Cardiac Output Determination during Progressive Exercise in Cystic Fibrosis*

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Cardiac output (\(Q\)) determination using the equilibrium CO\(_2\)-rebreathe indirect Fick technique (Equil) to estimate mixed venous PC\(_{O_2}\) (FvCO\(_2\)) has been validated during steady state (SS) exercise in subjects with lung disease. A modification of the exponential method using a low concentration of CO\(_2\) with an exponential rise in PetCO\(_2\) (Ex) during rebreathing to estimate FvCO\(_2\) has been validated during nonsteady state exercise. The purpose of the present study was to validate the Ex method in subjects with lung disease. \(Q\) was measured by Ex at every second work load during Prog. \(Q\) was measured after 5 min of SS exercise by both Ex and Equil. Arterial PC\(_{O_2}\) was estimated from PetCO\(_2\). There was no significant difference in the \(Q\)-Vo\(_2\) relationship during Prog exercise between the combined control and mild (FEV\(_1\) > 70%) CF subjects or the moderate and severe CF subjects. \(Q\) can be determined in the nonsteady state using the exponential CO\(_2\)-rebreathe indirect Fick technique in subjects with CF, allowing for noninvasive examination of cardiopulmonary interaction during exercise at a wide range of work loads.

\(\text{CF} = \text{cystic fibrosis}; \text{Equil} = \text{equilibrium CO}_2\text{-rebreathe indirect Fick technique}; \text{Ex} = \text{exponential rise in PetCO}_2; \text{Prog} = \text{progressive}; \text{FvCO}_2 = \text{mixed venous PC}_2; \text{Q} = \text{cardiac output}; \text{RER} = \text{respiratory exchange ratio}; \text{SS} = \text{steady state}\)

Measurement of cardiac output (\(Q\)) on a routine basis in the exercise laboratory requires the use of noninvasive techniques. In subjects with lung disease, the CO\(_2\)-rebreathe indirect Fick method has been validated during steady state exercise,\(^1,2\) but these studies are limited to relatively low work loads and do not allow for the evaluation of dynamic changes.

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Recently, the CO\(_2\)-rebreathe indirect Fick method has been validated during nonsteady state exercise for healthy control subjects\(^3\) and patients with coronary artery disease.\(^4\)

The two main techniques for estimating mixed venous PC\(_{O_2}\) (FvCO\(_2\)) are the equilibrium and exponential methods. In subjects with lung disease, the equilibrium technique for estimating FvCO\(_2\) has been found to be the most reliable. There are, however, several disadvantages to this method. There are technical difficulties involving appropriate choices of bag volume and CO\(_2\) concentrations for rebreathing to result in an equilibrium plateau for the estimation of FvCO\(_2\). The relatively high concentrations of CO\(_2\) employed are poorly tolerated and unpleasant during high carbon dioxide production (VCO\(_2\)), eliminating the possibility of measurements close to maximal exercise.

These difficulties have been surmounted by mathematical refinements of the exponential method of CO\(_2\)-rebreathing, originally proposed by Defares,\(^5\) improving its reliability.\(^6\) In this method, a bag of fixed volume is filled with a fixed low concentration of CO\(_2\). During rebreathing, there is an exponential rise in the endtidal PC\(_{O_2}\) (PetCO\(_2\)). Linear regression and iterative techniques are then employed to estimate the FvCO\(_2\) from the measured PetCO\(_2\).

Cardiac output determinations using the indirect Fick technique also require measurements of V\(_{CO_2}\) and arterial PC\(_{O_2}\) (PaCO\(_2\)). In the study by Mahler and co-workers\(^1\) of chronic obstructive lung disease patients, PaCO\(_2\) could not be estimated accurately from PetCO\(_2\) using the method previously derived for normal subjects.\(^7\) However, recent work in cystic fibrosis (CF) has shown no significant difference in the estimated and measured PaCO\(_2\), even in those with advanced lung disease.\(^2\) This then makes it possible to perform bloodless studies of \(Q\).

The following study was done to validate the measurement of \(Q\) during nonsteady state exercise using the exponential method of CO\(_2\)-rebreathe in subjects with CF.

**METHODS**

The subjects were 14 stable CF patients (6 male and 8 female subjects; 6 of 14 with FEV\(_1\) < 70 percent predicted) and 14 healthy control subjects (7 male and 7 female patients). Control subjects were volunteers who were not participants in an organized training program. No control subject had previously performed a progressive exercise test. The study had the approval of the Scientific and Ethics Committee of Chedoke-McMaster Hospitals. Written informed consent was obtained for each study. Weight and height were recorded. Weight was also expressed as a percentage of ideal weight for height.\(^8\) A baseline hemoglobin concentration was measured...
from a peripheral venous sample. The FEV₁ was measured by spirometry and expressed as a percentage of predicted value (for those less than 18 years of age⁴ and for those over 18¹⁹). Diffusing capacity (Dco) was determined by single breath carbon monoxide diffusing capacity and expressed as a percentage of predicted value (for those less than 18 years of age and for those over 18¹⁹).

The subjects performed a progressive exercise test using an electronically braked cycle ergometer with increments of 100 kpm/min to symptom-limited exhaustion. Exhaustion was judged as an inability to continue pedalling at 60 rpm and a rapidly rising respiratory exchange ratio (RER) to above 1.0. All study subjects except for one CF patient had a final RER above 1.0. Exercise was expressed as absolute work load (kpm/min), oxygen consumption (VO₂/L/min), VO₂/kg, and as a percentage of predicted value at maximum.¹⁵

The subjects breathed through a low resistance, low dead space valve, and end tidal gas was sampled at the mouth. Minute ventilation (Ve), tidal volume, respiratory rate, VO₂, VCO₂, work load, and heart rate (electrocardiograph using a 2 lead) were measured continuously on-line through an automated exercise system. Maximal heart rate was expressed as a percentage of that predicted based on age.¹⁴ Oxygen saturation was not recorded; however, no subject had a Dco less than 65 percent of that predicted. Recent work in CF suggests that significant desaturation is unlikely to occur in this situation.¹⁵

After 1 min of exercise at every second work load, measurements were made to determine ḞVCO₂ using the exponential method. The subject was switched at end-expiration into a rebreathing circuit with a bag containing 1.5 times the tidal volume of 4 percent CO₂ and 96 percent O₂. After rebreathing for 15 s at a rate of 40 breaths per minute, the subject was turned out of the bag and into the on-line circuit. For 15 s prior to and throughout the rebreathe, ṖetCO₂ was continuously analyzed by mass spectrometer and recorded on-line with a computer with a sampling frequency of 200 Hz. The system was previously calibrated with five known PCO₂ concentrations. Results were analyzed later from the stored computer values.³ The subject did not have the work load increased until 1 min from the start of the rebreathe. Work loads which did not have Q determinations lasted 1 min; those which did lasted 2 min.

After a 45 to 60 min rest period, 12 control subjects and all CF patients performed a steady state exercise test at 50 percent of their achieved maximal work load. After at least 5 min and when the subject appeared to be in steady state with respect to VO₂ and VCO₂, a rebreathe was performed while exercise continued. The subjects were randomly assigned to perform either an exponential rebreathe as described above or an equilibrium rebreathe. When steady state was reestablished following the rebreathe, approximately 2 to 5 min later, a second rebreathe was performed, using the other method.

**Estimation of ḞVCO₂**

For the determination of ḞVCO₂, the exponential method evaluates the rise in PEtCO₂ as a monoeponential curve with respect to time (Fig 1). For the purposes of analysis, the values between 1.5 and 13 s are used for VO₂ less than two thirds maximum and between 1.5 and 11 s for higher VO₂. This is done to avoid the effect of recirculation, which occurs sooner at higher work levels and result in higher PEtCO₂ values. The PEtCO₂ is linearized to time by log transformation and successive iterations of the asymptote are performed so that a best fit line is derived using least squares linear regression analysis. Using the fitted line, the PEtCO₂ value at 20 s is used as the estimate of ḞVCO₂.⁴

The equilibrium method of determining ḞVCO₂ uses a bag with 10 to 15 percent CO₂, remainder O₂, at a volume of two thirds to three fourths the vital capacity. At end expiration, the subject is turned into the rebreathing circuit. The subject breathes deeply for 12 to 15 s. A well-performed rebreathe achieves a plateau in PEtCO₂ after 6 to 10 s before recirculation occurs. If a plateau is not achieved, a correction may be applied using the data at 6 and 10 s and extrapolating to 20 s. The equilibrium plateau represents complete mixing not only between the bag and lungs but also between the alveolar gas and pulmonary blood. The plateau value between 6 and 10 s is used as the estimate of ḞVCO₂. A downstream correction is applied to this value to correct for alveolar-to-blood ṖCO₂ differences.⁴ Results were recorded on-line (Mingograf 81) and analyzed later from the direct recordings.

**Calculation of Q**

With both methods, the ḞVCO₂ value is converted to a venous CO₂ content. All subjects had a hemoglobin concentration of at least 12 g/dl so that a correction was not made when converting partial pressures to content with an assumed hemoglobin value of 15 g/dl. A mean of the five PEtCO₂ values preceding the rebreathe is used to estimate PaCO₂ using the relationship derived by Jones and colleagues which adjusts for the breathing pattern. This value is then converted to an arterial CO₂ content. Q is calculated by dividing the measured V̇CO₂ during the 15 s preceding the rebreathe by the venoarterial CO₂ content difference.

**Statistical Analysis**

Group comparisons of baseline date and exercise results were analyzed by unpaired Student's t-tests. For the purposes of analyzing the Q data, control subjects and mild CF patients (FEV₁ > 70 percent predicted, eight patients) were compared by linear regression analysis to a group of moderate (50 percent < FEV₁ < 70 percent, four patients) and severe (FEV₁ < 50 percent, two patients).
CF patients with respect to the Q-\(\dot{V}_O_2\) relation during progressive exercise. These groupings were done to separate those for whom could conceivably have a cardiopulmonary interaction affecting the cardiac response (the moderate and severe group) from those for whom this interaction is not significant (those with an FEV\(_1\) greater than 70 percent of predicted). Q results at steady state using the exponential and equilibrium methods were also compared by linear regression analysis, using the combined control and mild CF group and moderate to severe CF group. The slope and intercept of the Q-\(\dot{V}_O_2\) relation were compared to previous work\(^{a}\) by unpaired t-tests. Values are expressed as mean ± SD. A significance value of p<0.05 was used throughout. \(\dot{V}CO_2\) values at steady state were compared with paired t-tests.

**RESULTS**

The CF patients weighed less than control subjects in both absolute terms and with respect to percentage of ideal weight. The CF group also had significant obstructive lung disease compared to control subjects (Table 1).

The CF group achieved a lower maximal work output both absolutely and relatively (Table 2). There was no difference in absolute maximal heart rates, but the CF group had lower heart rates expressed as percentage of predicted values. Absolute maximal ventilation was lower in the CF group but represented a greater relative ventilation when expressed as FEV\(_1\)/min. The heart rate and ventilatory responses of the CF group suggest a pattern typically referred to as a ventilatory limitation to exercise. The highest \(\dot{V}_O_2\) at which Q was determined was 94.6±5.40 percent of \(\dot{V}_O_2\)max in the control group and 93±11.39 percent of \(\dot{V}_O_2\)max in the CF group (p>0.05).

Comparing the combined control and mild CF group to the moderate and severe CF group during progressive exercise, there was no difference in the \(\dot{V}_O_2\)-work output relation (Fig 2). The regression equation for the total study population was

\[
\dot{V}_O_2 (\text{ml/min}) = 172.7 + 2.081 \text{(work (kpm/min)}),
\]

\[r^2 = 0.946, \text{see} = 189.3\]

Comparing these two groups, there was no difference in the Q-\(\dot{V}_O_2\) relation during progressive exercise (Fig 3). Most values fell within the 95 percent confidence intervals established by Faulkner and co-workers\(^{10}\) for different levels of steady state exercise. The regression equation for the total study population was

\[
Q (\text{ml/kg/min}) = 94.5 + 4.46 \dot{V}_O_2 (\text{ml/kg/min}),
\]

\[r^2 = 0.740, \text{see} = 31.18\]

During steady state exercise, \(\dot{V}CO_2\) did not differ between the equilibrium (62.1±3.34 mm Hg) and exponential (61.6±4.38 mm Hg) methods. The derived Q was 12.5±3.34 L/min for the exponential method and 12.0±3.49 L/min for the equilibrium.
method. The regression equation comparing methods did not differ between the combined control and mild CF group and the moderate and severe CF group. In the total population, the regression equation showed a slope not different from 1 and an intercept not different from 0 (Fig 4).

**DISCUSSION**

We have demonstrated the validity of \( \dot{Q} \) measurements during incremental exercise in CF patients. We have also demonstrated that exponential and equilibrium methods give similar \( \dot{Q} \) results during steady state exercise.

Our results support previous steady state studies in CF which suggested that \( \dot{Q} \) responses \( \dot{V}_{O_2} \) for during exercise were normal.\(^{17}\) We have been able to extend these results over the full range of exercise capacity in our subjects.

Most of our data points fell within the 95-percentile confidence interval described by Faulkner's group\(^ {16} \) in their study of 50 normal adult subjects at various steady state work loads, using the exponential method. McKelvie and colleagues\(^ {3} \) found comparable results in seven healthy control subjects during progressive exercise, using the exponential method. Although our intercept (94.5) is not different from that of McKelvie et al\(^ {1} \) (87.5), our slope (4.46) is lower (5.59). However, there are very few points above a \( \dot{V}_{O_2} \) of 35 ml/kg/min in the study by McKelvie and co-workers.\(^ {3} \) When our analysis is limited to values in the same range, our slope and intercept do not differ from their study.

This may point to a limitation of the methodology during nonsteady state exercise. At high workloads, \( V_E \) rises faster than and out of proportion to \( \dot{V}_{CO_2} \). Thus \( PaCO_2 \) may be falling while \( PaCO_2 \) is rising. These changes may result in a disproportionate increase in the venoarterial CO\(_2\) content difference as compared to \( \dot{V}_{CO_2} \). This would result in an underestimation of \( \dot{Q} \) at high work loads. Although we have limited data at high work loads, it was unusual for our points to fall below the 95-percentile confidence interval of Faulkner's group. We reviewed our \( \dot{Q} - \dot{V}_{O_2} \) data with respect to measurements made when the RER was greater or less than 1.0 (Fig 5). This is when \( V_E \) and \( \dot{V}_{CO_2} \) are rising out of proportion to \( \dot{V}_{O_2} \). There was a tendency for values to be lower at high \( \dot{V}_{O_2} \) when the RER was greater than 1.0. As McKelvie and co-workers found,\(^ {3} \) a test-retest variance of the measurement of \( \dot{Q} \) in the nonsteady state of 13 percent, our small underestimation at high work loads may be hidden in the inherent variability of the measurement. However, it should be noted that the variability in this method compares very favorably to that encountered with more invasive procedures such as dye-dilution.\(^ {18} \)

Our \( PaCO_2 \) values were similar with both techniques. This is consistent with previous work which compared the two techniques during steady state.
exercise. Heigenhauser and Jones noted that the equilibrium method required downstream correction while the exponential method did not. This may relate to the concentration of CO₂ used for rebreathing. In the equilibrium method, a high concentration is used to block CO₂ excretion. In the exponential method, the low CO₂ concentration allows for excretion. Although controversies exist as to the cause of this, this gradient requiring correction occurs only when CO₂ excretion is blocked.

It has often been suggested that there is an increase in oxygen cost of exercise in subjects with lung disease due to the increased work of breathing. We did not find any difference in our groups in their VO₂-work output relation. Similar findings were recently also reported in subjects with chronic obstructive lung disease. This is consistent with previous work in CF demonstrating the small percentage of oxygen consumption which can be attributed to the cost of breathing during exercise. This may be due to the relatively small muscle mass of the respiratory muscles as compared to that of the legs during cycle ergometry. Even if the respiratory muscles dramatically increase their VO₂, their mass may represent less than 5 percent of the leg muscle mass. Given the variability in the VO₂ measurement within subjects upon restesting, this difference in oxygen cost may be extremely difficult to detect.

Exercise capacity in CF may be limited by a variety of factors. Several studies have concluded that lung function and nutritional status are of primary importance. A recent study to assess Q in 50 CF patients during steady state exercise found that cardiac function did not influence exercise performance. These authors did find that some patients had an attenuated stroke volume response and they wondered about the possibility of pulmonary hypertension secondary to hypoxemia as a cause. An alternative explanation is that those subjects with more advanced pulmonary disease are more malnourished. Malnourished CF subjects have deceased stroke volume responses to exercise compared with well nourished patients with similar pulmonary impairment. It has been demonstrated that when the same work load is performed by a small muscle mass and a large one, the Q-VO₂ response is the same but the heart rate response is greater for the small mass. This implies a decreased stroke volume response when the work is performed by a smaller muscle mass. Although not the subject of the current paper, we found that the heart rate-VO₂ response is different between the control and CF groups, with the CF group having a greater slope. This difference persists when the study population is divided into those with an FEV₁ greater than 70 percent of predicted and those with an FEV₁ less than 70 percent predicted. This suggests the importance of cardiopulmonary interaction on cardiac function during exercise. However, this difference is minimized when lean body mass is added to the regression equation suggesting that mass is the more important factor.

REFERENCES
3 McKelvie RS, Heigenhauser GJF, Jones NL. Measurement of cardiac output by CO₂ rebreathing in unsteady state exercise. Chest 1987; 92:777-82
5 Defares JG. Determination of \( \text{FiCO}_2 \) from the exponential \( \text{CO}_2 \) rise during rebreathing. J Appl Physiol 1989; 13:159-64
7 Jones NL, Robertson DC, Kane JW. Difference between endtidal and arterial \( \text{PaO}_2 \) in exercise. J Appl Physiol 1979; 47:954-60
9 Dickman ML, Schmidt CO, Gardner RM. Spirometric standards for normal children and adolescents (age 5 through 18 years). Am Rev Respir Dis 1971; 104:660-87
14 Jones NL. Clinical exercise testing. 3rd ed. Toronto: WB Saunders, 1988; 186-96
18 Hanson JS, Tabakin BS. Simultaneous and rapidly repeated cardiac output determinations by dye-dilution method. J Appl Physiol 1964; 19:275-78
21 Katsardis CV, Desmond KJ, Coates AL. Measuring the oxygen cost breathing in normal adults and patients with cystic fibrosis. Respir Physiol 1986; 65:257-66