Systemic recirculation assessed in apnoeic anaesthetized patients using carbon dioxide concentration measurements during stepwise expiration

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Background. Mixed venous partial pressure of carbon dioxide has often been estimated in anaesthesia, usually by rebreathing techniques. This assumes equilibrium between respired gas and mixed venous blood before significant recirculation can occur, and requires vigorous rebreathing and precise identification of equilibrium. Modern clinical sidestream capnometers do not measure gas composition as rapidly as the devices used in previous studies, and cannot measure end-tidal values adequately during vigorous rebreathing. In contrast, a single-staged exhalation provides a stable sample for more accurate measurement of gas composition, and clinical measurements then allow examination of the evidence that equilibration occurs before recirculation. Theoretically, this assumption is optimistic, although it forms the basis of a method for non-invasive measurement of cardiac output. We used measurements of staged exhalation to study the evidence for equilibrium more closely.

Methods. We studied 19 patients during general anaesthesia. The lungs were inflated with mixed exhaled gas. Stepwise expiration allowed exhaled gas to be analysed over ~1 min. The rate of increase in exhaled carbon dioxide fraction was related to the duration of expiration.

Results. Carbon dioxide concentration continued to change throughout the study period. The lack of equilibrium of carbon dioxide concentration over this time supports simulation studies which predict recirculation from well-perfused body compartments within 20 s, and that the subsequent increase of carbon dioxide reflects the wash in of multiple body compartments.

Conclusions. This method allows adequate time for full response of sidestream analysers. Recirculation is an important early feature affecting breath-hold estimates of mixed venous carbon dioxide. Carbon dioxide accumulation during apnoea or rebreathing will have prompt effects on arterial carbon dioxide values and a constant mixed venous composition cannot be assumed when methods based on partial rebreathing are used over this time period.


Keywords: carbon dioxide, measurement; measurement techniques, carbon dioxide; ventilation, apnoea

Accepted for publication: February 28, 2009

The lung equilibrates alveolar gas with pulmonary capillary blood. During a breath hold, or when exhaled gas is rebreathed, the lung can act as a simple tonometer and this should allow estimation of the composition of mixed venous blood. If alveolar gas is not altered by a fresh inhalation, then transfer of gas across the alveolar-capillary membrane decreases and alveolar gas equilibrates with mixed venous blood passing through the capillaries. Several methods are used to measure this process and to detect and define an equilibrium. However, the actual equilibrium and the factors that affect it remain controversial. Early studies analysed discrete gas samples, but later methods used continuous carbon dioxide analysis to examine the composition of rebreathed gas.
To allow accurate estimation of mixed venous composition, equilibrium should be obtained before blood can recirculate from the systemic circulation, which would increase the mixed venous CO$_2$ concentration. On the basis of the assumption that rebreathing does not affect the composition of mixed venous blood, the partial rebreathing technique for measuring cardiac output was developed. This uses measurements obtained during both non-rebreathing and partial rebreathing episodes to determine cardiac output. The validity of the assumption that mixed venous composition remains constant is crucial to the method. In the past, workers assumed that since the capacity of the body for CO$_2$ was great, the influence of recirculation would be small. However, a large proportion of the venous return is from a small quantity of well-perfused tissue. The effect of blood from these tissues on venous composition will be considerable, and this will render the assumption invalid. We reasoned that changes in mixed venous composition might be detected by analysing a single staged expiration after an inspiration of exhaled gas, which is a manoeuvre that can be easily done with patients during routine anaesthesia. We argued that if equilibration occurred promptly, then the rate of change in alveolar CO$_2$ would become zero before mixed venous CO$_2$ values began to increase. However, if the exhaled concentration values continue to increase, then this indicates that systemic recirculation has affected alveolar CO$_2$ before equilibration has been achieved.

Previous studies of rebreathing were done in respiratory laboratories, often using a mass spectrometer for gas analysis, which typically has a rapid response, although some studies were done with infrared analysers. However, modern standard anaesthetic monitors have a slower response, so that end-tidal values are not recorded satisfactorily during rapid breathing (see online Appendix). We therefore measured the rate of increase of alveolar CO$_2$ during a slow stepwise expiration to assess the rate of alveolar/capillary equilibration and detect the presence of recirculation.

### Methods

We obtained approval for the study from the Lothian Research Ethics Committee. We studied 19 patients who required tracheal intubation and mechanical ventilation for general or gynaecological surgery. We excluded patients who had evidence of slow expiration, detected by observation of the expired flow signal, because this would result in a slowly changing exhaled gas sample. We also excluded patients with a BMI >40 kg m$^{-2}$. Volume-controlled ventilation was with an enclosed rising bellows circle anaesthesia system (Aestiva5, GE Healthcare, Hatfield, Herts, UK). Initial ventilator adjustment was by the clinician managing the patient, with an initial tidal volume of 500 ml and a respiratory frequency between 8 and 12 bpm, adjusted to obtain an end-tidal CO$_2$ between 4.5% and 5.5%. Anaesthesia was maintained with sevoflurane in a mixture of air and oxygen. To allow gas samples to be diverted for return to the patient, the fresh gas flow into the circle system was adjusted to give a total flow between 4 and 5 litre min$^{-1}$, and relative flows of air and oxygen to give a mean inspired oxygen fraction between 0.4 and 0.55. Data were only sampled from patients who remained haemodynamically stable (mean arterial pressure and heart rate within clinically acceptable values) during the measurement period.

Gas flow and airway pressure were measured using a D-Lite sensor (Part number 733950, GE Healthcare, Helsinki, Finland) and a Datex Ohmeda respiration module (type M-CAIOV-X; Datex Ohmeda S/5, Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). Respired gas was sampled from the flow measurement device using a standard sampling tube and analysed for oxygen, CO$_2$, and anaesthetic vapour concentrations using sidestream gas analysis by the Datex analyzer module. We recorded digital data from the S/5 monitor at 25 Hz via a PC serial interface cable to a laptop computer using commercial software designed to acquire trend, waveform, and numerical data (Datex-Ohmeda S/5 Collect).

We inserted the measuring circuit between the D-Lite sensor and the circle connection (Fig. 1). The first wide bore three-way tap (A) allowed switching from the circle system to the measuring system, and a second three-way tap (B) allowed gas exhaled by the patient to pass either...
60 ml withdrawals can also be seen. (B) Enlargement of the section deflation, 60 ml withdrawn. Successive episodes of flow associated with deflation, 120 ml withdrawn from the patient; e, second step of deflation, 120 ml withdrawn from the patient at point c. c, inflation with exhaled gas from the reservoir bag; d, first step of deflation, 60 ml withdrawn from the patient; e, second deflation, 60 ml withdrawn. Successive episodes of flow associated with 60 ml withdrawals can also be seen. (n) Enlargement of the section between the vertical dashed lines, showing the points of measurement. T1, T2, and T3 are the times of the end of the first three withdrawals of gas from the lung. C1, C2, and C3 are the concentrations of carbon dioxide of this gas in the airway, immediately before the next stepwise deflation. This indicates the composition of gas withdrawn at the corresponding times T1, T2, and T3.

Fig. 2 (a) A typical recording of airway flow, pressure, and exhaled carbon dioxide concentration during a progressive expiration. Note that there is a delay in the carbon dioxide concentration changes and thus the gas composition trace is not synchronous. This can be seen by noting that point a, on the flow trace, corresponds with inspired gas, which is the first part of the carbon dioxide trace near zero. The trace is labelled as follows: a, mechanical ventilation: inspiration; b, mechanical ventilation: expiration. At the end of this expiration, by turning tap A, the patient was interrupted, and taps A and B were turned to allow slow stepwise deflation. This indicates the composition of gas withdrawn at the end of this expiration, by turning tap A, the patient was interrupted, and taps A and B were turned to allow slow stepwise deflation. Each manoeuvre took about 60 s. We recorded between 4 and 8 manoeuvres in each patient, with more than 180 s between each manoeuvre. A typical recording of airway flow, pressure, and exhaled CO2 concentration during the described manoeuvre is shown in Figure 2a.

The records were analysed by exporting the digital data into a commercial data acquisition and analysis package (Spike 2, v 5.19, Cambridge Electronic Design, Cambridge, UK), which has data display and processing software for averaging of signal periods. Data were then processed using Excel (Microsoft, Seattle, WA, USA) and analysed statistically using GraphPad Prism v 5.00 (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

Measurements were made from the flow signal to obtain the time at the end of each step of deflation, and from the CO2 concentration signal of the mean CO2 concentration at the end of this period of apnoea. Concentration was measured as the mean of a 0.4 s series of values immediately before each next successive step of expiratory flow (Fig. 2a, times T1, T2, T3, and concentrations C1, C2, C3, ...). A typical example of these times and concentrations, taking T1 as zero, is shown in Figure 3a. We calculated the change in CO2 concentration for each of the successive time periods (e.g. C2−C1) and the time over which this change in concentration had occurred (e.g. T2−T1). This allowed calculation of the rate of change of the CO2 concentration as (C2−C1)/(T2−T1). This rate of change of concentration was related to the mean time over which the change had occurred, that is, (T1+T2)/2 (Fig. 3a), and the relationship between rate of change of concentration and time was fitted to an exponential function using a robust method (GraphPad Prism). The values for all the expirations measured in an individual patient were pooled to allow a single fit. As can be seen in Figure 3a, this fitting process gave an asymptote value which is the persistent increase in CO2 associated with apnoea.

In addition, the data were analysed using two previous methods compared by da Silva and colleagues. The first was the linear intercept method of Auchincloss and colleagues. This method uses a plot of rate of change of CO2 with time. The second was fitting an exponential function to the CO2/time values, which was the method C described by da Silva and colleagues. Both of these processes were done using data from a single expiration, and the mean of the mixed venous values was taken for each patient.

into a previously emptied 2 litre anaesthesia reservoir bag or to be withdrawn in known volumes into an aspirating syringe. The measurement sequence was as follows:

First, the three-way tap in the gas pathway (A) was used to direct exhaled gas from two successive expirations via tap B into the reservoir bag. Then, mechanical ventilation was interrupted, and taps A and B were turned to allow the captured exhaled gas sample to be passed back from the reservoir bag into the patient’s lungs. The tap at the reservoir bag (B) was then turned to allow slow stepwise expiration of this inspired volume. The first volume step was 120 ml, which we estimated would be a suitable value for the anatomical dead space in these circumstances. This volume was withdrawn as soon as possible: subsequent volumes of 60 ml were withdrawn every 10 s until the airway pressure decreased to atmospheric. Each manoeuvre took about 60 s. We recorded between 4 and 8 manoeuvres in each patient, with more than 180 s between each manoeuvre. A typical recording of airway flow, pressure, and exhaled CO2 concentration during the described manoeuvre is shown in Figure 2A.

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Finally, because we were studying possible recirculation, we studied the time period from 20 s onwards during the stepwise expiration in more detail. A separate exponential fit was made to the rate of change of CO₂ with time over this period.

**Results**

We studied 23 patients, and obtained satisfactory results during stable anaesthesia in 19 (13 were female). Haemodynamic instability occurred in three patients, and an apparatus fault in another. The mean age was 63 yr (range 30–86, SD 16), and their mean BMI was 27 kg m⁻² (range 18–36, SD 5). Four had a thoracic epidural sited for postoperative analgesia, four were hypertensive on therapy, and two were receiving renal transplants and had established brachiocephalic arteriovenous fistulae for haemodialysis. One patient had been prescribed an inhaled β₂ agonist for occasional wheeze, but had no evidence of prolonged expiratory flow during anaesthesia. None of these clinical features appeared to systematically affect the data obtained. All of the patients had a stable arterial pressure and heart rate during the study period, and pulse oximeter values were all >93%.

Because the method of preparing gas for inflating the patient with the test breath always yielded gas with a CO₂ content less than end-tidal, all the data series showed persistent progressive increases in CO₂ concentration with time. There was no evidence of an equilibrium, that is, no two successive values of exhaled gas had equal CO₂ composition. The initial rate of increase was considerable, and the rate of change then decreased to a stable but persistent positive value in the later samples. The asymptote for this persistent rate of increase in CO₂ with time had a median value of 0.021 (quartiles 0.016, 0.026) %CO₂ s⁻¹. However, these values are derived from curve fitting using all the data from the expiration, and are likely to be heavily affected by the early values. Figure 4 shows all the measured values for the rate of change of CO₂ concentration in the later samples. These indicate that there is a persistent increase in CO₂ in these later samples, with no evidence of an equilibrium (i.e. no rate of change). We also calculated the 'mixed venous' values using the methods of Auchincloss and colleagues and Da Silva and colleagues. These values were 7.74 (6.60–8.05) and 7.68 (6.71–8.19), respectively (median and quartile values). These values were not statistically different, and both sets are greater values than would be expected for true measurements of mixed venous composition.

**Discussion**

Non-invasive measurement of mixed venous CO₂ has been used for many years. The advantages of studying CO₂ to estimate cardiac output were lucidly summarized by Butler, and stem from its large solubility in blood. The recognition of equilibrium between alveolar gas and mixed venous blood is not simple and different methods have been proposed, some of which were compared by da Silva and colleagues. The most successful methods generally use rebreathing to mix and sample alveolar gas. They have an additional advantage. By ensuring that all the gas in the system has nearly the same composition, the influence of regional differences in both V/Q and regional ventilation (ventilation/unit volume) is reduced and a
closer equilibrium between alveolar gas and mixed venous blood may be approached. This concept has been applied successfully to the estimation of arterial partial pressure from end-tidal gas samples.\textsuperscript{11} However, these rebreathing methods require a rapidly responding gas analyser. We found that the response time of the analyser that we used was not sufficient to measure end-expired gas concentrations reliably during rebreathing (see online Appendix). These findings support observations by others, who also reported that similar analysers are also affected by positive pressure ventilation.\textsuperscript{12} Many previous studies by respiratory physiologists used mass spectrometers, which have a more rapid response, and are less affected by changes in airway pressure. Because the recognition of a ‘true’ plateau indicating full equilibration between gas and blood is also difficult,\textsuperscript{6} many workers have used extrapolation methods which rely on assuming that mixed venous composition is constant over a period of up to 20 s.\textsuperscript{13} Consequently, we chose to use a variation of the breath-holding method, because we could accurately control a prolonged expiration in our anaesthetized subjects. We re-used exhaled gas and did not require preparation of specialized gas mixtures containing carbon dioxide. The disadvantage of this method is a minimum slope has to be detected, rather than a change in slope that would occur when the inspired gas contains more CO\textsubscript{2} than the mixed venous blood. However, even with this latter pattern, detection of a change from uptake to excretion does not necessarily define mixed venous concentration, since this must occur before recirculation.\textsuperscript{6} A measure of the difficulty of satisfactorily identifying ‘equilibria’ is shown by some early studies that suggested rebreathing could also be used to estimate mixed venous oxygen,\textsuperscript{14} despite the very unfavourable physical features of oxygen carriage. Theoretical\textsuperscript{15} and experimental\textsuperscript{16} studies later showed that plateaux are unlikely to represent true equilibria.

Fitting these data to useful descriptive functions is difficult because the method, although simple in concept, has several practical confounding factors, in particular lung inhomogeneity in both volume and ventilation/perfusion ratio, the influence of oxygenation on the carriage of carbon dioxide, the effect of tissue volume and blood capacity on equilibration with gas volumes, and not least the problem of recirculation.\textsuperscript{17} Fitting a simple mathematical function to our values is certainly not physiologically valid since there are at least two time-dependent processes: equilibration of mixed venous blood with lung tissue and gas, and a progressively increasing recirculation. This is shown in an example from one of our data sets shown in Figure 5. Here the data points before 20 s have been fitted to one exponential to estimate the first process, and the data points after 20 s to another, to represent recirculation (although this would be a multi-compartment process, the fast component would predominate). The result is seen to be two approximately continuous curves. Although both arbitrary separation of the processes at 20 s and the use of single exponentials are approximations, they do allow the data to be presented simply. A consequence of this difficulty is that although very good fits to exponential functions were obtained, and the curve fitting methods showed moderate agreement, the predictions of mixed venous values were unrealistic, and showed a considerable range of values. Previous workers, using rebreathing methods, used an iterative method to optimize the fit, and assumed that mixed venous equilibration would occur within 20 s.\textsuperscript{1}

Our data were obtained in a way similar to those of Stock and colleagues,\textsuperscript{18} who studied breath-holds in volunteers, and the present data support their findings. The rate of increase reported by these workers between 20 and 60 s of apnoea is very similar to ours, and contrast with those previously reported by Eger and Severinghaus,\textsuperscript{19} although these workers studied longer periods and probably did not define exactly the changes in the first minute. Direct studies using marker substances show that recirculation is a prompt process.\textsuperscript{20} The effects of recirculation on mixed venous CO\textsubscript{2} have often been considered to be small because of the large capacity for body tissues for CO\textsubscript{2}. However, because the size and thus the capacity of well-perfused tissues are small, their buffering capacity is similarly small.\textsuperscript{21} Recirculation through well-perfused tissue can therefore increase mixed venous carbon dioxide quickly. The impact of this effect depends on the relative distribution of blood flow and also on the metabolic contribution of each tissue bed to carbon dioxide production. It will be large when the time constant of the well-perfused tissue is short, because the weighting effect on venous composition of the blood flow from these tissues is large. For example, in a well-established model,\textsuperscript{22} viscera constitute 4% of the perfused tissues, but receive 46% of the resting cardiac output. As a result, the time constant of this body compartment is short, and the large flow from these tissues results in their having a large effect on the composition of mixed venous blood.
Recirculation during slow expiration test

In conclusion, we have confirmed in patients during anaesthesia for major surgery the predictions from physiological models, that an equilibrium between exhaled gas and mixed venous blood is unlikely before recirculation occurs. This has considerable implications for the partial rebreathing method for cardiac output measurement,\textsuperscript{23} and some techniques now limit rebreathing time to limit the effect.\textsuperscript{24}

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

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