Sources of error in partial rebreathing pulmonary blood flow measurements in lungs with emphysema and pulmonary embolism†

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Background. Studies of the accuracy of partial rebreathing measurements of pulmonary blood flow (PBF) in patients with abnormal lungs have not fully explained the sources of error.

Methods. We used computer models of emphysema and pulmonary embolism incorporating both ventilation-perfusion (V/Q) and ventilation-volume (V/V) heterogeneity to investigate systematic errors in partial rebreathing PBF measurements. We studied (i) errors produced under usual conditions, (ii) effects of recirculation, (iii) effects of alveolar–proximal airway and alveolar-capillary \(PCO_2\) and \(VCO_2\) differences, (iv) effects of alveolar \(V/Q\) inhomogeneity and (v) effects of rebreathing time.

Results. In the pulmonary embolism model the systematic error is only acceptable (<10%) when the simulated PBF is low (2–3 litre min\(^{-1}\)). In the emphysema model PBF is underestimated by more than 20% at all cardiac outputs studied. Four sources of systematic errors were found. (i) Alveolar–proximal airway \(PCO_2\) gradients and flux differences between the proximal airway and alveolar compartments contribute most to the systematic error. (ii) \(V/Q\) inhomogeneity causes \(PCO_2\) gradients between the alveolar compartments and pulmonary capillary blood, and between pulmonary capillary compartments. (iii) Rebreathing times are inadequate in the presence of \(V/V\) mismatch. (iv) The apparent effect of venous blood recirculation is small in emphysema but significant in pulmonary embolism.

Conclusions. We conclude that PBF cannot be measured accurately by partial rebreathing in lungs with emphysema or embolism. Systematic errors are caused mainly by errors in end-tidal \(PCO_2\) values.

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Partial rebreathing is a non-invasive technique for measuring pulmonary blood flow (PBF), which is based on a differential form of the Fick equation. Numerous studies have investigated the accuracy of this method but few studies have assessed the accuracy of this method in subjects with abnormal lungs. Odenstedt and colleagues evaluated a non-invasive cardiac output instrument that uses partial rebreathing (NICO, Novametrix Medical Systems Inc., CT, USA) in critically ill patients and found it to provide an accurate estimate of cardiac output (CO). This monitor uses a number of corrections to the classical partial rebreathing method, some of which have not been published. Gama de Abreu and colleagues studied the performance of the partial rebreathing technique and found that it deteriorates when dead-space is increased or the lungs are injured.

The partial rebreathing method is based on the mass balance of CO\(_2\) between the circulation and the ventilation before and after a short period of partial rebreathing during
which $P_{ACO_2}$ and the CO₂ excretion rate change but PBF and mixed venous CO₂ content remain constant. Under these conditions PBF is given by:

$$PBF = \frac{\Delta V_{CO_2}}{\Delta C_{CO_2}}$$

where $\Delta V_{CO_2}$ and $\Delta C_{CO_2}$ are the changes in the pulmonary capillary CO₂ excretion rate and pulmonary end-capillary CO₂ content respectively during rebreathing. In the non-invasive partial rebreathing method $\Delta V_{CO_2}$ and $\Delta P_{CO_2}$ (changes in $P_{CO_2}$ during rebreathing) are estimated from proximal airway CO₂ excretion rate and end-tidal $P_{CO_2}$ measurements. The systematic errors in the non-invasive partial rebreathing method were analysed by Yem and colleagues using a computer model of a normal homogeneous lung. Diseases affecting gas exchange are likely to degrade the method, but the extent and nature of these effects have not been studied and are not well understood.

There are multiple potential causes of error in partial rebreathing measurements. It is well known that in diseased lungs the end-tidal $P_{CO_2}$ often does not represent arterial $P_{CO_2}$ well. Ventilation-perfusion mismatch is known to create regions of different alveolar partial pressures in lungs and hence results in increased differences between end-tidal and arterial CO₂ partial pressure. Ventilation-volume mismatch alters the partial pressure equilibration time constants after a perturbation in ventilation and is therefore likely to cause errors in partial rebreathing measurements.

We studied the effects of rebreathing time, re-circulation, alveolar-proximal airway $P_{CO_2}$ differences and alveolar-pulmonary capillary $P_{CO_2}$ differences on systematic errors in partial rebreathing estimates of cardiac output using mathematical models of emphysema and embolism.

**Materials and methods**

**The models**

We have developed a mathematical model of the cardiorespiratory system that can simulate normal subjects and subjects with emphysema and embolism. The model incorporates both ventilation-perfusion ($V/Q$) and ventilation-volume ($V/W$) heterogeneity. The model was developed using a rational approach designed to yield mutually consistent sets of parameters and was evaluated against published measured data. The model predicts dynamic and steady state behaviour of gases covering a wide solubility range.

The model simulates tidal breathing through a branched respiratory tree and incorporates the effects on CO₂ dynamics of lung tissue mass, vascular transport delays, multiple body compartments and realistic blood-gas dissociation curves, and is implemented using Matlab and Simulink (Mathworks, Natick, MA, USA).

A block diagram of the model is shown in Yem and colleagues. The emphysema model has a pure shunt of <1% in addition to three perfused alveolar compartments and shunt. The grey areas indicate alveolar compartments that have similar $V/Q$ ratios. WG, Weibel generations.

**Fig 1** Respiratory tree of the emphysema model. The respiratory tree contains three perfused alveolar compartments and shunt. The grey areas indicate alveolar compartments that have similar $V/Q$ ratios. WG, Weibel generations.

The embolism model has a pure shunt of 20% and two alveolar compartments, and its airway structure is similar to Figure 1 with one less terminal branch. The volume, perfusion and effective ventilation of each alveolar compartment in the models are shown in Figure 2.

For the purposes of this study an additional airway deadspace, which can be switched in or out to simulate the rebreathing process, was incorporated into the model. The original model was verified by comparing dynamic and static predictions of arterial $P_{CO_2}$ with $P_{CO_2}$ measured in clinical studies. In addition, the modified model used in this study was verified by analysis of the mass balance of $O_2$, $N_2$ and CO₂ during a 10 min partial rebreathing run and by comparing capillary blood flow in each alveolar
compartment calculated using equation (1) with the true capillary flow at a PBF of 5 litre min⁻¹ with no recirculation.

Study 1: standard conditions
The model was run for 15 000 s with parameters shown in Table 1 and with the rebreathing dead-space by-passed to create a set of initial conditions for cardiac outputs 1.5 and 2–15 litre min⁻¹ in steps of 1 litre min⁻¹. The initial gas in the additional dead-space was air. At each cardiac output a series of datasets were generated by running the model from an appropriate initial condition and switching the additional dead-space for 50 s at intervals of 180 s. Ten rebreathing cycles were simulated. The PBF values were calculated from \(\text{PETCO}_2\) and airway \(V_{\text{CO}_2}\) averaged over single breaths obtained immediately before and at the end of the last rebreathing cycle. Complete CO₂ dissociation equations were used to calculate CO₂ content to avoid errors because of variations in the slope of the CO₂ dissociation curve.

Study 2: the effects of recirculation
The partial rebreathing method assumes that mixed venous blood concentrations of CO₂ remain constant immediately before and during the rebreathing phase of each measurement cycle. To examine the effects of changes in mixed venous \(\text{PCO}_2\) caused by recirculation, the model was modified by removing all the body compartments. The mixed venous \(\text{PCO}_2\) and \(\text{PO}_2\) inputs to the pulmonary capillaries were then kept constant at values appropriate to the cardiac output thus effectively removing the effects of recirculation of the inspired CO₂. The simulations described above in Study 1 were repeated.

Study 3: the effects of alveolar–proximal airway and alveolar-capillary \(\text{PCO}_2\) and \(V_{\text{CO}_2}\) differences
The partial rebreathing method is based on the mass balance of CO₂ at the pulmonary capillary-alveolar interface but uses measurements in the proximal airway. In both the emphysema and the pulmonary embolism models, there is significant ventilation, perfusion and volume in alveolar compartments with high \(V/V\) ratios. To examine the effects of the alveolar-proximal airway differences, PBF to each alveolar compartment was calculated using \(P_{\text{ACO}_2}\) and pulmonary capillary \(V_{\text{CO}_2}\) for each alveolar compartment averaged over a single breath. Total PBF was calculated by

\[
\mathcal{Q}_0=0.002 \text{ litre min}^{-1} \\
\mathcal{Q}_0=5.3 \text{ litre min}^{-1} \\
\dot{V}_A=1.7 \text{ litre min}^{-1} \\
V_2=0.36 \text{ l} \\
\tau_3=12.6 \text{ s} \\
\dot{V}_A=0.32 \\
\dot{V}_A=0.93 \\
\dot{V}_A=0.45 \text{ litre min}^{-1} \\
\dot{V}_A=4.2 \text{ litre min}^{-1} \\
\tau_3=0.23 \text{ l} \\
V_2=10.0 \text{ s} \\
\dot{V}_A=11.5 \\
\dot{V}_A=0.16 \text{ litre min}^{-1} \\
\dot{V}_A=1.9 \text{ litre min}^{-1} \\
\tau_3=3.1 \text{ l} \\
\tau_3=300 \text{ s} \\
\text{Mid } \dot{V}_A/\dot{Q} \text{ High } \dot{V}_A/\dot{Q} \Sigma V_{3a}=3.72 \text{ l} \\
\dot{V}_A=0.74 \text{ litre min}^{-1} \\
\dot{V}_A=1.8 \text{ litre min}^{-1} \\
\dot{V}_A=2.6 \text{ litre min}^{-1} \\
\dot{V}_A=2.5 \text{ litre min}^{-1} \\
\tau_3=19.7 \text{ s} \\
\dot{V}_A=1.0 \text{ l} \\
\tau_3=19.7 \text{ s} \\
\text{Mid } \dot{V}_A/\dot{Q} \text{ High } \dot{V}_A/\dot{Q} \Sigma V_{3b}=2.97 \text{ l} \\
\dot{V}_A=0.45 \text{ litre min}^{-1} \\
\dot{V}_A=4.5 \text{ litre min}^{-1} \\
\dot{V}_A=1.1 \text{ litre min}^{-1} \\
\dot{V}_A=5.1 \text{ litre min}^{-1} \\
\tau_3=2.0 \text{ l} \\
\tau_3=19.7 \text{ s} \\
\dot{V}_A=0.45 \text{ litre min}^{-1} \\
\dot{V}_A=1.1 \text{ litre min}^{-1} \\
\tau_3=2.0 \text{ l} \\
\tau_3=19.7 \text{ s} \\
\Sigma V_{3a}=3.72 \text{ l} \\
\Sigma V_{3b}=2.97 \text{ l} \\
\Sigma V_{3a}=3.72 \text{ l} \\
\Sigma V_{3b}=2.97 \text{ l} \]

Fig 2 (A) The emphysema model alveolar compartment parameters. (B) The pulmonary embolism model alveolar compartment parameters.
the summation of PBF values in each individual alveolar compartment and compared with PBF calculated using proximal airway measurements. The effects of alveolar-capillary gradients were examined by comparing individual compartment PBFs calculated using alveolar measurements with model capillary blood flow parameters. The simulations described in Study 1 were repeated with recirculation included and excluded.

**Study 4: the effects of V/Q spread**

The V/Q ratio in a compartment determines the steady-state PCO₂ in that compartment; therefore, it is likely the V/Q ratio affects the change in alveolar and capillary PCO₂ during rebreathing (ΔPCO₂). To examine the effect of V/Q inhomogeneity, the PCO₂ in the alveoli and pulmonary capillaries and the pulmonary capillary V̇CO₂ were analysed and compared with corresponding values in the mixed arterial and the proximal airway over a rebreathing cycle. The analysis was done for 50 s rebreathing time with and without recirculation, and 550 s rebreathing time with no recirculation.

**Study 5: the effects of rebreathing time**

The time constant for alveolar CO₂ turnover depends strongly on PBF and the ventilation-volume ratio of the alveolar compartments. Therefore the time required to achieve a quasi-equilibrium in PACO₂, PETCO₂ and airway V̇CO₂ after a perturbation is increased when PBF is low and when the ventilation-volume ratio is low. PBF values were calculated using an extended rebreathing time of 550 s to make sure that quasi-equilibrium was achieved. No recirculation was included in these simulations. The simulations described above in Study 1 were repeated.

**Results**

The modified model maintained mass balances of O₂, N₂ and CO₂ to within 5 x 10⁻⁸ mol during a 10 min partial rebreathing run. The difference between compartment pulmonary capillary flows calculated using equation (1) and the model capillary flow parameters at a PBF of 5 litre min⁻¹ were all <0.5%.

**Study 1: standard conditions**

Typical proximal airway P̄CO₂ and breath-by-breath proximal airway and pulmonary capillary V̇CO₂, generated using cardiac output values most closely approximating the conditions of the patients on whom the models are based, were recorded at end-expiration on the last completed breath before 50 s. The differences between the simulated true PBF and the PBF calculated from rebreathing measurements are shown in Figure 4A for the emphysema model and Figure 4B for the pulmonary embolism model, showing exhibits a large difference in V̇CO₂ at the pulmonary capillaries and at the proximal airway are not the same at the end of rebreathing and the difference is greater in emphysema. Changed P̄CO₂ and changed V̇CO₂ were recorded at end-expiration on the last completed breath before 50 s.

The differences between the simulated true PBF and the PBF calculated from rebreathing measurements are shown in Figure 4A for the emphysema model and Figure 4B for the pulmonary embolism model (Proximal airway curve), and also in Table 2. The errors vary systematically with the true cardiac outputs studied.

**Study 2: the effects of recirculation**

The effects of removing recirculation are shown in curve ‘Proximal airway+no recir’ of Figure 4A and B. Removal of recirculation reduces systematic error in the measurements. The reduction in error is up to 25% in the pulmonary embolism model, but only up to 4% in the emphysema model.

**Study 3: the effects of alveolar–proximal airway and alveolar-capillary P̄CO₂ and V̇CO₂ differences**

Systematic errors in PBF obtained using PACO₂ as an estimate of arterial P̄CO₂ and true pulmonary capillary V̇CO₂ (without recirculation) in the differential Fick equation are reduced to approximately −11 and −39% at COs of 5 and 15 litre min⁻¹, respectively, in emphysema (Fig. 4A) and −6 and −13% at COs of 5 and 15 litre min⁻¹ (corresponding to PBFs of 4.0 and 12.1 litre min⁻¹) respectively in embolism (Fig. 4B).
Table 3 summarizes the measurements made in each of the ventilated alveolar compartments, and each of the perfused pulmonary capillary compartments, generated using CO values of (i) 6 litre min\(^{-1}\) in the emphysema model and (ii) 4 litre min\(^{-1}\) in the pulmonary embolism model. The rebreathing period was 50 s. In emphysema, the change in \(P_{ACO2}\) during rebreathing (\(\Delta P_{ACO2}\)) was at most 0.029 kPa more than the change in \(P_{cCO2}\) (\(\Delta P_{cCO2}\)). The \(\Delta P_{CO2}\) is low in the mid-\(V/Q\) compartment, thus a small absolute difference between the alveolar and pulmonary capillary \(\Delta P_{CO2}\) causes a large difference in pulmonary capillary flow (17.5%). In embolism, the differences between \(\Delta P_{ACO2}\) and \(\Delta P_{cCO2}\) are both <0.008 kPa.

In emphysema, most of the CO2 exchange occurs in the mid-\(V/Q\) and high-\(V/Q\) compartments (83 and 68 \(\mu\)mol s\(^{-1}\) respectively before rebreathing). The mid-\(V/Q\) compartment has the largest error (17.5%) in pulmonary capillary flow calculated from alveolar values (\(Q_{AV}\)), followed by the high-\(V/Q\) compartment (4.3%). In embolism, the mid-\(V/Q\) compartment accounts for 42% of CO2 exchange (45 \(\mu\)mol s\(^{-1}\) before the rebreathing cycle), and has the larger error (3.8%) in pulmonary capillary flow calculated from alveolar values.

**Study 4: the effects of alveolar \(V/Q\) spread**

\(P_{CO2}\) in the ventilated alveolar compartments, generated using PBFs of (i) 6 litre min\(^{-1}\) in the emphysema model and (ii) 4 litre min\(^{-1}\) in the pulmonary embolism model, are shown in Figure 5. Before rebreathing, \(P_{CO2}\) levels reflect the quasi-equilibrium achieved after the previous rebreathing cycle. There are large differences in \(P_{CO2}\) between compartments. In emphysema, the proximal airway end-tidal \(P_{CO2}\) is \(\approx 3.5\) kPa while the arterial and mixed venous \(P_{CO2}\) are >7 kPa (Fig. 3). \(P_{CO2}\) in the mid-, high- and high-slow \(V/Q\) alveolar compartments is \(\approx 7.9, \approx 3.2\) and \(\approx 2.7\) kPa, respectively (Fig. 5). In pulmonary embolism, the
There are large differences in $\Delta P_{CO_2}$ between compartments (Table 3). In both models, $\Delta P_{CO_2}$ is smallest in the mid-$V/Q$ alveolar compartment. In the emphysema model, $\Delta P_{CO_2}$ in the high-$V/Q$ compartment is greater than the high-slow $V/Q$ compartment. $\Delta P_{CO_2}$ in the high-$V/Q$ slow compartment does not reach quasi-equilibrium in the 50 s rebreathing period (Fig. 5A).

Study 5: the effects of rebreathing time

At a rebreathing time of 550 s without recirculation, the changes in proximal airway $P_{CO_2}$ across all the cardiac outputs studied were >95% complete when rebreathing ended. In both emphysema, and embolism without recirculation, long rebreathing time paradoxically increased the errors in PBF (Fig. 4A and B) when recirculation was omitted. $P_{CO_2}$ and the $V_{CO_2}$ at the proximal airway are shown in Figure 6 for emphysema, with a rebreathing time of 550 s without recirculation. Both $P_{CO_2}$ and $V_{CO_2}$ reach quasi-equilibrium at 550 s. At 50 s into the rebreathing, the $\Delta P_{CO_2}$ of 0.557 kPa underestimates the equilibrium value by 20%, while $\Delta V_{CO_2}$ of $\sim$33.6 $\mu$mol s$^{-1}$ overestimates the equilibrium CO$_2$ exchange by 12%. The resulting overestimation of PBF partially compensates for underestimation of PBF resulting from other mechanisms.

Discussion

The present study found that PBF determined by the non-invasive partial rebreathing technique is underestimated by more than 20% in the emphysema model at all PBFs, and in the pulmonary embolism model when PBF is above $\sim$3 litre min$^{-1}$. In embolism, PBF is overestimated when PBF is below $\sim$2 litre min$^{-1}$. The ability of the partial rebreathing technique to estimate PBF is greatly reduced in the presence of ventilation, volume and perfusion inhomogeneity associated with emphysema and embolism.

This study identified four sources of systematic error in the partial rebreathing technique in the presence of ventilation, volume and perfusion inhomogeneity.

1. Ventilation–volume and ventilation–perfusion inhomogeneities cause $P_{CO_2}$ gradients and $V_{CO_2}$ differences between the proximal airway and the alveolar compartments.

2. Ventilation–perfusion inhomogeneity causes $P_{CO_2}$ and flux differences between pulmonary capillary compartments and uneven $P_{CO_2}$ gradients between the alveolar compartments and arterial blood.

3. Rebreathing times are inadequate especially when long alveolar gas turnover time constants exist.

4. In addition, the study found that the direct effect of recirculation of mixed venous blood is small in the emphysema model, but significant in the pulmonary embolism model.

Gama de Abreu and colleagues$^{10}$ evaluated the partial rebreathing method in sheep with induced lung injuries.
In their Phase II study they inflated a balloon in a branch of the pulmonary artery and therefore their study is similar to our embolism simulation. When a substantial fraction of the lung had a high \( V/Q \) ratio both our study and theirs found overestimation of PBF at PBFs of 1–2 litre min\(^{-1}\) and both studies found that PBF was underestimated by \(~6\) litre min\(^{-1}\) when true PBF was 10 litre min\(^{-1}\). In their Phase III study they increased alveolar dead-space and introduced lung damage, and their sheep model study may be considered to have produced similar \( V/Q \) and \( V/V \) lesions to our emphysema simulation. Both studies found \(~4.5\) litre min\(^{-1}\) underestimation at PBF of 6 litre min\(^{-1}\).

The limitations of the partial rebreathing method are not predictable from the differential indirect CO\(_2\) Fick principle. However, they are not unexpected as the technique measures the composition of expired gases, which can differ greatly from that of alveolar gases in inhomogeneous lungs. A commercially available device (NICO, Novametrix-Respironics, Wallingford, CT, USA) applies proprietary algorithms to correct measurements made from the proximal airways\(^{1,11,12}\) in an endeavour to compensate for such problems.

\textbf{\(V/Q\) inhomogeneity}

In the emphysema model the mid-\( V/Q \) compartment receives \(\approx90\%\) of the total PBF and pulmonary capillary flow calculated by the differential Fick equation (equation 1) is greater than nine times higher than the flow in the high-\( V/Q \) compartments (Table 3). The large PBF is associated with a small change in CO\(_2\) content (\(\Delta C_{O_2}\)) during rebreathing while the change in CO\(_2\) transfer (\(\Delta V_{O_2}\)) in this compartment is similar in magnitude to the \(\Delta V_{CO_2}\) in the high-\( V/Q \) compartment. Thus a small absolute error in the estimation of mid-\( V/Q \) compartment \(\Delta C_{O_2}\) results in a large percentage error in PBF.

In the emphysema model, most of the \( V_{CO_2} \) takes place in the mid-\( V/Q \) compartment (Table 3). However, the volume of the mid-\( V/Q \) compartment is \(\approx10\%\) of the total alveolar volume, thus this compartment has the lowest alveolar-capillary diffusion coefficient and hence the largest P\(CO_2\) gradient. Therefore the mid-\( V/Q \) compartment shows the greatest differences between alveolar and pulmonary capillary \(\Delta P_{CO_2}\).

In the embolism model, the differences in the \( V/Q \) ratio of the two compartments is much smaller, thus the percentage error in PBF in both compartments is much smaller. The error in PBF is larger in the mid-\( V/Q \) compartment, because the mid-\( V/Q \) compartment has larger perfusion and a smaller \(\Delta C_{CO_2}\) during rebreathing.

When the \( V/Q \) distribution is inhomogeneous the differential Fick principle can produce accurate estimates if PBF is calculated for each compartment individually and summed. However, the non-invasive partial rebreathing technique estimates PBF from proximal airway measurements, assuming the lung is one compartment, thus \( V/Q \) mismatch results in additional errors. \( P_{ACO_2} \) may be predicted from end-tidal P\(CO_2\) with precision that is similar to the precision with which \( P_{ACO_2} \) can be measured directly.\(^{13}\)

However, in the presence of abnormal lung function, the prediction equations\(^{13}\) do not predict arterial CO\(_2\) partial pressures well because of the complex relationships amongst end-tidal, mean alveolar and arterial CO\(_2\) partial pressures.\(^{13}\)

\textbf{Rebreathing times}

In lungs, which contain units with long gas turnover time constants, increased rebreathing time would be expected to improve estimates of PBF, particularly when recirculation is absent. Increasing the rebreathing time in the study, however, paradoxically increases the error in estimated PBF in the emphysema model and in the embolism model when recirculation is omitted (Fig. 4a and n). In emphysema after 50 s rebreathing with no recirculation, \(\Delta P_{CO_2}\) and \(\Delta V_{CO_2}\) are not at equilibrium (Fig. 6). Therefore \(\Delta C_{CO_2}\) is underestimated and \(\Delta V_{CO_2}\) is overestimated, causing PBF to be overestimated (equation 1). This overestimation partially compensates for the underestimation associated with \( V/Q \) and \( V/V \). Odenstedt and colleagues\(^{9}\) suggested that over- and underestimations may balance each other by coincidence.

\begin{table}
\caption{Changes in \( V_{CO_2}, P_{ACO_2}, C_{CO_2}, (\Delta V_{CO_2}, \Delta P_{CO_2}, \Delta C_{CO_2}) \) caused by rebreathing and \( Q_{AV} \) calculated using time-averaged alveolar and pulmonary capillary measurements. Rebreathing time was 50 s and no recirculation was included in these simulations. The percentage differences between the alveolar and pulmonary capillary estimated \( Q_{AV} \) are calculated for each compartments. The embolism model was simulated at CO of 6 litre min\(^{-1}\), and before rebreathing, time-averaged \( P_{ACO_2} = 3.9 kPa \) and \( P_{ACO_2} = 3.45 kPa \). The embolism model was simulated at CO of 4 litre min\(^{-1}\), and before rebreathing, time-averaged \( P_{ACO_2} = 3.12 kPa \) and \( P_{ACO_2} = 2.58 kPa \). *Indicates where a total does not exist.}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
 & \( V_{CO_2} \) (mol s\(^{-1}\)) & \( \Delta V_{CO_2} \) (mol s\(^{-1}\)) & \( P_{ACO_2} \) (kPa) & \( \Delta P_{ACO_2} \) (kPa) & \( \Delta C_{CO_2} \) (mol litre\(^{-1}\)) & \( Q_{AV} \) (litre min\(^{-1}\)) & \( Q_{AV} \) diff (\%) \\
\hline
Emphysema (6 litre min\(^{-1}\)) & & & & & & & \\
Mid (\( V_j/Q \)) & 82.69 & 12.14 & 7.86 & 0.24 & 0.103 & 8.10 & 0.085 & 160.0 & 4.52 & 17.5 \\
Hi (\( V_j/Q \)) & 67.69 & 10.30 & 3.24 & 0.24 & 0.680 & 3.49 & 0.651 & 1488 & 0.415 & 4.3 \\
Hi (\( V_j/Q \) slow) & 29.69 & 2.17 & 2.74 & 0.02 & 0.374 & 2.76 & 0.372 & 752 & 0.173 & 0.5 \\
Total & 180.1 & 24.61 & - - & - - & - - & - - & - - & 5.14 & 14.4 \\
Embolism (4 litre min\(^{-1}\)) & & & & & & & \\
Mid (\( V_j/Q \)) & 45.40 & 14.40 & 3.19 & 0.04 & 0.209 & 3.23 & 0.201 & 464 & 1.86 & 3.8 \\
Hi (\( V_j/Q \)) & 63.32 & 19.60 & 2.40 & 0.04 & 0.373 & 2.44 & 0.368 & 988 & 1.19 & 1.3 \\
Total & 108.7 & 34 & - - & - - & - - & - - & - - & 3.05 & 3.9 \\
\hline
\end{tabular}
\end{table}
Recirculation

The effect of CO₂ recirculation on the PBF estimate made from proximal airway measurements is different in the two disease models. In the pulmonary embolism model, the effect of CO₂ recirculation increases with increasing CO₂. CO₂ recirculation contributes ≈25% to systematic errors at PBF=11.3 litre min⁻¹ and ≈0% to systematic errors at PBF <3 litre min⁻¹. The effect of CO₂ recirculation on the PBF estimate made from proximal airway measurements is smaller in the emphysema model, because of the dominant effects of ventilation inhomogeneity and $V/Q$ mismatch. Figure 7 shows that when PBF estimates are made from alveolar measurements, the effect of CO₂ recirculation is much greater. Removing CO₂ recirculation in emphysema reduces the error in alveolar PBF estimates by 40% at PBF=15 litre min⁻¹. Therefore, based on the alveolar measurements, systematic error because of CO₂ recirculation is clearly observable and significant. However, in these diseases the proximal airway measurements are poor approximations of alveolar values, and as a result systematic error because of CO₂ recirculation is obscured by other systematic errors. Similarly, Figure 7 shows that when comparing the PBF estimates made from alveolar measurements in the pulmonary embolism model, removing CO₂ recirculation improves PBF estimates up to 75%.

In the presence of significant ventilation and perfusion inhomogeneities, removing CO₂ recirculation improves estimates only slightly. Therefore, using a shorter...
rebreathing time, which reduces the effect of CO₂ recirculation in a perfectly homogeneous lung, will not improve PBF estimates in an inhomogeneous lung.

Conclusions
In addition to sources of error found in a perfectly homogeneous lung, the ventilation, volume and perfusion mismatches in emphysema and pulmonary embolism create other sources of systematic errors in the partial rebreathing technique for measuring PBF. Almost all systematic errors found in the present study are because of incorrect $P_{CO_2}$ measurements. The majority of the systematic errors are caused by ventilation–volume inhomogeneity, while ventilation–perfusion inhomogeneity causes additional errors. The rebreathing time creates additional systematic errors because of the inability of the system to reach quasi-equilibrium. At rebreathing times that are long enough for quasi-equilibrium for the normal compartment but still inadequate for the abnormal compartments, systematic errors because of ventilation, volume and perfusion mismatches are reduced. The effect of CO₂ recirculation is much less in an inhomogeneous lung than in a normal lung. Manoeuvres such as shorter rebreathing time at high cardiac outputs will not reduce systematic errors significantly in an inhomogeneous lung.

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Fig 6 Analysis of long rebreathing time with no recirculation. Plots of end-expired $P_{CO_2}$ and CO₂ flux in the proximal airway. The $P_{CO_2}$ and CO₂ flux are normalized by subtracting the steady-state value before the start of the rebreathing. The vertical dashed line indicates where a 50 s rebreathing period would end, showing that at this time the equilibrium is not achieved.

Fig 7 Error in PBF estimates made from the simulated (theoretical) alveolar measurements, using the emphysema and pulmonary embolism lung models with and without CO₂ recirculation.


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