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Lung function and gas exchange in Eisenmenger syndrome and their impact on exercise capacity and survival ☆

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ABSTRACT

Background: Eisenmenger physiology may contribute to abnormal pulmonary mechanics and gas exchange and thus impaired functional capacity. We explored the relationship between lung function and gas exchange parameters with exercise capacity and survival.
Methods: Stable adult patients with Eisenmenger syndrome (N = 32) were prospectively studied using spirometry, lung volumes, diffusion capacity, and blood gas analysis, as well as same day measurement of 6-minute walk distance and cardiopulmonary maximal treadmill exercise. Patients were followed prospectively to determine survival (7.4 ± 0.5 years). Abnormalities were identified and appropriate comparisons were made between affected and unaffected individuals between respiratory mechanics, exercise function, and survival.
Results: Obstruction (FEV_1/FVC ratio <0.70) was found in 13 patients (41%), who were older but not otherwise different. Restriction was uncommon. Diffusion transfer coefficient, which was <80% in half the patients, correlated with exercise duration (r = 0.542, P = 0.005), and was worse in non-survivors (N = 6). Nearly all patients had a compensated respiratory alkalosis ($PaCO_2$ 32 ± 4.4 mm Hg). $PaCO_2$ was less reduced in older patients (r = 0.438, P = 0.022), and correlated independently with exercise duration (R = −0.463, P = 0.03), yet PaO_2, not $PaCO_2$, was associated with survival.
Conclusions: Eisenmenger patients show evidence of obstructive lung disease, diffusion abnormalities, and hypocapnia; likely from hyperventilation. Understanding expected lung mechanics and gas exchange may facilitate more appropriate clinical management.

1. Introduction

Eisenmenger syndrome (ES) develops from an unrestricted communication between the systemic and pulmonary circulation (such as a large intracardiac shunt or patent ductus arteriosus), which if unrepaired progresses to elevated pulmonary artery pressures, pulmonary vascular disease, and reversal of shunt leading to hypoxemia, cyanosis, and erythrocytosis [1]. There are several potential mechanisms for abnormal lung mechanics, in addition to the pulmonary vascular changes themselves. These include scoliosis, present in roughly 10% of patients with congenital heart disease, or significant enlargement of the heart and/or central pulmonary arteries that may have space-occupying effects [2]. Patients with ES have very impaired exertional capacity, the lowest of any group of patients with congenital heart disease [3]. It is unknown to what extent, if any, lung function contributes to this physical limitation.

Our institution recently published a large series evaluating restrictive lung disease in congenital heart patients including ES [4]. However, patients with obstructive lung disease were excluded, and the study did not focus on the unique aspects of ES. While there are few studies describing pulmonary function parameters such as obstructive lung disease in other groups with pulmonary arterial hypertension (PAH) [5–7], including a small number of patients with Eisenmenger physiology [8], none, to our knowledge, have specifically explored lung mechanics specifically in ES, nor their potential impact on exercise capacity or survival. Therefore, in this prospective study we aim to

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describe all aspects of lung mechanics and gas exchange specifically in a stable cohort of ES patients, and explore their prognostic value.

2. Methods

Consecutive adults with ES seen at our tertiary referral center between 2003 and 2005 were prospectively invited to participate and all patients gave informed consent. The study received approval from the Ethics Committee at the Royal Brompton Hospital. Inclusion criteria were known ES syndrome patients with a resting oxygen saturation <92%, seen as stable outpatients. Inpatients or those with acute illness such as bronchitis/pneumonia or recent large-volume hemoptysis were initially excluded, but invited to participate after resolution of the issue and return to outpatient status. Patients with difficulty complying with test instructions (such as those with developmental delay) were excluded from tests needing cooperation (i.e. spirometry or cardiopulmonary exercise) but eligible for other portions of the study and subsequent analysis.

Each patient underwent spirometry, lung volumes, diffusion capacity quantification, and earlobe capillary blood gas measured at rest. All testing was done in a single visit and in accordance with accepted clinical standards [9]. Spirometry was performed three times and results averaged. Lung volumes were measured in an enclosed gas cabin using Helium dilution. Diffusion of carbon monoxide (CO) was quantified and corrected for hemoglobin measured on the test day.

Patients also underwent a 6-minute walk test and a maximal cardiopulmonary exercise testing on the test day. Oxygen saturation and heart rate at baseline and at the end of the 6 minute walk test were recorded in addition to distance walked. Maximal cardiopulmonary treadmill exercise testing was performed using a modified Bruce protocol with continuous measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [10,11].

All patients were followed prospectively at the Royal Brompton Hospital. Any deaths were recorded together with date and mode of death, if known. For survivors, date of last clinic visit was used for survival analysis. All patients were accounted for within six months of the time of final analysis.

2.1. Statistical analysis

Spirometry, lung volume, and diffusion results were reported as percent of predicted ($\%_{pred}$) values for historic normal individuals matched for age, gender, and height. This allowed categorization into accepted severity categories (mild/moderate/severe), defined below. Statistical comparisons between categories, when described, were made using appropriate parametric testing (Students *t*-test or chi-square test). Strength of association between continuous variables was measured using Pearson's correlation coefficient. A single forward step-wise multivariate analysis was done to determine the potential interaction of $PaCO_2$ and age as predictors of exercise duration. Analysis was performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, Illinois). No correction was made for multiple tests as this was a descriptive study. Because there were only 6 deaths, survival analysis was limited to simple comparisons between survivors and non-survivors. Results are expressed as mean ± SD unless stated otherwise. $P < 0.05$ was considered statistically significant.

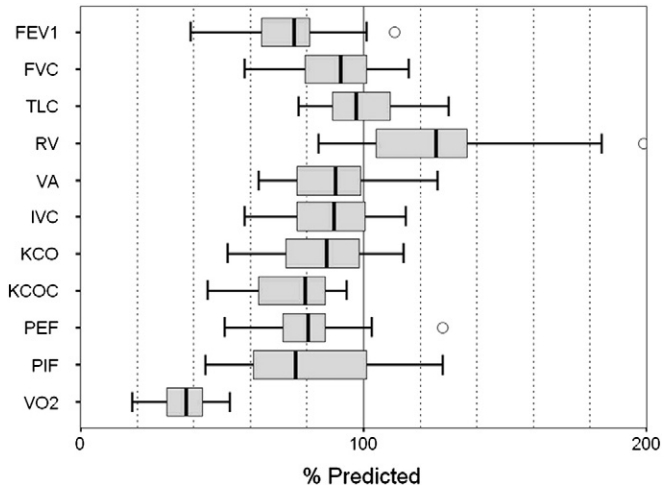

Fig. 1. Box plots showing mean, interquartile range, maximum and minimum values for major lung function variables, expressed as a percent of predicted values for age/gender matched populations. Outliers are shown as open circles. FEV1 = force expiratory volume in 1 s. FVC = forced vital capacity. TLC = total lung capacity. RV = residual volume. VA = alveolar volume. IVC = inspiratory vital capacity, KCO = carbon monoxide diffusion coefficient, KCOC = carbon monoxide diffusion coefficient corrected for measured hemoglobin, PEF = peak expiratory flow, PIF = peak inspiratory flow, VO2 = peak oxygen consumption.

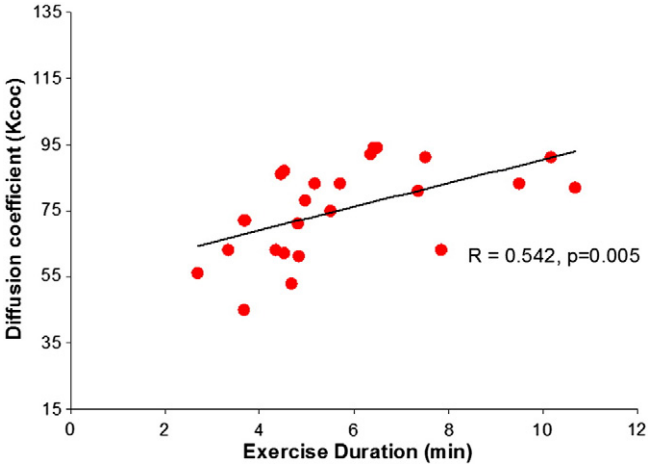

Fig. 2. Association between diffusion coefficient (corrected for hemoglobin) and exercise duration during cardiopulmonary exercise.

3. Results

Thirty-two patients were enrolled in the study, of which 23 (71%) were female. Mean age was 41 ± 14 years, resting oxygen saturation 81 ± 7%, hemoglobin 20 ± 3 g/dl, all consistent with confirmed Eisenmenger physiology. Three patients had atrial septal defects, 20 had ventricular septal defects, and 9 had a patent ductus arteriosus as their main source of shunting. Not all patients could or wished to complete all aspects of the study. Six patients had some form of developmental delay. Boxplots for major lung function variables expressed as a percentage of predicted values are shown (Fig. 1), including percent predicted peak VO_2 during exercise. Additionally, peak VO_2 (N = 27) was 11.1 ± 3.4 ml/kg/min, Ve/VCO_2 slope was 82 ± 68, anaerobic threshold was 8.76 ± 2.5 ml/kg/min, and respiratory exchange ratio was 0.98 ± 0.1, all consistent with significantly reduced exercise capacity as previously documented [12,13].

3.1. Obstructive or restrictive lung disease

Reliable spirometry data were obtained in 31 patients. Forced Expiratory Volume (FEV_1) was 3.86 ± 1.05 L, or 75 ± 16%$_{pred}$, range 39–111%. Forced vital capacity (FVC) was 4.62 ± 1.65 L, or 89 ± 18%$_{pred}$, range 44–116%. There were 13 patients (42%) with evidence of obstruction, defined as FEV_1/FVC ratio <0.70. Based on the %$_{pred}$ FEV_1, there was 1 patient with grade 1 (FEV_1 >80%$_{pred}$), 11 with grade 2 (FEV_1 50–80%$_{pred}$), and 1 with grade 3 (FEV_1 <50%$_{pred}$) according to the 2011

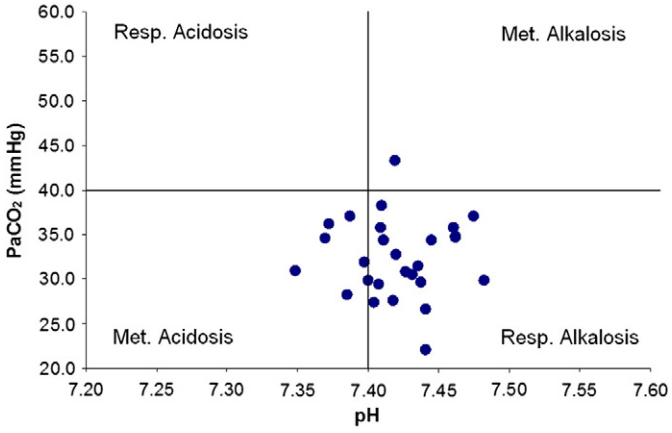

Fig. 3. Scatterplot of $PaCO_2$ and pH demonstrating acid/base status of the patient cohort. The majority of patients had a respiratory alkalosis with varying degrees of metabolic compensation.