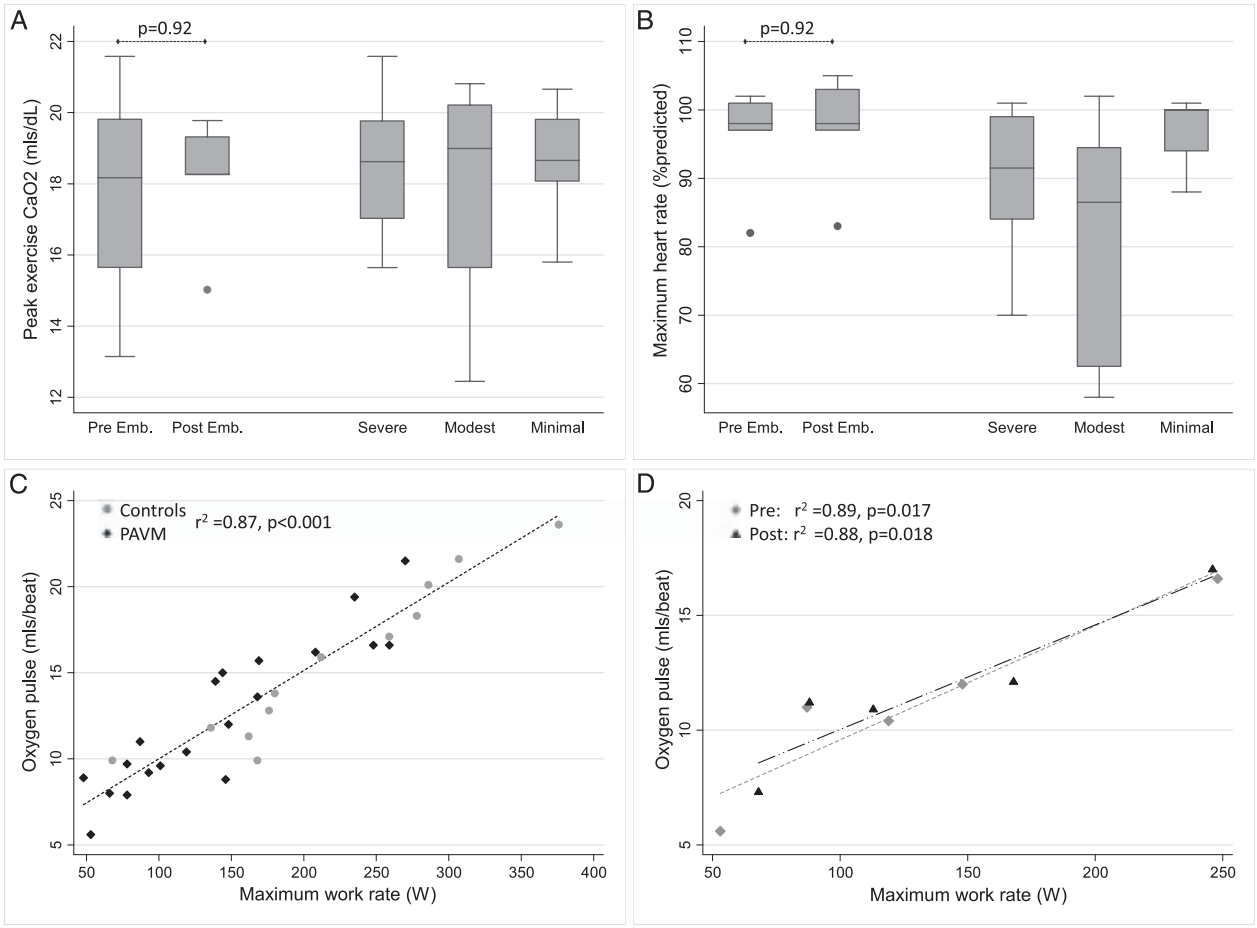


Figure 2 – *Oxygen delivery and consumption demographics. A and B, Each graph shows two box plots indicating the patients with PAVMs studied both preembolization and postembolization (left) and three indicating all 21 patients with PAVMs stratified into three tertiles (n = 7 each) by severity of resting hypoxemia while seated (right): severe (SaO2, 80%-89%), modest (SaO2, 90%-94%), and minimal (SaO2, 95%-96%). Box plots indicate median, interquartile range, and 2 SDs for variables, with dots at extremes representing outliers. A, CaO2 at peak exercise calculated by (hemoglobin × SaO2 × 1.34)/100. B, Heart rate at peak exercise as percent of predicted maximum. C and D, The relationship of peak oxygen consumption per heart beat (oxygen pulse [mL/beat]) vs peak work rate in study participants. C, Oxygen pulse in all 21 patients with PAVMs (◆) vs control subjects (●). Note that there is one symbol per individual and that the linear regression line fits both control and PAVM values. Data exclude one outlier (patient taking β-blockers). D, Oxygen pulse in five patients with PAVMs preembolization (◆) and postembolization (▲). Note the similar values between preembolization and postembolization, and general preservation of oxygen consumption per heart beat (ie, oxygen pulse). The one individual with an increased peak oxygen pulse and maximum work rate had sleep apnea and anemia. CaO2 = oxygen content, arterial. See Figure 1 legend for expansion of other abbreviations.*

multivariate regression analyses were performed using the variables in Table 1. As expected, 84% of the variance in the maximum work rate was explained by a model using BMI and peak $\dot{V}O_2$, with a complex nonlinear relationship between peak $\dot{V}O_2$ and maximum work rate (Table 2). Sixty percent of peak $\dot{V}O_2$ variance was explained by anaerobic threshold and the $\dot{V}E/\dot{V}CO_2$ slope (Table 2). Thus, patients achieved higher maximum work rates if they had a lower BMI, higher anaerobic threshold (most likely reflecting better conditioning), and less steep $\dot{V}E/\dot{V}CO_2$ slope.

## Discussion

In this study, we demonstrate that for patients with PAVMs in the chronically adapted state and absence of pulmonary hypertension, hypoxemia need not be associated with reduced exercise tolerance, impaired peak $\dot{V}O_2$, or dyspnea. The strengths of the study are the unique patient group, studied in high numbers for such a rare condition. Relatively few patients have both severe hypoxemia and the likelihood of full correction postembolization as had the group specifically selected for the pre- and postembolization study. Our extensive clinical experience with PAVMs[1,11-13,15,28,29,35] and CPET[36] made us confident about the safety of maximally exercising these patients with hypoxemia on room air.

Study limitations included the number of patients studied and the absence of invasive measurements of blood gases and cardiac output. For this rare disease in which

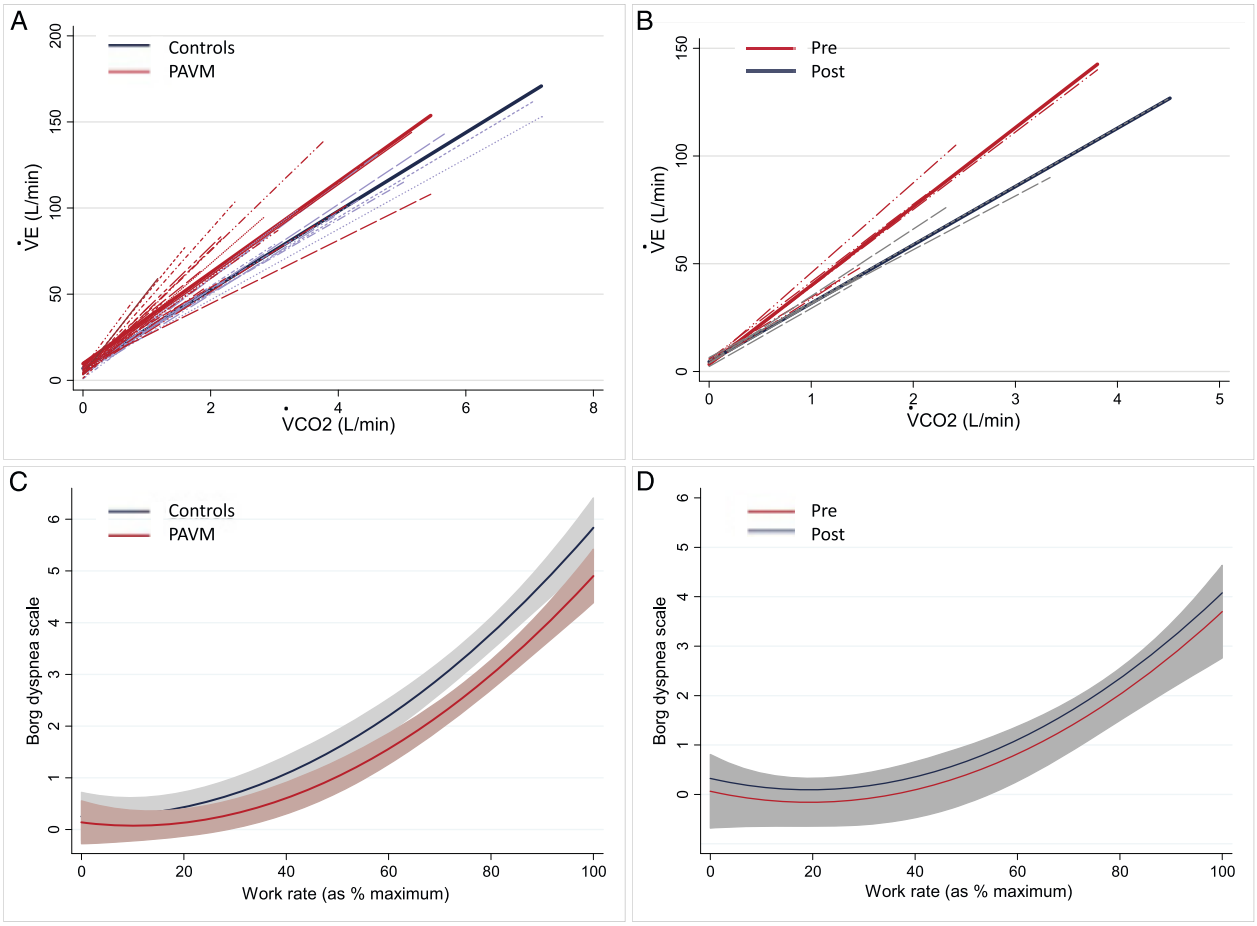


Figure 3 – *Ventilatory relationships and dyspnea at rest and during exercise: A and B, Pictorial representation of V̇E/V̇CO2 gradients in study participants, with dotted and dashed lines representing individual participants and thick lines representing the respective regression lines (A, 21 patients with PAVMs and 12 control subjects; B, the five patients with PAVMs studied both preembolization and on restudy postembolization). The slopes for treated patients in B were similar to those of control subjects in A (P = .09). C and D, Dyspnea reported by Borg scale score (0-10) at stated percentage of maximum work rate achieved. Graphs indicate the best fit lines and 95% CIs by quadratic regression (C, 21 patients with PAVMs and 12 control subjects; D, the five patients with PAVMs studied both preembolization and postembolization). In D, the fitted lines lay within both sets of 95% CIs by quadratic regression, and a single CI is indicated for clarity. V̇CO2 = $CO_2$ production; V̇E = minute ventilation. See Figure 1 legend for expansion of other abbreviation.*

such studies have been performed previously,[3,6,7] we judged the optimized patient participation rates and larger resultant cohort to be more important than providing invasive data again in another small cohort. The control group, although not fully matched, demonstrated a very similar breathing reserve to patients (27% vs 28%), justifying inclusion for selected comparisons of dyspnea.

The findings support and extend elegant, but small physiologic studies of patients with severe hypoxemia and PAVMs.[3-8] These defined right-to-left shunting as the predominant cause of hypoxemia[3-8] and demonstrated that increased flow through PAVMs is matched by an increase in cardiac output and total pulmonary blood flow (alveolar and shunt) in proportion to the right-to-left shunt fraction.[7] These findings have not been followed up because of a focus on pulmonary hypertension in the field[12,19-27] and in terms of prophylaxis.

The current study highlights the successful compensatory mechanisms that preserve oxygen delivery in patients with hypoxemia and PAVMs. The data demonstrate that compensation is achieved not only through erythrocytosis (provided that iron levels are sufficient[28]) and/or higher heart rates,[37] but also through maintenance of the oxygen pulse, which is the product of the stroke volume and tissue oxygen extraction. Because an early PAVM study demonstrated that oxygen extraction (the arteriovenous oxygen content difference) was lower than predicted,[7] the most likely mechanism to sustain a normal oxygen pulse in the current study would be a higher stroke volume. The intriguing and still unanswered questions

**TABLE 2** ] Multiple Regression Analyses of Work Rate and Peak $\dot{V}O_2$ in 21 Patients With PAVMs

| Model | Regression Coefficient | 95% CI | *P* Value |
|---|---|---|---|
| A, log (% work rate achieved) | | | |
| BMI, kg/m$^2$ | −0.031 | −0.045 to −0.017 | < .001 |
| Peak $\dot{V}O_2$ % predicted | 0.029 | 0.01 to 0.047 | .004 |
| (Peak $\dot{V}O_2$ % predicted)[a] | −0.0001 | −0.0002 to −0.00006 | .039 |
| B, peak $\dot{V}O_2$ % predicted achieved | | | |
| Anaerobic threshold | 4.80 | 1.62 to 7.99 | .005 |
| $\dot{V}E/\dot{V}CO_2$ slope | −1.01 | −1.88 to −0.14 | .026 |

Univariate analyses for these parameters are presented in e-Tables 2 and 3. For each multivariate model, the variables identified as making a significant contribution to the final model, once adjusted for the presence of other variables within the model, are presented. Model A: the distribution for percent predicted work rate achieved was skewed and normalized by log transformation (data supplied). Log-transformed work rate, therefore, was used as the dependent variable for regression performed in n = 20 because an outlier identified on a normal quantile plot was excluded (adjusted $r^2$ for the model, 0.84; $P < .0001$). Interaction terms were not significant in this model. Model B: multiple regression of final model for peak $\dot{V}O_2$ (adjusted $r^2$ for model, 0.60; $P = 0{\cdot}0001$). The distribution for peak $\dot{V}O_2$ % predicted was skewed by log transformation (data supplied). Peak $\dot{V}O_2$, therefore, was used as the dependent variable for regression. Higher-order variables and interaction terms were not significant in this model. See Table 1 legend for expansion of abbreviations.

[a]The square of peak $\dot{V}O_2$ % predicted.

relate to how stroke volume would be regulated in this manner and whether such a fundamental adaptive response to sustain oxygen delivery could be specific to hypoxemia resulting from a particular rare disease. If an increased cardiac output is part of general compensations to hypoxemia, this could be relevant to coronary syndromes in patients with acute exacerbations of COPD[38,39] and higher mortality rates in medical patients with marginal reductions in $Sao_2$.[40]

In the current PAVM literature, compromised gas exchange due to right-to-left shunts though PAVMs is usually discussed in terms of hypoxemia and the $O_2$ shunt. Right-to-left shunting also causes a $CO_2$ shunt, effectively impairing $H+/CO_2$ clearance.[15,34] The current data and previous studies[3,6,7] indicate that the ventilatory stimulus from the combined $O_2$ and $CO_2$ shunts not only is sufficient to maintain normocapnia but also, as noted by the low resting serum bicarbonate levels, may cause an overshoot. Greater ventilation attributed to impaired $H+/CO_2$ clearance was inversely associated with peak $\dot{V}O_2$ and exercise capacity. We speculate that the reason patients did not report associated dyspnea is that incremental CPET did not allow capture of the most appropriate sensation of dyspnea. In our wider group of treated patients reported recently,[28] four spontaneously commented on an improved breathing pattern during less-intense exercise, such as swimming, yoga, and singing. Further study is required to explain these findings.

In summary, patients with PAVMs tolerate hypoxemia due to right-to-left shunt well. Acute falls in arterial oxygen content appear to be offset by increased heart rate.[37] Longer term compensation involves both secondary erythrocytosis[28] and, as emphasized in this study, additional mechanisms to preserve oxygen delivery per heartbeat. Greater ventilatory effort associated with impaired $H+/CO_2$ clearance appears to limit exercise tolerance but is not interpreted as dyspnea by patients.

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