

Sources of Error in Noninvasive Pulmonary Blood Flow Measurements by Partial Rebreathing

A Computer Model Study

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Background: Partial rebreathing is a noninvasive method for measuring pulmonary blood flow (PBF). This study examines the systematic errors produced by the partial rebreathing technique utilizing a comprehensive mathematical model of the cardiorespiratory system of a healthy, 70-kg adult male.

Methods: The model simulates tidal breathing through a branched respiratory tree and incorporates the effects on carbon dioxide dynamics of lung tissue mass, vascular transport delays, multiple body compartments, and realistic blood-gas dissociation curves. Four studies were performed: (1) errors produced under standard conditions, (2) effects of recirculation, (3) effects of alveolar-proximal airway partial pressure of carbon dioxide (P_{CO_2}) differences, and (4) effects of rebreathing time.

Results: Systematic errors are less than 10% when the simulated PBF is between 3 and 6 l/min. At 2 l/min, PBF is overestimated by approximately 35%. At 14 l/min, PBF is underestimated by approximately 40%. At PBF of greater than 6 l/min, recirculation causes approximately 60% of the systematic error, alveolar-proximal airway differences cause approximately 20%, and alveolar-arterial differences cause approximately 20%. The standard rebreathing time of 50 s is shown to be excessive for PBF of greater than 6 l/min. At PBF of less than 3 l/min, errors are caused by inadequate rebreathing time and alveolar-arterial gradients.

Conclusions: Systematic errors in partial rebreathing cardiac output measurements have multiple causes. Our simulations suggest that errors can be reduced by using a variable rebreathing time, which should be increased at low PBF so that quasi-equilibrium in the alveoli can be achieved and decreased at high PBF to reduce the effects of recirculation.

THE noninvasive partial rebreathing method for measuring pulmonary blood flow (PBF) was initially developed by Gedeon *et al.*¹ The technique requires the subject to breathe through an altered dead space and uses a differ-

ential form of the Fick mass balance equation to calculate PBF from end-tidal airway carbon dioxide partial pressures (P_{ETCO_2}) and airway carbon dioxide flux. PBF is calculated from measurements taken before and after a short period (30–50 s) of rebreathing. This technique eliminates the need to estimate mixed venous carbon dioxide concentration and the differential format reduces the error caused by alveolar-arterial partial pressure of carbon dioxide (P_{CO_2}) gradients. The derivation of the differential form of the Fick principle is discussed in Appendix A. Some studies comparing the partial rebreathing technique with the thermodilution technique^{2,3,4,5} suggest that the technique yields errors that are acceptable for clinical application. Recent independent evaluation of the partial rebreathing method as implemented in a commercial instrument (NICO; Novamatrix, Wallingford, CT), however, have suggested that the technique overestimates low cardiac outputs⁷ and underestimates high cardiac outputs.^{6,7,8} The objective of this study is to identify and quantify potential sources of error in measurements of PBF by the partial rebreathing technique. We studied the impact of rebreathing time, recirculation, and alveolar-proximal airway differences using mathematical modeling.

Materials and Methods

We evaluated the partial rebreathing technique using a comprehensive mathematical model of the cardiorespiratory system of a healthy, 70-kg adult male. The model simulates tidal breathing through a branched respiratory tree and incorporates the effects on carbon dioxide dynamics of lung tissue mass, vascular transport delays, multiple body compartments, and realistic blood-gas dissociation curves. It is implemented using Matlab and Simulink (Mathworks, Natick, MA). (See Appendix B for further details of the model.) For the purposes of this study, an additional variable dead space that can be switched in and out to simulate the rebreathing process was incorporated into the model. A block diagram of the model of the cardiorespiratory system is shown in figure 1.

Study 1: Standard Conditions

The model was run for 6,000 s with parameters shown in table 1 and with the rebreathing dead space bypassed to create a set of initial conditions for cardiac outputs

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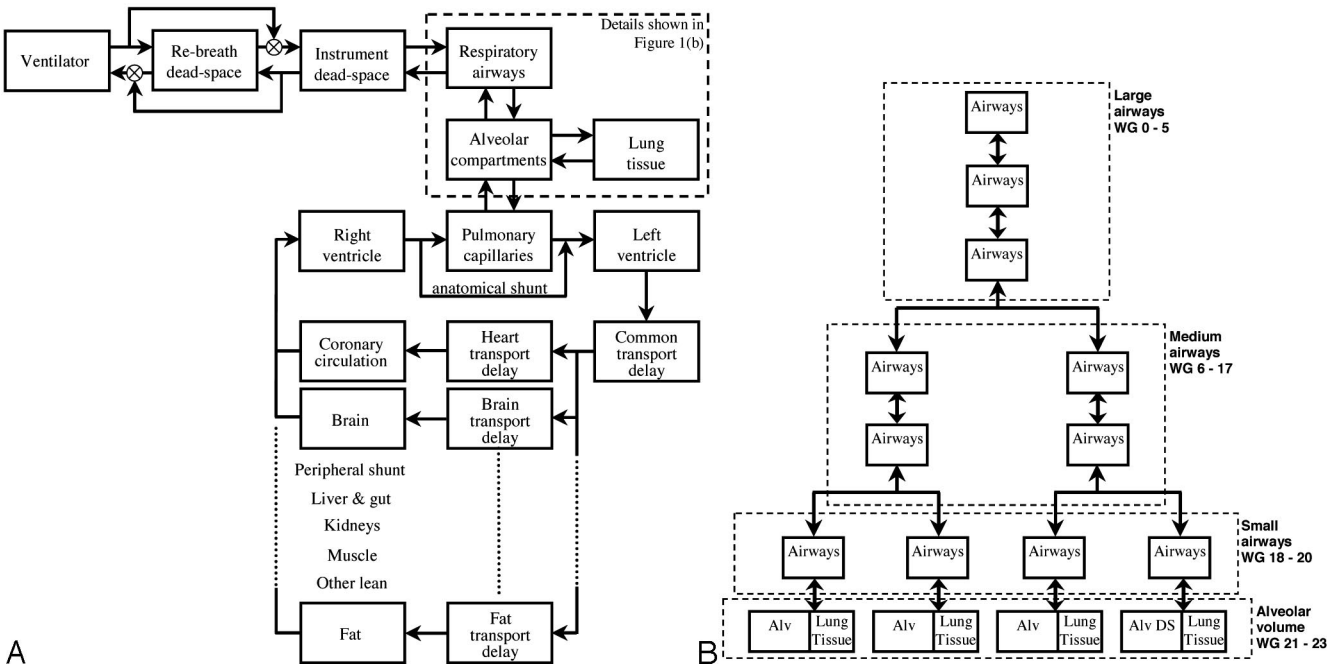


Fig. 1. Block diagram of the comprehensive cardiorespiratory system with variable extrapulmonary dead space. (A) The cardiorespiratory system includes body compartments for coronary circulation, brain, peripheral shunt, liver and gut, kidneys, muscle, other lean tissues, and fat. (B) The respiratory system incorporates a 14-compartment approximation to Weibel's lung model. In this study, the alveolar dead space was set to zero. Each block represents one compartment with diffusive transport and storage, and the arrows between the blocks represent convective transport. WG = Weibel generations; Alv = alveolar; DS = dead space.

1.5 l/min and 2–14 l/min in steps of 1 l/min (representing true nonshunted PBF from 1.47 to 13.72 l/min). The initial gas in the additional dead space was air. At each cardiac output, a series of data sets were generated by running the model from an appropriate initial condition and switching the additional dead space in for 50 s at intervals of 180 s. The PBF values were calculated from PETCO₂ and airway carbon dioxide flux averaged over single breaths taken immediately before the start and end of the 10th rebreathing cycles, using equation A3.

Study 2: Effects of Recirculation

The partial rebreathing method assumes that mixed venous blood concentrations of carbon dioxide remain constant immediately before and during the rebreathing

phase of each measurement cycle. To examine the effects of changes in mixed venous PCO₂ caused by recirculation, the model was modified by removing all the body compartments. The mixed venous PCO₂ and partial pressure of oxygen (PO₂) inputs to the pulmonary capillaries were kept constant at values appropriate to the cardiac output. The simulations described above in study 1 were repeated.

Study 3: Effects of Alveolar-Proximal Airway Differences in Pco₂ and Carbon Dioxide Flux

The partial rebreathing method is based on the mass balance of carbon dioxide at the pulmonary capillary-alveolar interface but uses measurements in the proximal airway. The duration of rebreathing is selected to be long enough for a quasi-steady state in alveolar PCO₂ (PACO₂), PETCO₂, and airway carbon dioxide flux to be reached but short enough to keep recirculation effects small. To examine the effects of using PETCO₂ and proximal airway carbon dioxide flux measurements instead of PACO₂ and pulmonary capillary carbon dioxide flux measurements, PBF values were calculated using PACO₂ and pulmonary capillary carbon dioxide flux averaged over a single breath. No recirculation was included in these simulations.

Study 4: Effects of Rebreathing Time

The time constant for alveolar carbon dioxide turnover depends strongly on PBF because of the high solubility

Table 1. Model Parameters

Tidal volume, ml	750
Respiratory rate, breaths/min	10
Alveolar volume, l	2.03
Anatomical dead space, l	0.171
Standard instrument dead space, ml	50
Oxygen consumption, mmol/s	193.1
Carbon dioxide production, mmol/s	159.9
FIO ₂	0.35
I:E ratio	1:2.33
Anatomical shunt, %	1
Intrapulmonary shunt, %	1
Hemoglobin, g/100 ml of whole blood	15
Base excess, mEq/l	0

FIO₂ = fraction of inspired oxygen.

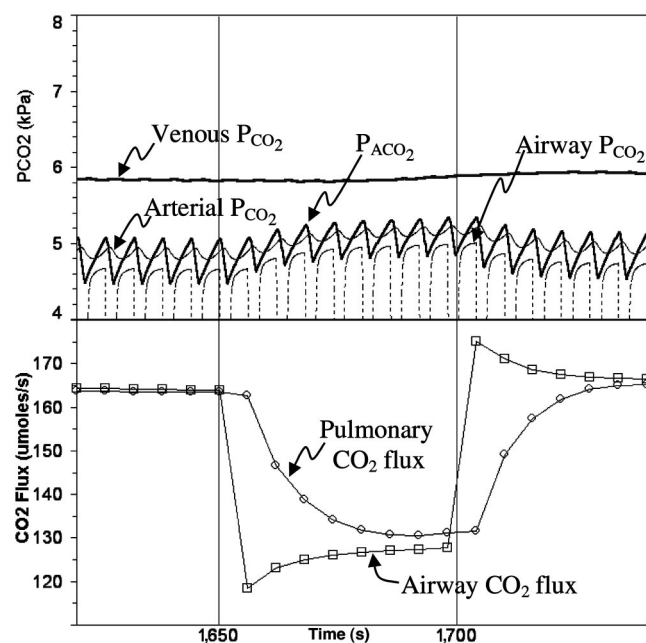


Fig. 2. Simulated airway P_{CO_2} , P_{ACO_2} , mixed venous P_{CO_2} , arterial P_{CO_2} , and airway and pulmonary capillary carbon dioxide flux for the 10th rebreathing cycle for simulated cardiac outputs of 4 l/min. Rebreathing time: 50 s; rebreathing dead space: 150 ml. Dashed line = airway P_{CO_2} ; thickest line = P_{ACO_2} ; thin line = arterial P_{CO_2} ; thick line = venous P_{CO_2} ; line with open square = airway carbon dioxide flux; line with open circle = pulmonary carbon dioxide flux.

of carbon dioxide in blood. Therefore, the time required to achieve a quasi-steady state in P_{ACO_2} , P_{ETCO_2} , and airway carbon dioxide flux after a perturbation is increased when PBF is low and decreased when PBF is high. To examine the effects of rebreathing time, three investigations were performed:

1. Pulmonary blood flow values were calculated using an extended rebreathing time of 300 s. No recirculation was included in these simulations. The simulations described above in study 1 were repeated.
2. The percentage of the step change in P_{ETCO_2} completed during 50 s of rebreathing was determined using results from (1) above.
3. The rebreathing times necessary for P_{ETCO_2} to change through 95% of the change achieved after 300 s of rebreathing were determined for each PBF using results from (1) above. Simulated partial rebreathing measurements with recirculation were repeated using these rebreathing times at each value of PBF.

In all studies, additional data sets were generated using simulated rebreathing dead space volumes of 50, 100, 150, and 200 ml.

Results

Study 1: Standard Conditions

Typical proximal airway P_{CO_2} and breath-by-breath proximal airway and pulmonary capillary carbon dioxide

Table 2. Model Predictions under Standard Conditions

Simulated CO, l/min	1.5	4	10
Nonshunted PBF, l/min	1.47	3.92	9.8
$\dot{V}CO_2$ before rebreathing, $\mu\text{mol/s}$	159	163	166
$\dot{V}CO_2$ after rebreathing, $\mu\text{mol/s}$	130	128	126
$\Delta\dot{V}CO_2$, $\mu\text{mol/s}$	29	35	40
Before rebreathing			
P_{ETCO_2} , kPa	4.54	4.66	4.74
C_{ACO_2} , mm	19.9	20.1	20.2
After rebreathing			
P_{ETCO_2} , kPa	5.06	4.98	4.95
C_{ACO_2} , mm	20.68	20.62	20.55
ΔC_{ACO_2} , mm	0.78	0.52	0.35
\dot{Q}_p , l/min	2.22	4.00	6.97
Error, %	51	2	-28

C_{ACO_2} = arterial carbon dioxide concentration; PBF = pulmonary blood flow; P_{ETCO_2} = end-tidal pressure of carbon dioxide; \dot{Q}_p = pulmonary blood flow; $\dot{V}CO_2$ = carbon dioxide output.

flux, generated using a PBF value of 4.0 l/min with the additional dead space set at 150 ml, are shown in figure 2 for the 10th rebreathing period. The rebreathing period was 50 s, and the rebreathing cycle was repeated every 180 s. The 10th rebreathing period starts at 1,650 s and finishes at 1,700 s. Between 1,620 s and 1,650 s, both P_{CO_2} levels and carbon dioxide flux reflect the quasi-equilibrium achieved after the ninth rebreathing cycle. Changed P_{CO_2} was read at 1,700 s, which is the end of the 10th rebreathing period. Changed carbon dioxide flux was taken from the last completed breath before 1,700 s.

The difference between the simulated true PBF and the PBF calculated from rebreathing measurements (table 2) is shown in figure 3 (curve a). The results show errors that vary systematically with the true PBF. At low simulated PBF (< 4.5 l/min), the partial rebreathing tech-

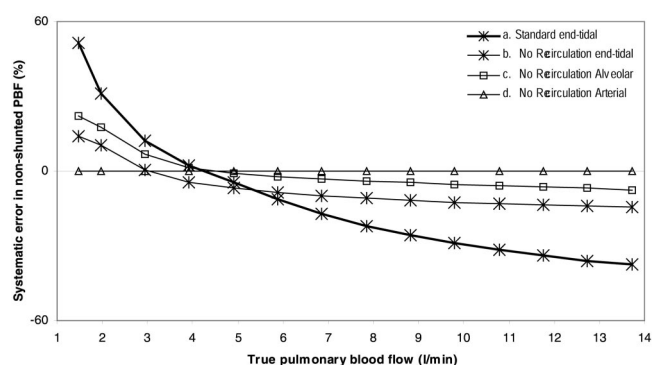


Fig. 3. Plot of the systematic error in the simulated partial rebreathing measurements of PBF as a function of simulated true PBF. Rebreathing dead space set to 150 ml. Thick line with asterisk = standard model applying P_{ETCO_2} and airway carbon dioxide flux; thin line with asterisk = no recirculation model, differential Fick equation evaluated using P_{ETCO_2} and airway carbon dioxide flux; line with open square = no recirculation model, differential Fick equation evaluated using P_{ACO_2} and alveolar carbon dioxide flux; line with open triangle = no recirculation model, differential Fick equation evaluated using arterial P_{CO_2} and pulmonary capillary-alveolar carbon dioxide flux.

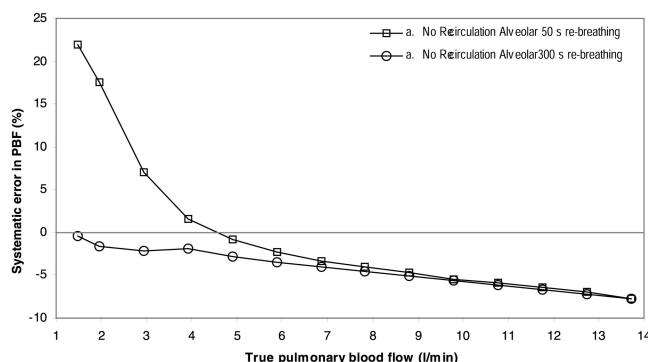


Fig. 4. Plot of the systematic error in the partial rebreathing measurements of PBF as a function of simulated true PBF. Line with open square = no recirculation model, differential Fick equation evaluated using P_{ACO_2} and alveolar carbon dioxide flux with 50 s rebreathing time; line with open circle = no recirculation model, differential Fick equation evaluated using P_{ACO_2} and alveolar carbon dioxide flux with 300 s rebreathing time.

nique tends to overestimate PBF, while at high cardiac outputs (> 4.5 l/min), the technique tends to underestimate PBF. The results indicate that the measurements are most accurate with systematic error less than 10%, when the simulated PBF is between 3 and 6 l/min.

Study 2: Effects of Recirculation

The effects of removing recirculation are shown in curve b of figure 3 (additional dead space set to 150 ml). Removal of recirculation clearly reduces the systematic error in the measurements. At low simulated PBF (< 4.5 l/min), study 2 produced systematic errors approximately 75% less than those of study 1, while at high cardiac outputs (> 4.5 l/min), study 2 produced systematic errors approximately 60% better than those of study 1. They indicate, however, that even in the absence of recirculation, the partial rebreathing technique tends to overestimate PBF at low cardiac outputs and underestimate PBF at high cardiac outputs.

Study 3: Effects of Alveolar-Proximal Airway Differences on P_{CO_2} and Carbon Dioxide Flux

Results obtained using P_{ACO_2} as an estimate of arterial P_{CO_2} and true pulmonary capillary carbon dioxide flux (without recirculation) in the differential Fick equation, shown in curve c of figure 3, are clearly more accurate than the results from either study 1 or study 2. PBF is, however, still underestimated at high cardiac outputs and overestimated at low cardiac outputs.

Results obtained using arterial P_{CO_2} and pulmonary capillary carbon dioxide flux (without recirculation) in the direct Fick equation, shown in curve d of figure 3, produced excellent results across the entire range examined.

Study 4: Effects of Rebreathing Time

1. Figure 4 compares results obtained with a rebreath-

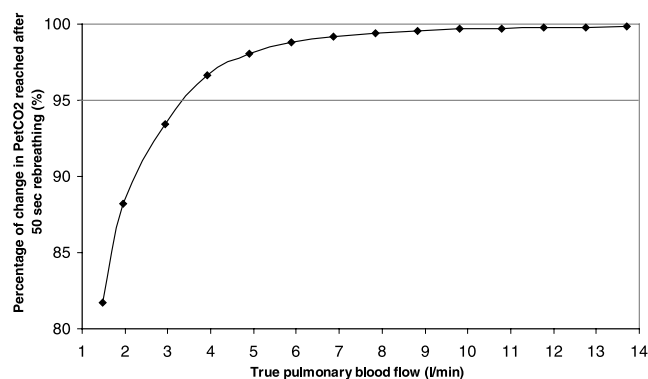


Fig. 5. Percentage of quasi-equilibrium change in P_{CO_2} reached after 50 s rebreathing time versus simulated true PBF. One hundred percent change is change after 300 s of rebreathing during simulation.

ing time of 50 s (using alveolar P_{CO_2} and carbon dioxide flux measurements) with equivalent results obtained with a 300-s rebreathing time (curves a and b, respectively). The systematic errors after 300 s of rebreathing are very small for low PBF but are very similar to the 50-s rebreathing results for PBF greater than approximately 6 l/min. PBF is underestimated over the entire range after 300 s of rebreathing.

2. The percentage of the step change in P_{ETCO_2} achieved after 50 s of rebreathing is shown in figure 5. The result demonstrates that for low PBF, 50 s is not long enough for the P_{CO_2} level to reach a quasi-equilibrium (95% of complete change). For PBF greater than approximately 3.5 l/min, 50 s is long enough to achieve an adequate quasi-equilibrium.

3. The rebreathing time (quantized into whole breaths) required for P_{CO_2} to change through at least 95% of the complete step is shown in the bar chart in figure 6. The result demonstrates an approximate inverse relation between the PBF and the required rebreathing time. For PBF less than approximately 3 l/min, the required rebreathing period is longer than 50 s, and for PBF greater than approximately 3 l/min, the required rebreathing period is less than 50 s.

Pulmonary blood flow measurements made from P_{ETCO_2} and airway carbon dioxide flux using the variable rebreathing period shown in the chart with recirculation are also shown in figure 6 (curve c). For the entire PBF range, the results fall between curve a, depicting standard end-tidal measurements, and curve b, depicting no-recirculation end-tidal measurements. This result demonstrates that the variable rebreathing method improves the standard method, and in some cases, the improvement is as good as the no-recirculation case.

In all the studies, no PBF measurement varied by more than 5% when the volume of the additional dead space was varied between 50 and 200 ml. All further discussion relates only to results obtained with additional dead space of 150 ml.

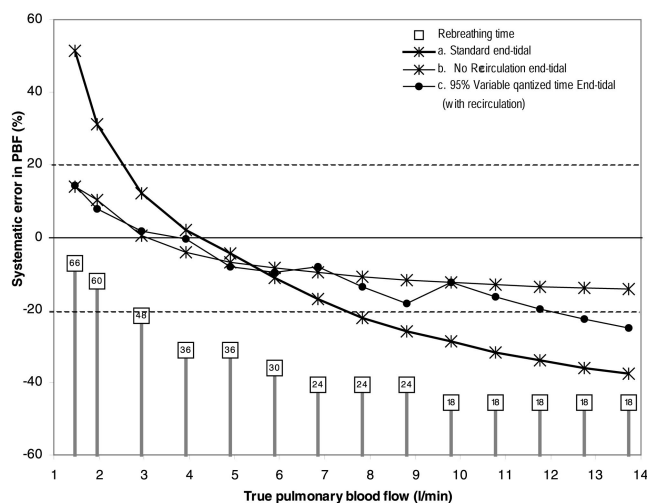


Fig. 6. Systematic error using variable rebreathing periods. Plot of the percentage systematic error in the simulated partial rebreathing measurements using variable rebreathing periods, as a function of Model's true PBF, separated into standard model, differential Fick equation evaluated using P_{ETCO_2} and airway carbon dioxide flux (thick line with asterisk); no recirculation model, differential Fick equation evaluated using P_{ETCO_2} and airway carbon dioxide flux (thin line with asterisk); and standard model, differential Fick equation evaluated using P_{ETCO_2} and airway carbon dioxide flux using variable rebreathing periods and with recirculation (line with solid circle). Bars = variable 95% complete quasi-equilibrium rebreathing time, quantized into integer multiples of complete breaths.

Discussion

This study found that PBF determined by the partial rebreathing technique is overestimated at low cardiac outputs and underestimated at high cardiac outputs, which was observed experimentally by Tachibana *et al.*,⁶ Nilsson,⁷ and van Heerden *et al.*⁸ This technique yields PBF measurements that are biased toward normal values, which is a characteristic that is not desirable in the clinical environment. Under normal conditions, measured PBF is within 10% of the true value in the simulated adult when the true PBF is in the approximate range of 3–5.5 l/min. This limitation in the measurement range is not predictable from the differential indirect carbon dioxide Fick principle.

This study has identified four sources of systematic error in the partial rebreathing technique:

1. Recirculation of mixed venous blood with increased carbon dioxide content
2. Carbon dioxide partial pressure gradients and flux differences between the proximal airway and the alveolar compartment
3. P_{CO_2} and P_{O_2} gradients between the alveolar compartments and pulmonary capillary blood
4. Rebreathing times at low PBFs are inadequate to achieve quasi-equilibrium in the alveolar compartment, and rebreathing times at high PBFs are too long, causing errors due to recirculation.

Recirculation

The partial rebreathing technique assumes that mixed venous P_{CO_2} remains constant during a measurement. During rebreathing, carbon dioxide excretion decreases, while carbon dioxide production is maintained; therefore, carbon dioxide is accumulated in the body. The first evidence of this accumulation is an increase in mixed venous P_{CO_2} (fig. 2). The increases begin earlier and hence have a greater effect on P_{ACO_2} when the cardiac output is high. Our simulated measurements, in which we used constant mixed venous P_{CO_2} and P_{O_2} (effectively simulating a body of infinite capacity for storing carbon dioxide), suggest that increases in mixed venous P_{CO_2} during rebreathing cause approximately 60% of the total systematic error in measured PBF at high cardiac outputs (fig. 3, curve b).

Proximal Airway-Alveolar Compartment Differences

End-tidal airway carbon dioxide partial pressure differs from mean P_{ACO_2} , even in an ideal, single-compartment homogenous lung because of the time delay and mixing caused by the gas movement in the airways during tidal expiration. Using simulated alveolar values of P_{CO_2} and carbon dioxide flux for PBF calculations further approximately halved the systematic errors in the airway measurements when mixed venous P_{CO_2} was fixed (fig. 3, curve c). We found that in our model, the breath-by-breath difference between carbon dioxide flux change in the proximal airway and the carbon dioxide flux change in the pulmonary capillaries during rebreathing was small. The small difference indicates that the component of the systematic error related to proximal airway-alveolar compartment differences is due mainly to P_{CO_2} differences.

The residual systematic error can only be due to the alveolar-capillary P_{CO_2} gradient. Our cardiorespiratory model simulates an alveolar-capillary diffusion barrier using published diffusion coefficients.⁹ The alveolar-capillary P_{CO_2} gradient increases with cardiac output due to decreased capillary residence times, hence creating a systematic error in PBF that increases with PBF.

Rebreathing Times

The time constant for carbon dioxide in an alveolar compartment is approximately inversely proportional to the product of the solubility of carbon dioxide in blood and the PBF. Hence, we expect that the rebreathing times required to achieve quasi-equilibrium of P_{CO_2} in the alveolar compartment should be shorter at high PBF and longer at low PBF, when mixed venous conditions are constant. Figure 4 (curve b), in which PBF measurements were obtained using a 300-s rebreathing time and simulated alveolar values with no recirculation, suggests that the systematic errors in measured PBF at low cardiac outputs are almost entirely due to incomplete rebreath-

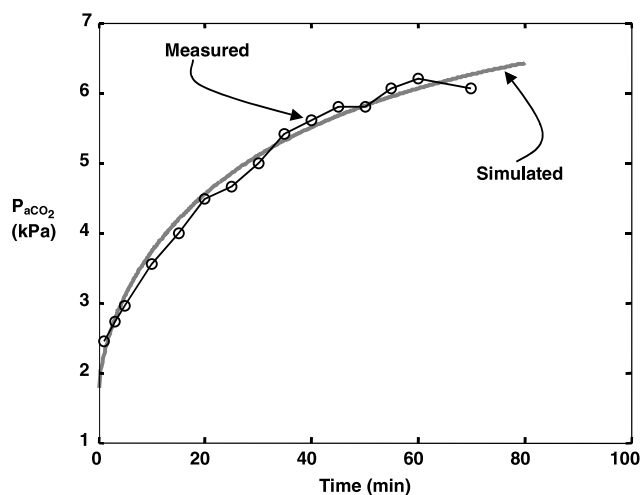


Fig. 7. The P_{aCO_2} response after changing the ventilation from hyperventilation at 21.6 l/min for 20 min to 4.8 l/min for 80 min. Ventilation was reduced at $t = 0$. Line with open circle = measured arterial P_{CO_2} ; line = cardiorespiratory model simulated arterial P_{CO_2} .

ing. Figure 5 suggests that the rebreathing time could be optimized by making it a function of PBF. Figure 6 (curve c), in which rebreathing times follow the values indicated to achieve 95% of equilibrium changes (quantized into integer multiples of complete breaths), shows that shorter rebreathing times at high PBFs substantially reduce the systematic errors caused by recirculation. While the selection of the rebreathing time requires an *a priori* knowledge of PBF, a practical approach might be to select the rebreathing time based on past measurements of PBF.

Limitations of the Study

The main limitation of this study is that it was performed using a mathematical model and not live subjects. The cardiorespiratory model used in this study is based on well-documented physiologic and anatomical data, but it does have limitations. The model airway is a lumped approximation to the human respiratory tree, which might affect the magnitude of end-tidal to alveolar P_{CO_2} gradients. The model has a fixed cardiac output distribution, which might affect the calculated systematic errors, particularly at low PBF, when cardiac output might be preferentially distributed to organs with short recirculation times. We expect, however, that modeling limitations affect only the magnitude of the error calculations, not their form.

Because of the nature of this study, the effects of measurement errors are not included. The magnitude of the changes in P_{ETCO_2} and carbon dioxide flux depends on the size of the additional dead space used to cause partial rebreathing. Hence, measurement errors would affect PBF measurements obtained with small additional dead space more than those obtained with larger dead

spaces. However, our model does not simulate measurement errors, and thus, the effects of varying the size of the additional dead space in this study are small.

There are a large number of variables that might affect the accuracy of the partial rebreathing method. This study has addressed variables closely associated with the fundamental assumptions that underpin this measurement technique. Further investigation is required to assess the relative effects of other variables such as tidal volume,⁶ body size, hemoglobin concentrations, and others.

Conclusion

This study found that the partial rebreathing technique for the measurement of PBF is strongly biased toward normal values; it tends to overestimate at low cardiac outputs and underestimate at high cardiac outputs. Three important mechanisms contributing to systematic errors in PBF measurements have been identified: recirculation; alveolar-proximal airway P_{CO_2} and carbon dioxide flux differences; and rebreathing times, which are inadequate at low PBF and excessive at high PBF. We have shown that the systematic errors at low PBF can be reduced if rebreathing times are increased and the effects of recirculation can be reduced by limiting the rebreathing time when PBF is high. We suggest that the partial rebreathing technique might be improved either by making the rebreathing time a function of predicted PBF or by correcting calculated cardiac output. Further investigations should explore these possibilities.

Appendix A: Derivation of the Differential Form of the Indirect Fick Equation

In a single-compartment lung under steady state conditions and neglecting fluctuations related to tidal breathing, the Fick mass balance for carbon dioxide can be written:

$$\dot{V}_{CO_2} = \dot{Q}_p(C\bar{V}CO_2 - C_{aCO_2}) \quad (A1)$$

where \dot{V}_{CO_2} is the airway carbon dioxide flux, \dot{Q}_p is pulmonary blood flow, $C\bar{V}CO_2$ is mixed venous carbon dioxide concentration, and C_{aCO_2} is arterial carbon dioxide concentration.

During partial rebreathing, an additional dead space is added to the patient airway, causing P_{ETCO_2} to rise and airway carbon dioxide excretion to decrease. If \dot{Q}_p and mixed venous carbon dioxide content remain constant during the rebreathing period, a new quasi-equilibrium is established. Equation A1 can be applied to the new conditions as follows:

$$\dot{V}'_{CO_2} = \dot{Q}_p(C'\bar{V}CO_2 - C'_{aCO_2}) \quad (A2)$$

where the prime indicates the new quasi-equilibrium conditions. Subtracting equation A2 from equation A1 and simplifying yields:

$$\dot{V}_{CO_2} - \dot{V}'_{CO_2} = \dot{Q}_p(C'_{aCO_2} - C_{aCO_2})$$

which can be rearranged as:

$$\dot{Q}_p = \Delta\dot{V}_{CO_2}/\Delta C_{aCO_2} \quad (A3)$$

where $\Delta\dot{V}_{CO_2} = \dot{V}_{CO_2} - \dot{V}'_{CO_2}$ and $\Delta Caco_2 = \Delta C'aco_2 - Caco_2$. The change in arterial carbon dioxide concentration was calculated from the change in $P_{ET}CO_2$ using the blood-gas dissociation curves of Olszowka and Fahri.¹⁰

Appendix B: The Cardiorespiratory Model

The model (fig. 1) incorporates a 14-compartment approximation to Weibel's lung model "A,"¹¹ simulating diffusive and convective transport and storage of gases in the lungs. The airways terminate in one unperfused and three perfused alveolar compartments. Lung tissue carbon dioxide storage is simulated using two lung tissue compartments.¹² Intrapulmonary and anatomical shunt are included. Ventilation and \dot{V}/\dot{Q} heterogeneity can be simulated by varying the inspired gas distribution and by varying the fraction of the cardiac output perfusing the three perfused alveolar compartments. The model simulates alveolar-capillary diffusion,⁹ intraventricular and intravascular mixing,¹³ variable transport delays,¹⁴ intravascular storage,¹⁵ and carbon dioxide and oxygen storage, production, and consumption in eight anatomically appropriate body compartments.¹⁶ Nonlinear blood-gas dissociation curves¹⁰ include the Haldane and Bohr effects. The tissue dissociation curves are after Farhi and Rahn¹⁷ and after Cherniack and Longobardo.¹⁸ The respiratory flow waveform was selected to match a mechanically ventilated subject: constant inspiratory flow followed by exponential expiratory flow. The model has been verified against published human data.^{19,20} One of the comparisons is shown in figure 7. It shows the $Paco_2$ measured in an anesthetized patient after the ventilation was reduced from 21.6 l/min to 4.8 l/min,²⁰ compared with the cardiorespiratory model $Paco_2$ after the same ventilation change.

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