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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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