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Original Research

PULMONARY PHYSIOLOGY

The Impact of Sickle Cell Disease on Exercise Capacity in Children

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Background: **Little is known about pulmonary vascular complications in children with sickle cell disease (SCD). We hypothesized that transfer factor (diffusing capacity of the lung for carbon monoxide [DLCO]) may be used as a surrogate for the size of the pulmonary vascular bed and that pulmonary vascular abnormalities in children with SCD may limit exercise capacity.**

Methods: **Fifty stable patients with SCD aged 10 to 18 years and 50 healthy control subjects matched for race and age were recruited. Incremental ergometer cardiopulmonary exercise testing was performed using respiratory mass spectrometry for exhaled gas analysis. A rebreathing maneuver was used to measure functional residual capacity, effective pulmonary blood flow (Qpeff), and DLCO, and helium dilution was used to calculate minute ventilation, oxygen consumption, and CO_2 production.**

Results: **In the 89 evaluable subjects, there were no ventilatory differences between SCD and control subjects. Qpeff was consistently 15% to 20% greater in subjects with SCD than control subjects at all stages, but DLCO corrected for both surface area and hemoglobin was only about 7% to 10% greater in subjects with SCD at all stages. As a result, the DLCO/Qpeff ratio was considerably lower in SCD at all stages. Arteriovenous oxygen content difference was about one-third less in SCD at all stages.**

Conclusions: **Contrary to our hypothesis, failure to maintain a sufficient Qpeff to compensate for anemia led to exercise limitation. The ratio of pulmonary capillary blood volume to flow is reduced throughout, implying subtle pulmonary vascular disease; however, this was not a factor limiting exercise.**

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Abbreviations: AVO = arteriovenous content difference; CO = carbon monoxide; DLCO = diffusing capacity of the lung for carbon monoxide; Hb = hemoglobin; PVR = pulmonary vascular resistance; Qpeff = effective pulmonary blood flow; RBM = rebreathing test; RMS = respiratory mass spectrometry; SCD = sickle cell disease; Vc = pulmonary capillary blood volume

Detailed studies of cardiopulmonary exercise testing in children with sickle cell disease (SCD) are limited,[1-3] and currently the pathophysiology of exercise limitation is unclear. By using the 6-min walk test, both Liem and colleagues[4] and Campbell and colleagues[5] recently identified that the degree of anemia was the main factor limiting exercise capacity together with restrictive lung function abnormalities and number of acute chest crises.[4] Children with SCD have more adipose tissue with reduced fitness and exercise performance compared with control subjects.[6,7] Resting energy expenditure in children with SCD is increased and may be associated with raised markers of inflammation and oxidative stress.[8,9] Finally, pulmonary hypertension is emerging as a leading cause of morbidity and mortality in adult patients with

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SCD[10-14] and has been reported to be common in children with SCD.[10,15-18] However, we have demonstrated in resting adolescent patients with SCD that although there is high pulmonary blood flow, pulmonary vascular resistance (PVR) is not increased; indeed, PVR is lower in patients compared with control subjects. High pulmonary blood flow seems solely related to anemia.[19] These findings do not preclude abnormality when under stress—for example, during exercise. Transfer factor (diffusing capacity of the lung for carbon monoxide [DLCO]) may be used as a surrogate for the size of the pulmonary vascular bed.[20,21]

We hypothesized that despite having no symptoms or findings suggestive of a raised pulmonary vascular resistance, pulmonary vascular abnormalities in young adolescents with SCD may already be limiting exercise capacity compared with matched control subjects. We, therefore, studied adolescents with SCD during rest, exercise, and recovery using noninvasive respiratory mass spectrometry (RMS) to measure in particular DLCO to determine subtle pulmonary vascular abnormalities during the stress of exercise.

Materials and Methods

Exercise Physiology

Noninvasive RMS permits the measurement of physiologic variables during both rest and exercise. Using a rebreathing protocol, the disappearance of acetylene and oxygen determines the effective pulmonary blood flow (Qpeff) (defined as being in contact with ventilated alveoli), effective stroke volume (Qpeff/heart rate), and oxygen consumption, respectively. Their ratio (Fick principle) determines the arteriovenous content difference (AVO).

Similarly, the disappearance of carbon monoxide (CO) determines the DLCO. DLCO is a surrogate measure of pulmonary capillary blood volume (Vc) in contact with ventilated alveoli, from the equation $1/DLCO = 1/Dm + 1/(\theta \times Vc)$, where Dm and θ are constants. Thus, a change in DLCO from rest to exercise can be regarded as a measure of the distensibility of Vc as a response to exercise—in other words, a change in ventilated pulmonary capillary volume.

The use of an inert insoluble gas in a closed rebreathing system enables measurement of functional residual capacity. Helium dilution mixed expired gas analysis, again measured by RMS, allows the determination of minute ventilation, alveolar ventilation, and physiologic dead space, together with oxygen consumption and CO_2 production.

Subjects

Fifty (26 female) patients aged 10 to 18 years with known hemoglobin SS or SC disease were recruited from the pediatric hematology outpatient clinic at St. George's Hospital, London, England. Inclusion criteria were as follows: age > 10 years, height > 125 cm, genotype SS or SC only, and at least one African Caribbean parent. Exclusion criteria were HIV positivity and history of cerebrovascular accident or congenital heart disease. All children were well and free of any vasoocclusive crises for a minimum of 14 days before exercise testing. Fifty (25 female) healthy control subjects matched for race, sex, and age were recruited from friends and siblings of patients. Ethics approval was granted by Wandsworth Local Ethics Committee (ref No. 04/Q0803). Informed written consent was obtained for each child in keeping with UK medical research council guidelines.[22] History and examination, including Tanner pubertal staging,[23] were performed. Pulmonary symptoms, including number of hospital admissions with painful vasoocclusive crises in the previous 2 years and total number of admissions with acute chest syndrome, were recorded. Hemoglobin (Hb), reticulocyte count, percent fetal Hb, and Hb electrophoresis were measured. Standing height (± 1 mm, Harpenden stadiometer; Holtain Ltd) and weight (± 0.1 kg) using electronic scales (Seca) were measured, from which BMI and body surface area were calculated.

The Exercise Protocol

The ergometer exercise protocol has been previously described.[24] In summary, following training and 10 min of seated rest, all subjects undertook 5 × 20 s rebreathing tests (RBM) every 3 min. Following this, they sat on the bicycle with their mouth in constant contact with the mouthpiece; at this point, the mixed expired gas analysis program was started. This was interrupted every 3 min by a further 12-s RBM, which coincided with the last 20 s of each exercise stage. The exercise stages began with rest, then backpedaling at zero load, followed by forward pedaling, with an initial load of 25 W/m^2 increasing every 3 min by 15 W/m^2 until exhaustion. At this point, the subject remained seated for 9 min of recovery time with mixed expired gas analysis continuing and a further three RBMs every 3 min. Hydration was encouraged prestudy and poststudy, and oxygen saturation level and heart rate were measured continuously by a pulse oximeter probe placed over the right supraorbital artery and secured with a bandana. Exercise was terminated if oxygen saturation fell below 91%.

An Innovision 2000 RMS machine (Innovision A/S) and identical protocols were used as in previous studies.[20,21,25] The gas composition (medical grade) used for inert gas rebreathing was 35% oxygen, 5% sulfur hexafluoride, 0.3% acetylene, 0.3% stable isotope CO (CO^{18}), and 60% nitrogen (CK Gas Products Ltd).

Data Analysis

All rebreathing traces were visually reviewed to ensure the software correctly identified the point of complete gas mixing, the point of pulmonary recirculation, any gas leaks from the mouth, and other artifacts.[23] DLCO was corrected for Hb using the formula: corrected DLCO = measured DLCO × (9.38 + actual Hb/1.7 × actual Hb).[26] All outlying results for any parameter (> 1.5 × interquartile range) were included, but extreme results (> 3 × interquartile range) were excluded. Results are presented as mean and 95% CIs in all cases and corrected for surface area where stated. Comparisons between control subjects and subjects with SCD were made by Mann-Whitney *U* tests using SPSS v20 (IBM). Because of the number of contrasts, $P \leq .01$ was taken as significant. To examine the overall effect of SCD on a variable, the sign test was used, with $P \leq .01$ taken as significant. The study was powered so that 40 patients in each group would have an 80% chance of detecting an approximately 20% change in any parameter assuming SDs similar to previous studies.[20,21]

Results

Demographics are summarized in Table 1. Of 100 subjects recruited, four did not attend, two had oxygen saturation < 91% at rest, and five were excluded for persistent mouth leak; therefore, 89 of 100