Estimation of Mixed Venous \( P_{\text{CO}_2} \) for Determination of Cardiac Output in Children*

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**Study objectives:** Cardiac output (Q) can be estimated noninvasively during exercise by employing \( \text{CO}_2 \)-rebreathing techniques (equilibrium and exponential) to estimate the oxygenated mixed venous \( P_{\text{CO}_2} \) (PvCO\(_2\)). It has been found in adults and children that the equilibrium method underestimates Q as a result of overestimation of PvCO\(_2\), unless PvCO\(_2\) is “downstream corrected.” In adults, it has been found that the exponential method does not require downstream correction and yields values similar to those obtained by the equilibrium method with downstream correction. The objectives of this study were as follows: to test whether the exponential method gives similar results to the equilibrium method with downstream correction in children; to verify that downstream correction is required in children; and to test whether a single equation could be used in adults and children to predict Q from oxygen consumption (Vo\(_2\)).

**Design:** Descriptive.

**Setting:** Exercise laboratory of a university hospital.

**Participants:** 23 children (16 boys, 7 girls) with a mean age of 11.0±1.9 years (7.1 to 13.9 years), and 12 adults (7 men, 5 women) with a mean age of 33.6±7.2 years (24 to 48 years).

**Interventions:** While performing steady-state exercise on an ergometer, PvCO\(_2\) was determined in 14 children using both the equilibrium and exponential methods, and in all other subjects using the equilibrium method alone.

**Measurements and results:** For the 14 children who underwent testing by both the equilibrium and exponential methods, the uncorrected equilibrium PvCO\(_2\) was significantly different from both the corrected PvCO\(_2\) and the exponential PvCO\(_2\). We found a strong relationship between Q (L/min), calculated using the downstream corrected values of PvCO\(_2\), and Vo\(_2\) (L/min) \((r^2=0.95)\), and this relationship was similar to that obtained by dye dilution in other studies. When weight was included, it was determined that one equation could be used for children and adults: \( Q \) (L/min) = 1.42+5.80 \( \cdot \) Vo\(_2\) (L/min)+0.06 \( \cdot \) wt (kg), \( r^2=0.97\), SEY=0.67.

**Conclusions:** \( \text{CO}_2 \)-rebreathing techniques can be used to determine Q in children; the exponential method gives values that are similar to the equilibrium method with the downstream correction; and one prediction can be used for Q in adults and children. (CHEST 1997; 111:474-80)

**Key words:** equilibrium rebreathing method; exercise; exponential rebreathing method

**Abbreviations:** PEqCO\(_2\)=end-tidal \( P_{\text{CO}_2} \) at equilibrium; PFrCO\(_2\)=end-tidal \( P_{\text{CO}_2} \); \( P_{\text{CO}_2} \)=oxygenated mixed venous \( P_{\text{CO}_2} \); FVCO\(_2\) eq.cor=corrected equilibrium FVCO\(_2\); FVCO\(_2\)exp=exponential FVCO\(_2\); Q=cardiac output; SE=standard error; \( V_{\text{CO}_2}\)=carbon dioxide production; \( V_{o_2}\)=oxygen consumption

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Cardiac output (Q) can be determined noninvasively during exercise using the indirect \( \text{CO}_2 \)-rebreathing method. By this technique, oxygenated mixed venous \( P_{\text{CO}_2} \) (PvCO\(_2\)) is estimated using one of two methods: the equilibrium method of Collier\(^1\) or the exponential method of Defares.\(^2\) In the equilibrium method, a relatively high concentration of \( \text{CO}_2 \) is rebreathed, which leads to an equilibration of \( \text{CO}_2 \) in the lungs and blood and a plateau in the
end-tidal P_{CO_2} (PETCO_{2}, at equilibrium known as PEqCO_{2}). In the exponential method, a low concentration of CO₂ is rebreathed, which results in an exponential rise in the PETCO_{2}.

In exercising adults, it has been found that the equilibrium method overestimates FVCO_{2} as determined by PEqCO_{2}, resulting in an underestimation of the Q in comparison to dye-dilution measures.\textsuperscript{3,4} This led to the development of a correction factor for FVCO_{2} that is known as the “downstream correction factor” (FVCO_{2}=PEqCO_{2}−[0.24·PEqCO_{2}−11]).\textsuperscript{5} However, this correction does not appear to be necessary using the exponential method.\textsuperscript{5} The reason for this downstream correction with the equilibrium method remains unclear, but it is likely related to the absence of outward movement of CO₂ from the blood to the rebreathing bag during this method.\textsuperscript{5}

In children, there has been some controversy over whether downstream correction is necessary when using the equilibrium method to determine Q. Godfrey and coworkers\textsuperscript{7} found that the overestimation of FVCO_{2} that had been seen in adults\textsuperscript{4,5,9} was also present in children,\textsuperscript{7} but Godfrey\textsuperscript{10} suggests that the use of the downstream correction in children gives an overly high estimate of Q, so that the uncorrected plateau value for FVCO_{2} should be used.\textsuperscript{10} Paterson and coworkers,\textsuperscript{11,12} however, found that the use of the downstream correction in children gave values that were close to those obtained by dye dilution on similar populations,\textsuperscript{11} and that the equilibrium method with downstream correction allowed reliable and consistent measurement of Q.\textsuperscript{12}

It has been demonstrated recently that the exponential method gives Q estimates similar to those of the equilibrium method, after the downstream correction, during steady-state exercise in cystic fibrosis patients and healthy control subjects over the age of 14 years.\textsuperscript{13,14} The exponential method is well tolerated, as it requires the use of a lower concentration of CO₂ than does the equilibrium method, and it can be used during progressive exercise testing.\textsuperscript{14} The aims of the present study were as follows: (1) to compare the exponential method for determination of FVCO_{2} using new computer analysis techniques with the equilibrium method in children; (2) to confirm that downstream correction of FVCO_{2} was required in healthy children from 7 to 13 years of age when the equilibrium method was used; and (3) to test whether a single equation could be used in children and adults for prediction of Q from oxygen consumption (\(\text{VO}_2\)).

We hypothesized the following in exercising children: (1) FVCO_{2} obtained by the exponential method would be similar to that obtained by the equilibrium method using the downstream correction; (2) when plotted against \(\text{VO}_2\), corrected values for Q would be similar to those obtained by others using dye dilution; and (3) when plotted against \(\text{VO}_2\), the values for Q in children and adults would not differ when downstream correction was employed.

**Materials and Methods**

**Subjects**

Hospital staff and their children were recruited for the study. Data obtained from prematurely born children who were participating in a long-term follow-up study and from children who had undergone exercise testing for growth hormone secretion were also employed. Subjects were excluded if they had an FEV\textsubscript{1} of <80% of their predicted value based on age, race, sex, and height.\textsuperscript{15,16} The study had the approval of the Institutional Review Board of the Montreal Children’s Hospital/McGill Research Institute. For children, an informed consent was obtained from one of the parents as well as from the child.

**Methods**

For each subject, height was measured in stocking feet on a stadiometer and weight was measured using an electronic balance. Respiratory spirometry was performed according to American Thoracic Society criteria.\textsuperscript{17}

To determine maximal work capacity, all subjects, except the two being evaluated for growth hormone secretion, performed a maximal progressive test using an electronically braked cycle ergometer. The workload was increased in 1-min increments, which were chosen according to the sex and height of the subject so that exhaustion would occur within 5 to 10 min.\textsuperscript{16} The maximum workload was the highest workload at which a subject was able to maintain a pedaling speed of 60 rpm. Heart rate was monitored continually and recorded via ECG. Inspired ventilation was measured by a dry gas meter (Parkinson Cowan; Manchester, UK). Exhalation was via a unidirectional valve to a variable-volume mixing chamber adjusted to the subject’s vital capacity. Mixed expired gas was analyzed and recorded continuously for fractional concentrations of oxygen and carbon dioxide using a mass spectrometer (Marquette Electronics; Milwaukee). \(\text{VO}_2\) and carbon dioxide production (\(\text{VCO}_2\)) were calculated using the nitrogen balance technique, based on values for ventilation and mixed expired concentrations of oxygen and carbon dioxide obtained during the last 10 s of each workload. Details of the method have been described previously.\textsuperscript{18,19}

After a rest period of at least 30 min, a steady-state exercise test was performed at approximately half maximal work capacity in adults and children with the exception of two adult men who were evaluated at two-thirds maximal work capacity in order to increase the range of \(\text{VO}_2\) measured. For the two children being tested for growth hormone levels, the steady-state test was performed at half the predicted maximal work capacity based on sex and height.\textsuperscript{10} Exercise at a constant workload was performed until steady-state conditions were reached for \(\text{VO}_2\), \(\text{VCO}_2\), and heart rate. This usually occurred within 4 to 5 min.

At steady state, a rebreathing procedure was performed using the equilibrium method in which each subject rebreathed from a bag containing a mixture of a high concentration of CO₂ (11 to 13.5%) and oxygen (78.5 to 79%) at a volume of two-thirds the vital capacity.

In children, after steady state had been reestablished (a
minimum of 60 s), a second rebreathing procedure was performed using the exponential method. For this, the subject rebreathed a mixture of 4% CO₂ and 96% oxygen at a volume of 1.5 to 2 times the tidal volume.

\[ PFCO_2 = \text{calculated for the equilibrium method using the method of Collier}^4 \text{ in which the plateau value of PetCO}_2 \text{ between 6 and 10 s (PetCO}_2) \text{ was determined; the extrapolation procedure described by Denison et al}^5 \text{ was used when an absolute plateau was not obtained. The downstream correction applied to this value to correct for alveolar-to-blood PCO}_2 \text{ differences.}^5 \text{ For the exponential method, PFCO}_2 \text{ was calculated using the method of Defares.}^2 \text{ PetCO}_2 \text{ values between 1.5 and 13 s were used for Vo}_2 < 5 \text{ max and those between 1.5 and 11 s for higher values of Vo}_2, \text{ to avoid the effects of recirculation. PetCO}_2 \text{ was linearized to time by log transformation and successive iterations of the asymptote were performed to derive a best fit line using least squares linear regression analysis. Using the fitted line, the projected PetCO}_2 \text{ value at 20 s of rebreathing was used as the estimate of PFCO}_2.}^{20}

\[ Q = \text{determined by dividing the VCO}_2 \text{ by the venous-arterial CO}_2 \text{ content difference, which was derived from the CO}_2 \text{ tensions,}^{21} \text{ assuming a hemoglobin of 150 g/L at pH of 7.40, and an oxygen saturation of 97% for arterial blood. It was assumed that the oxygen saturation of the mixed venous blood was 100% during the rebreathing procedure, because of the high concentration of oxygen in the rebreathing gas mixture. Vo}_2 \text{ and VCO}_2 \text{ were calculated for the 15 s prior to each rebreath. PaCO}_2 \text{ was estimated from PetCO}_2 \text{ using a correction factor as described by Jones}^5.\]

\[ \text{PaCO}_2 = 5.5 + 0.9 \cdot \text{PetCO}_2 - 0.0021 \cdot \text{tidal volume}. \]

PFCO₂ was estimated by the equilibrium method.

**Analysis of Data**

PFCO₂ as obtained by the equilibrium method, with and without downstream correction, was compared to that obtained by the exponential method using analysis of variance. The relationships between the corrected and uncorrected PFCO₂ values obtained by the equilibrium method and the values obtained by the exponential method were assessed by linear regression analysis.

\[ Q = \text{obtained by the equilibrium method with and without downstream correction was plotted against Vo}_2 \text{ and assessed by linear regression analysis. Stepwise linear regression analyses were also performed to look at the effects of weight, sex, and subject category (adults, normal children, prematurely born children, children being evaluated for growth hormone levels).} \]

For regression equations, slopes and intercepts were compared with those in the literature using the unpaired t test; because the standard errors (SEs) were not available for the values from the literature, the differences between the values obtained in this study and those in the literature were divided by the standard errors of the values obtained in this study.

**Results**

A total of 14 children (11 boys and 3 girls), mean age 11.7 ± 1.6 years, range 8.2 to 13.9 years, successfully underwent steady-state exercise tests in which PFCO₂ was measured by both the exponential and equilibrium methods. Eight were healthy children of hospital staff, four were healthy prematurely born children, and two were otherwise healthy children who had undergone testing for growth hormone secretion due to short stature. Nine other children (five boys and four girls) underwent steady-state exercise tests in which PFCO₂ was obtained by the equilibrium method alone. Five were children of hospital staff and four were prematurely born. The mean age of the 23 children was 11.0 ± 1.9 years, range 7.1 to 13.9 years. Twelve adults (seven men and five women), mean age 33.6 ± 7.2 years, range 24 to 48 years, underwent steady-state exercise tests in which PFCO₂ was measured by the equilibrium method.

\[ \text{PvCO}_2 \]

In exercising children, there was a closer agreement between the downstream corrected equivalence PVCO₂ and exponential values than between the uncorrected equivalence and exponential measures. As is seen in Figure 1, the equilibrium downstream corrected values of PVCO₂ plotted against the exponential values, fell closer to the line of identity than did the uncorrected equivalence values of PVCO₂. Mean PVCO₂ by the exponential method was 62.0 ± 5.1 mm Hg. By the equilibrium method, absolute PVCO₂ was 68.4 ± 4.9 mm Hg, and corrected PVCO₂ was 63.0 ± 3.7 mm Hg. By analysis of variance, there was a significant difference between the mean uncorrected equivalence value and the mean values obtained by the other two methods (p=0.012).

When the uncorrected equivalence PVCO₂ was plotted against exponential PVCO₂ in mm Hg (Fig 1, filled squares), we found a slope of 0.89 (SE, 0.1) and an intercept of 14.1 (SE, 6.8). For corrected equivalence PVCO₂ (PVCO₂ eq,corr) vs exponential PVCO₂ (PVCO₂ exp) (Fig 1, open squares), we found a slope of 0.67 (SE, 0.08) and an intercept of 21.7 (SE, 5.2). In adults, Heigenhauser and Jones⁶ found the following relationship between the PVCO₂ eq,corr and the PVCO₂ exp:

\[ \text{PVCO}_2 \text{ eq,corr} (\text{kpa}) = 2.38 + 0.7 \cdot \text{PVCO}_2 \text{ exp} (\text{kpa}) \quad (1) \]

When our regression equation is expressed in kilopascals,

\[ \text{PVCO}_2 \text{ eq,corr} (\text{kpa}) \]

\[ = 2.89 (\text{SE, 0.69}) + 0.67 (\text{SE, 0.08}) \quad (2) \]

the slope and intercept are not significantly different from those obtained by Heigenhauser and Jones.⁶

In a later study from the same group,²⁰ values fell
closer to the line of identity, with a slope of 0.975 and an intercept of 1.46. Their data encompassed a much broader range than did ours, and our values can be superimposed on their concordance plot.

Cardiac Output

Downstream corrected equilibrium \( \dot{Q} \) in liters per minute plotted against \( \dot{V}O_2 \) in liters per minute for all adults and children gave us the following regression equation:

\[
\dot{Q} \text{ (L/min)} = 1.79 \text{ (SE, 0.40)} + 7.89 \text{ (SE, 0.31)}
\cdot \dot{V}O_2 \text{ (L/min)}, \quad r^2=0.95 \quad (3)
\]

for submaximal exercise with a range of \( \dot{V}O_2 \) from 0.5 to 2.5 L/min. This equation is very similar to that obtained using the combined values from two previously published dye dilution studies, one involving pubertal boys\(^9\) and the other involving young men:\(^8\)

\[
\dot{Q} \text{ (L/min)} = 1.75 + 7.95 \cdot \dot{V}O_2 \text{ (L/min)}, \quad r^2=0.48 \quad (4)
\]

This relationship can be seen in Figure 2.

A small difference in the \( Q-\dot{V}O_2 \) relationship between children and adults was determined using stepwise linear regression analysis and a grouping factor, \( gp \) (0 for children and 1 for adults):

\[
\dot{Q} \text{ (L/min)} = 2.40 \text{ (SE, 0.39)} + 7.05 \text{ (SE, 0.36)}
\cdot \dot{V}O_2 \text{ (L/min)} + 1.21 \text{ (SE, 0.35)} \cdot gp,
\quad r^2=0.96 \quad (5)
\]

This difference is eliminated when weight (\( wt \)) is factored into the equation

\[
\dot{Q} \text{ (L/min)} = 1.42 \text{ (SE, 0.33)} + 5.80 \text{ (SE, 0.53)}
\cdot \dot{V}O_2 \text{ (L/min)} + 0.06 \text{ (SE, 0.01)} \cdot wt \text{ (kg)},
\quad r^2=0.97 \quad (6)
\]

When calculated without an intercept for comparison with the equation suggested by Jones,\(^5\)

\[
\dot{Q} \text{ (L/min)} = 5.5 \cdot \dot{V}O_2 \text{ (L/min)} + 0.06 \cdot wt \text{ (kg)} \quad (7)
\]

the equation becomes

\[
\dot{Q} \text{ (L/min)} = 6.25 \text{ (SE, 0.64)}
\cdot \dot{V}O_2 \text{ (L/min)} + 0.075 \text{ (SE, 0.016)}
\cdot wt \text{ (kg)} \quad (8)
\]

which has coefficients that are not significantly different from those proposed by Jones. Sex was not a contributing factor to the regression equation, nor was subject category (term, prematurely born, or undergoing testing for growth hormone secretion) a contributing factor among children.

When \( Q \) and \( \dot{V}O_2 \) were expressed in mL/min/kg, the following equation was obtained:

\[
\dot{Q} \text{ (mL/min/kg)} = 83.5 \text{ (SE, 20.0)} + 6.2 \text{ (SE, 0.8)}
\cdot \dot{V}O_2 \text{ (mL/min/kg)}, \quad r^2=0.66 \quad (9)
\]
Using the $F\text{CO}_2$ obtained by the equilibrium method with the downstream correction, we found a very high correlation, $r^2=0.95$, between $Q$ and $\text{VO}_2$ in healthy adults and children of both sexes (equation 3, Fig 2). Our results agree closely with those of dye dilution studies23,24 (equation 4, Fig 2). We found that there was a slight additional effect when a grouping factor, indicating whether a subject was a child or an adult, was included, but this effect disappeared when weight was included as one of the independent variables in the stepwise linear regression equation. We therefore suggest, for ease of use and applicability to both children and adults, that the following equation (equation 6) be used in the prediction of $Q$: $Q = (L/min) = 1.42 + 5.80 \cdot \text{VO}_2$ (L/min) + 0.06 $\cdot$ wt (kg), $r^2 = 0.97$, standard error of the estimate (SEE) = 0.67. Using a forced intercept of zero, our equation (equation 8) was not significantly different from that of Jones (equation 7), which was extrapolated from values in the literature. Since the exponential method is reliable in determination of $Q$ in mild to moderate lung disease13 as well as in severe lung disease in adults,25 we would suggest that the indirect Fick method may be applicable to a wide patient population, although arterial Pco$_2$ may need to be measured directly in patients with severe airflow limitation.26 In addition, because the exponential method is well tolerated and can be used during progressive exercise, the indirect Fick method can be used for the determination of $Q$ in a wide variety of clinical and research studies.

Our results are in keeping with studies in adults3,4,27 and children,11 that found good agreement between $Q$ calculated using downstream corrected equilibrium values for $P\text{CO}_2$ and that measured by dye dilution techniques. Furthermore, Gadhoke and Jones28 found that the relationship between $Q$ and $\text{VO}_2$ did not differ between boys and men. While Godfrey et al7,29 acknowledged the existence of an alveolar to blood gradient in children that was no different from that found in adults, they suggested that the uncorrected value for $P\text{CO}_2$ should be used in children to avoid overestimation of cardiac output. It is unclear why our results differ from those of Godfrey et al. While the use of an infrared analyzer to measure Pco$_2$ can affect CO$_2$ readings due to collision broadening,30 this would not explain the difference as we used a mass spectrometer, which is not subject to collision broadening, and Godfrey et al controlled for the effects of collision broadening in their study (personal communication). Paterson and Cunningham11 suggested that the CO$_2$ dissociation derived by Godfrey et al may have raised the values of $Q$ in children, as compared to the curve of McHardy, which we used in our study, or that of Comroe. In the present study, 

In our study, for men alone, the following equation was obtained:

$$Q = 80.3 \pm 22.8 + 5.8 \pm 0.9$$

which has a slope and intercept not significantly different from the equation described by Faulkner and coworkers22 in their study of 50 normal adult male subjects at various steady-state work loads using the exponential method (Fig 3):

$$Q = 66 + 5.2 \cdot \text{VO}_2 (\text{L/min/kg}) \quad (10)$$

Values in children were slightly higher:

$$Q = 97.1 \pm 27.5 + 5.9 \pm 1.0$$

$$\cdot \text{VO}_2 (\text{L/min/kg}), \quad r^2 = 0.60 \quad (12)$$

and, when results for adults and children were combined, the grouping factor (adults vs children) contributed significantly to the regression equation ($r^2$ increased from 0.66 to 0.71).

**DISCUSSION**

We found in healthy children that $P\text{CO}_2$ obtained using the exponential method was similar to the downstream corrected equilibrium value, but significantly different from the uncorrected equilibrium value. This is similar to what has been described in adults.6,13,20 This suggests that in children, as in adults, either the equilibrium method with downstream correction or the exponential method can be used when calculating $P\text{CO}_2$. 

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21743/)

**Figure 3.** $Q$ (mL/min/kg) vs $\text{VO}_2$ (mL/min/kg). Most of the values for adults (“X” = absolute and asterisk = corrected) fall within the 95% confidence interval for values of Faulkner et al using the exponential method. The values for children (solid squares = absolute and open squares = corrected) are somewhat higher.
both children and adults were evaluated using the same exercise apparatus and protocol, and both groups had similar values to those obtained by dye dilution.

When \( Q \) in mL/min/kg, calculated using the corrected \( F\text{VCO}_2 \), was plotted against \( \text{VO}_2 \) in mL/min/kg, most of our data points for adults fell within the 95th percentile confidence interval described by Faulkner et al\(^{22}\) in their study of 50 normal adult male subjects at various steady-state work loads using the exponential method (Fig 3), although our values tended to be somewhat higher. Differences between our values and those of Faulkner et al may result from slight differences in the equations used to convert partial pressures to contents as the equations used by Faulkner et al were not specified. Most of our data points for children using the downstream correction were higher than those predicted by the 95th percentile confidence interval of Faulkner et al (Fig 2). In our stepwise regression analysis for prediction of \( Q \), we found a difference between children and adults. In their study, Faulkner et al found a lower intercept for the normalized relationship in men older than 40 years of age who had a \( \text{VO}_2 \) of <30 mL/min/kg, and suggested that the difference in intercepts may be due to body fat in excess of 18%. We did not have data on body fat on all the adults and children who we tested, but we speculate that as children tend to have a lower body fat percentage than adults, this is a possible explanation for their relatively higher values for \( Q \) per kilogram of body weight.

It should be noted that our prediction equations apply to adults and children performing submaximal exercise, with a range of \( \text{VO}_2 \) from 0.5 to 2.5 L/min. We cannot comment on whether they are applicable to the determination of \( Q \) at higher levels of \( \text{VO}_2 \).

We conclude that \( \text{CO}_2 \)-rebreathing techniques, equilibrium and exponential, may be used in children to estimate \( Q \) noninvasively. In children, as in adults, the downstream correction factor should be applied to \( F\text{VCO}_2 \) obtained by the equilibrium method. With this, a prediction equation for \( Q \) is obtained, based on \( \text{VO}_2 \), which is very similar to that obtained from dye dilution studies. When weight is included in the equation, the relationship is further strengthened, and one equation can be used to describe \( Q \) in children and adults.

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