Noninvasive, Automated and Continuous Cardiac Output Monitoring by Pulmonary Capnodynamics

Breath-by-breath Comparison with Ultrasonic Flow Probe


Background: Cardiac output monitoring is most important where cardiovascular stability is potentially threatened, such as during major surgery and in critically ill patients. However, continuous monitoring of cardiac output is still not performed routinely during anesthesia and critical care, because of invasiveness, expense, and inaccuracy of available technologies.

Methods: A technique termed the capnodynamic method was tested for breath-to-breath measurement of pulmonary blood flow from lung carbon dioxide mass balance, using measured carbon dioxide elimination and end-tidal concentration. A prototype measurement system was constructed for a feasibility study in six anesthetized sheep. Large and rapid fluctuations in cardiac output were generated by repeated dobutamine and esmolol challenge. Measurements were compared with an indwelling ultrasonic flow probe placed on the ascending aorta or pulmonary artery.

Results: Cardiac output measured by the flow probe varied between zero and 8.67 l/min, with a mean of 3.50 l/min. Overall mean bias [SD of the difference] between the methods (capnodynamic − flow probe) was 0.025 [0.094] l/min, r = 0.79 (P < 0.001). During periods of stability in cardiac output of 5 min or more, mean bias was −0.20 [0.55] l/min. The method successfully indicated two cardiac arrest events, which were induced in one of the animals.

Conclusions: The method satisfactorily tracked wide fluctuations in cardiac output in real time. The capnodynamic method may have potential for continuous noninvasive cardiac output monitoring in patients undergoing anesthesia for major surgery, and in critical care, on a routine basis.

CARDIAC output measurement is most important where cardiovascular stability and the adequacy of perfusion of vital organs are potentially threatened, such as during major surgery and in critically ill patients. In these situations continuous, real-time monitoring is desirable, because acute fluctuations and rapid deterioration can occur unexpectedly, e.g., where sudden blood loss complicates an operation. Although real-time monitoring of arterial blood pressure is safely and cheaply performed via an indwelling peripheral arterial line and is almost routine during major surgery and critical care, continuous monitoring of cardiac output is still not performed routinely. This is because of the absence until now of inexpensive, practical, noninvasive technologies.

Established techniques for measurement of cardiac output, such as thermodilution via a pulmonary artery catheter, are invasive and occasionally associated with serious complications, or are time-consuming and heavily dependent on the operator’s attention and skill, as in the case of Doppler echocardiography. Improvements in this field are occurring, such as the development of pulse contour techniques, transpulmonary thermodilution, and improved thoracic bioimpedance devices, but these all have their limitations, such as the need for invasive central or peripheral cannulation or repeated calibration, or poor accuracy under clinical conditions.

Techniques based on pulmonary gas exchange measurement are among the oldest methods used for cardiac output measurement and are attractive because of their potentially noninvasive nature. Recent developments have produced systems or devices based on partial carbon dioxide rebreathing (NICO; Novametrix, Murrysville, PA) or inert gas uptake, using either traditional closed- (Innomicor, Innovision, Odense S, Denmark) or open-circuit methods. In addition, inert gas methods have been described using forced oscillatory inspired gas concentration, and differential lung uptake via a double-lumen endobronchial tube (the throughflow method). However, none of these alternatives allows cardiac output monitoring that is truly continuous and noninvasive, while being easily adaptable to a typical anesthetic environment. A need remains for the development of a continuous cardiac output measurement system, providing breath-by-breath monitoring, suitable for routine use in patients undergoing general anesthesia or in intensive care.

In the current study, an automated method is described, based on measured carbon dioxide elimination, which allows continuous calculation of effective pulmonary capillary blood flow (Qc) with every breath and is responsive to acute changes in cardiac output. We have termed this the capnodynamic method. A prototype measurement system was constructed and a feasibility study was conducted in vivo in a sheep model. The study was designed to test the ability of the method to
deliver real-time tracking of large and rapid fluctuations in cardiac output during repeated dobutamine and esmolol challenge, by continuous comparison with an indwelling ultrasonic flow probe.

Materials and Methods

Outline of the Capnodynamic Method

The method is a development of the "differential Fick" principle,\textsuperscript{12} using paired sets of measurement of both carbon dioxide elimination rate ($\dot{V}_{\text{CO}_2}$) and alveolar partial pressure (approximated by the end-tidal partial pressure [$P_{\text{e}}\text{CO}_2$]). These are measured with every breath, while continual cyclic alternation takes place in the level of alveolar ventilation of the lungs. In the current experiment, alveolar ventilation was varied by a stepwise change of 200 ml in expired tidal volume ($V_T$) from an electronic ventilator (Bear AV500 anesthetic ventilator, Bear Corp, Riverside, CA) automated by analog output from the computer, which was continued for the duration of the cardiac output measurement experiment.

A 12-breath cycle was used (6 smaller breaths followed by 6 larger breaths, each representing a "half cycle"). This generates acute changes in carbon dioxide balance in the lung, from which paired measurements are derived, each pair consisting of breaths from different half cycles. Breath pairs are matched either within a ventilatory cycle, or between cycles separated by time. This depends on whether carbon dioxide elimination by the lung is stable, as indicated by the pattern of cyclic fluctuation in $P_{\text{e}}\text{CO}_2$, or unstable. $Q_c$ is calculated with each breath by one or the other of two related equations, the calibration and continuity equations, during stable and unstable cycles, respectively. These equations, which are both derived from consideration of a simple alveolar compartment lung model, are each based on fundamentally different assumptions regarding the stability of $Q_c$ and mixed venous carbon dioxide content ($C\text{VCO}_2$) at the time of measurement. The mathematical basis of the method is outlined in the appendices.

The Capnodynamic Equations

Stable carbon dioxide elimination was said to exist where the cyclic pattern of change in $P_{\text{e}}\text{CO}_2$ was similar between successive cycles. (This was defined as the absolute magnitude of change in $P_{\text{e}}\text{CO}_2$ between all successive breaths within each half cycle being within 0.5 mmHg of that between the corresponding breaths in the preceding half cycle.) At this point, stable $C\text{VCO}_2$ and $Q_c$ were assumed, and the calibration and capacitance equations were computed. Figure 1 shows the typical pattern of changes in measured variables in one animal resulting from a 12-breath cyclic alternation in expired $V_T$ from 400 to 600 ml, and the points at which the equations were applied. Derivation of the equations is given in appendix 2.

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
If not stable: & Continuity equation \\
\hline
If stable: & Calibration equation \\
\hline
\end{tabular}
\caption{Overview of the Capnodynamic Equations}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{A typical pattern taken from one animal, of changes in measured variables: carbon dioxide elimination rate ($\dot{V}_{\text{CO}_2}$), end-tidal partial pressure ($P_{\text{e}}\text{CO}_2$), and rate of change in partial pressure ($dP_{\text{e}}\text{CO}_2/dt$), resulting from a 12-breath cyclic alternation in tidal volume ($V_T$) from 400 to 600 ml. The points at which the cardiac output equations may be applied are indicated, depending on the stability of the pattern of carbon dioxide elimination between successive half cycles.}
\end{figure}

1. The calibration equation:

For two breaths $i$ and $j$, which are sufficiently close in time to one another that $C\text{VCO}_2$ and $Q_c$ are assumed to have not changed:

$$
Q_c = \frac{P_b \cdot [V_{\text{CO}_2} - \dot{V}_{\text{CO}_2}] - \dot{Q}_c \cdot S_{\text{CO}_2} \cdot [P_{\text{e}}\text{CO}_2 - P_{\text{e}}\text{CO}_2]}{\dot{V}_{\text{CO}_2} - \dot{V}_{\text{CO}_2}},
$$

(E1)

\[S_{\text{CO}_2}, the solubility coefficient of carbon dioxide in blood at a given partial pressure, was obtained from the equations of Kelman\textsuperscript{13,14} using a previously published algorithm\textsuperscript{15} employing a measured hemoglobin, body temperature, and arterial oxygen saturation, with an assumed base excess of zero. VeffCO$_2$, the effective volume of distribution of carbon dioxide in the lung, was determined on the following breath $j + 1$ by the capacitance equation.

2. The capacitance equation:

$$
\text{VeffCO}_2 = \frac{P_b \cdot [V_{\text{CO}_2} - \dot{V}_{\text{CO}_2}] - \dot{Q}_c \cdot S_{\text{CO}_2} \cdot [P_{\text{e}}\text{CO}_2 - P_{\text{e}}\text{CO}_2]}{dP_{\text{e}}\text{CO}_2/dt - dP_{\text{e}}\text{CO}_2/dt},
$$

(E2)

A mutual solution to these two equations was obtained.
iteratively. This lung volume was corrected as described by Sainsbury et al.\textsuperscript{16} using an assumed dead space of one third of the $V_t$.

Mixed venous carbon dioxide content ($C_{\text{VCO}_2}$) was then calculated for breath $i$ (or $j$):

$$C_{\text{VCO}_2} = S_{\text{CO}_2} \cdot \frac{P_{\text{F}CO_2}}{P_B} + \frac{dP_{\text{F}CO_2}}{dt} \cdot \frac{V_{\text{effCO}_2} - V_{\text{CO}_2}}{Q_c} \cdot \frac{P_B}{Q_c}.$$  \hspace{1cm} (E3)

Where the pattern of change in $P_{\text{F}CO_2}$ between successive cycles was not similar, stable $C_{\text{VCO}_2}$ and $Q_c$ could not be assumed. The continuity equations were used.

3. The continuity equations:

Using $Q_c$ and $C_{\text{VCO}_2}$ determined from the calibration equation E1 at a previous breath ($Q_c$ and $C_{\text{VCO}_2}$), $Q_c$ on a subsequent breath $k$ ($Q_c$) was calculated, assuming that metabolic body carbon dioxide production was unchanged:

$$Q_c = \frac{dP_{\text{F}CO_2}}{dt} \cdot \frac{V_{\text{effCO}_2} - V_{\text{CO}_2}}{Q_c} \cdot \frac{P_B}{Q_c}.$$  \hspace{1cm} (E4)

where

$$C_{\text{VCO}_2} = S_{\text{CO}_2} \cdot \frac{P_{\text{F}CO_2}}{P_B} + \frac{dP_{\text{F}CO_2}}{dt} \cdot \frac{V_{\text{effCO}_2} - V_{\text{CO}_2}}{Q_c}.$$  \hspace{1cm} (E5)

Equations E4 and E5 are interdependent functions of each other, which were solved iteratively by bisection, with a tolerance of 1% or less. This system of equations allows for changes in $Q_c$ to be followed on a breath-by-breath basis from a series of variables, all of which can be readily measured noninvasively.

Pulmonary shunt fraction ($Q_s/Q_t$) was estimated by the shunt equation using pulse oximetry measurement ($S_{\text{PO}_2}$) and an assumed mixed venous saturation ($S_{\text{VCO}_2}$) of 70%.

$$\frac{Q_s}{Q_t} = \frac{100 - S_{\text{PO}_2}}{100 - S_{\text{VCO}_2}}.$$  \hspace{1cm} (E6)

Finally, to obtain total pulmonary blood flow (cardiac output) $Q_t$:

$$Q_t = Q_c + Q_s.$$  \hspace{1cm} (E7)

Experimental Protocol

After approval from the institutional ethics committee at the Howard Florey Institute, Melbourne, Victoria, Australia, six sheep varying in weight from 35 to 45 kg were anesthetized with thiopentone, followed by maintenance with isoflurane in a 50–50 air–oxygen mixture at a fresh gas flow rate of 4 l/min from the anesthetic machine. After tracheal intubation, the animals were attached to a standard circle absorber breathing system and ventilated with a mean minute ventilation of 100–150 ml · kg$^{-1}$ · min$^{-1}$ at a rate of 10 breaths/min. An arterial line was inserted for systemic blood pressure monitoring and blood gas sampling to obtain a hemoglobin concentration. A pulse oximetry probe was placed on the animal’s ear and a rectal temperature was recorded, to optimize accuracy of carbon dioxide solubility calculation. All of the sheep had been previously instrumented with indwelling ultrasonic transit time flow probes (Transonics Systems Inc., New York, NY), a device that has been previously shown in anesthetized pigs during cardiopulmonary bypass to provide excellent moment-to-moment blood flow measurement in both aortic and pulmonary artery placement.\textsuperscript{17} In the current study, in four of the sheep, the probes were placed on the ascending aorta, and in the other two, the probes were placed on the pulmonary artery.

The capnodynamic cardiac output measurement system was attached to the breathing system in the common dead space, distal to the Y-piece and just proximal to the breathing system filter. The system consisted of a Fleisch pneumotachograph (Hans Rudolph Inc., Kansas City, KS) attached to a differential pressure transducer (Validyne Corp., Northbridge, CA) for measurement of expired tidal flow, and a sidestream gas sampling port feeding to a Datex Capnomac Ultima rapid gas analyzer (Datex-Ohmeda, Helsinki, Finland), which measures carbon dioxide by infrared absorption. Measured flow was initially calibrated by comparison of expired $V_t$, calculated by integration of expired tidal flow $versus$ time, against a Wright spirometer, verified by comparison with 1-l and 3-l dry gas syringes. Analog data from these devices was downloaded continuously to an analog–digital converter card on a Macintosh Power PC desktop computer (Apple Corporation, Redmond, CA), for computation with each breath. Figure 2 shows a schematic diagram of the measurement system.

With each breath, both $V_{CO_2}$ and $P_{\text{F}CO_2}$ were measured and corrected to body temperature and pressure saturated. $V_{CO_2}$ was calculated by integration and multiplication of expired flow and carbon dioxide partial pressure waveforms, with previous alignment of the waveforms to correct for delay in sidestream sampling by the gas analyzer (approximately 2 s). This was done by delaying flow data from the transducer in digitized form in a shift register, before multiplication with carbon dioxide concentration waveform data. $V_{CO_2}$ was secondarily calibrated against a volumetrically measured flow of pure carbon dioxide fed into a tidally ventilated 41 rubber bag and was found to be within 4% of the target value within the range of tidal volumes used. $dP_{\text{F}CO_2}/dt$ was estimated with each breath from the measured change of $P_{\text{F}CO_2}$ over a series of three breaths,
using least squares analysis assuming that the change follows an exponential washin/washout pattern, to obtain the slope of the tangent to the exponential curve with the first breath. This process delays calculation of $Q_c$ by two breaths.

After establishment of ventilation, and commencement of calculation of $Q_t$ with each breath, cardiac output was varied with alternating infusions of dobutamine (up to $12 \mu g \cdot kg^{-1} \cdot min^{-1}$) and esmolol boluses (up to 10 mg), with the intention of producing rapid changes in cardiac output as measured by the flow probe. Continuous, beat-to-beat cardiac output measurement data from the flow probe transducer ($Q_{fp}$) was downloaded, along with breath by breath data from the capnodynamic system.

Statistics

Primary comparison was made according to the approach of Bland and Altman\textsuperscript{18} to define mean bias, SD of the difference, and limits of agreement between $Q_{fp}$ and $Q_t$ with each breath. Correlation coefficients and intra-class correlation coefficients were also calculated.\textsuperscript{19} Secondary analysis examined bias and limits of agreement during periods of stability in $Q_{fp}$ of 5 min or more, to determine the accuracy and precision of the capnodynamic method in the absence of sudden pharmacologically induced swings in cardiac output.

Results

Data were collected continuously for an average of 80 min (range, 55–105 min) from each animal, giving just over 5,000 measurements. Table 1 summarizes measured variables relevant to the calculation of $Q_t$ in the equations given above. $Q_{fp}$ varied between 0 and 8.67 l/min, with a mean $Q_{fp}$ of 3.50 l/min. Calibration $Q_c$ was calculated wherever the conditions for stability in $P_{e\cdot CO_2}$ were met, on average approximately every 2 min. There were 11 periods of time where a calibration $Q_c$ was not recalculated for at least 10 min, including 2 periods of 20 min or more. These all coincided with wide variations in $Q_{fp}$. During these periods, the continuity $Q_c$ was calculated with each breath.

Figure 3 shows the parallel plot of continuous measurement of $Q_{fp}$ and $Q_t$ versus time. Data for the six subjects have been concatenated to display all data from the experiment, totalling 500 min. Mean bias ($Q_t-Q_{fp}$) was $-0.25$ l/min, with an SD of the difference of 0.94 l/min. The limits of agreement were $1.60$ and $2.10$ l/min.

Table 1. Summary of Measured and Calculated Variables from Combined Data for the Six Sheep

<table>
<thead>
<tr>
<th>Variable</th>
<th>$V_{CO_2}$, l/min</th>
<th>$P_{e \cdot CO_2}$, mmHg</th>
<th>$P_{aco_2}$, mmHg</th>
<th>$Cv_{CO_2}$, ml%</th>
<th>Temp, °C</th>
<th>$Sp_{O_2}$, %</th>
<th>$Q_s/Q_t$, %</th>
<th>$V_{eff CO_2}$, l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean [SD]</td>
<td>-0.130 [0.039]</td>
<td>30.3 [3.4]</td>
<td>31.8 [2.1]</td>
<td>53.7 [3.6]</td>
<td>38.6 [0.4]</td>
<td>99.0 [0.03]</td>
<td>3.4 [0.6]</td>
<td>2.2 [0.5]</td>
</tr>
</tbody>
</table>

$Cv_{CO_2}$ = mixed venous carbon dioxide content; $P_{aco_2}$ = arterial carbon dioxide tension; $P_{e \cdot CO_2}$ = end-tidal partial pressure; $Q_s/Q_t$ = pulmonary shunt fraction; $Sp_{O_2}$ = oxygen saturation measured by pulse oximetry; Temp = temperature; $V_{CO_2}$ = carbon dioxide elimination rate; $V_{eff CO_2}$ = effective volume of distribution of carbon dioxide in the lung.
l/min. Figure 4 shows the Bland and Altman plot of difference versus average, and figure 5 shows the correlation plot. The intraclass correlation coefficient was 0.79, and correlation coefficient $r$ was 0.79 ($P < 0.001$). Results are summarized in table 2. The line of best fit is shown in figure 5 and is described by the relation $y = 0.71x + 0.76$.

Throughout the experiment, there were 14 periods of stability in $Q_f$ of 5 min or more, occurring at various points of time across all six subjects, which totalled 80 min and 800 measurements. The mean $Q_f$ was 2.94 l/min during these periods of stability (range, 1.00–5.94 l/min), with a mean bias ($Q_t - Q_f$) of −0.20 l/min and an SD of the difference of 0.55 l/min. The intraclass correlation coefficient was 0.78, and the line of best fit was described by the relation $y = 0.82x + 0.21$.

In the second animal, which was killed, cardiac arrest was induced twice with a large esmolol bolus. The first arrest was followed immediately by resuscitation with a bolus of dobutamine. The sudden decline in cardiac output to near zero measured by the flow probe was successfully tracked by the capnodynamic method in both instances, with a delay of approximately half a minute. An enlargement of the time plot of the first event is shown in figure 6, which includes a plot of fractional end-tidal carbon dioxide concentration ($F_{\text{CO}_2}$). It can be seen that the capnodynamic method had a longer delay in registering the recovery in aortic blood flow after the dobutamine bolus, which closely followed the delay in recovery of $F_{\text{CO}_2}$. This is presumably due to profound washout of carbon dioxide from lung tissues and capillary blood during the 2 min of blood flow stasis, during which time ventilation continued.

**Discussion**

The use of a step change in alveolar ventilation to produce paired sets of gas exchange measurements for noninvasive cardiac output estimation was first described by Gedeon et al.\textsuperscript{20} in 1978 (achieved by a change in end-expiratory pause duration). Although comparison of their measurements with thermodilution was encouraging, these authors suggested that the utility of the method was limited by fluctuations in $C_{\text{CO}_2}$ caused by the respiratory maneuver itself and concluded that measurements could not be repeated more frequently than once every 15 min. A subsequent adaptation of this approach, partial carbon dioxide rebreathing, pioneered by Capek and Roy\textsuperscript{3} in 1988, involved the use of an automated partial rebreathing valve inserted into the breathing circuit, which is opened for a period of ap-
proximately 45 s to alter system dead space and alveolar ventilation of the lungs. This technique is used by the NICO device (Novametrix, Wallingford, CT), which allows intermittent cardiac output measurement once every few minutes. A number of studies have evaluated its accuracy and precision under clinical conditions. The partial carbon dioxide rebreathing technique is attractive because of its noninvasiveness and practicality, where the respiratory maneuver required is readily automated and does not significantly disturb normal ventilation and gas exchange. Furthermore, the effects on accuracy due to end-tidal to arterial carbon dioxide partial pressure gradients largely cancel out, because the equation used considers differences between individual measurements of end-tidal carbon dioxide concentration.

The method described in the current study shares these advantages but incorporates some important theoretical improvements, which provide a significant advance over existing cardiac output monitoring techniques based on gas exchange measurement. Although the calibration equation is similar to those on which the classic partial carbon dioxide rebreathing method is based, the carbon dioxide washin/washout terms (dPE\(\Delta CO_2/dt\)) have been retained, to permit correct mass balance calculation. Because dPE\(\Delta CO_2/dt\) approaches zero at the end of the half cycle, Qc becomes largely independent of V\(\epsilon\)CO\(_2\) in equation E1, and the correction this term produces is generally very small. However, it can still be important as a source of inaccuracy with partial carbon dioxide rebreathing, because washin/washout of carbon dioxide from the lung may not be complete at the end of each half cycle, particularly at low cardiac outputs.

To deliver continuous tracking of cardiac output in real time, the mathematical basis for the technique must allow it to respond to significant changes in both Qc and \(\dot{V}CO_2\) with each breath. This task is complicated by the interdependent relation between cardiac output and mixed venous gas content. If Qc increases acutely, for example, \(\dot{V}CO_2\) will decrease. The underlying theory of previous differential carbon dioxide Fick methods has assumed unchanging \(\dot{V}CO_2\) and Qc during each measurement period, and thus essentially “steady state” hemodynamics and gas exchange. For this reason, they have not been designed for breath-to-breath monitoring of cardiac output fluctuations. The continuity equation does not make these assumptions and, with retention of the carbon dioxide washin/washout terms (dPE\(\Delta CO_2/dt\)), this allows for continuous ongoing cardiac output monitoring with each breath.

Some other technologies, such as pulse contour techniques, currently deliver continuous tracking of cardiac output in real time. Our data confirm that this is also possible from a noninvasive method based on measurement of lung gas exchange. The bias and limits of agreement from this study are comparable with those found for partial carbon dioxide rebreathing and other technologies, including thermodilution and Doppler ultrasound, in a recent study in pigs in comparison with an aortic flow probe.

Its usefulness as a real-time cardiac output monitor is demonstrated by the data from the second animal, where cardiac arrest was induced twice. On both occasions, the method tracked the sudden decrease in cardiac output with each breath, although with a lag of half a minute, for the reasons described above. This response delay is partly due to the two-breath delay involved in calculating dPE\(\Delta CO_2/dt\) as described in the Materials and Methods section and also possibly due to delay in washout of carbon dioxide from lung tissues with sudden changes in alveolar carbon dioxide partial pressure. The response time may be shortened by one or two breaths by using a simpler method to estimate dPE\(\Delta CO_2/dt\) than the exponential approach we used, although some loss of accuracy in calculation of Qc and \(\dot{V}CO_2\) on the first

**Table 2. Comparison of Cardiac Output Measurements**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean [Range] (\dot{Q}_f), l/min</th>
<th>Mean Bias [SD] ((\dot{Q}_t)–(\dot{Q}_f)), l/min</th>
<th>ICC</th>
<th>(r) (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.50 [0.0–8.67]</td>
<td>–0.25 [0.94]</td>
<td>0.79</td>
<td>0.79 (&lt; 0.001)</td>
</tr>
<tr>
<td>Stable (\dot{Q}_f)</td>
<td>2.94 [1.0–5.94]</td>
<td>–0.20 [0.55]</td>
<td>0.78</td>
<td>0.78 (&lt; 0.001)</td>
</tr>
</tbody>
</table>

Comparison of cardiac output measured breath-to-breath by the capnodynamic method (\(\dot{Q}_t\)) with measurements made by the indwelling ultrasonic flow probe (\(\dot{Q}_f\)) in the six sheep. Mean bias and SD are shown as well as intraclass correlation coefficients (ICCs) and correlation coefficient \(r\) (with P value). Results are given overall for the experiment, and for the periods of stability (of 5 min or more) in \(\dot{Q}_f\).
couple of breaths of each half cycle would be expected. In the clinical setting, the response time of the method would be still sufficiently short to prompt timely intervention by the anesthesiologist, once alerted of a dangerous decrease in cardiac output.

Apart from its noninvasiveness, a major practical advantage of the method is that the hardware required to measure the required input variables (gas flow and concentration) is available as standard monitoring equipment on most modern anesthetic workstations. In addition, these are now generally equipped with one of the modern generation of software-controlled anesthesia ventilators, on which continuous cyclic modulation of tidal volume or respiratory rate should be readily achievable, allowing the process to be fully automated and “hands-free.”

Limitations of the method revolve around potential sources of error, both random and systematic. Random error in measurement of input variables (V\text{CO}_2 and P\text{ETCO}_2) with each breath may be minimized by some degree of data smoothing using a running average, although this will slow response time to sudden changes. Systematic errors with the capnodynamic method will overlap with those of the partial carbon dioxide rebreathing technique, which were explored by Yem et al.28 using a mathematical lung model. Modest errors were predicted from the presence of typical alveolar–arterial P\text{CO}_2 gradients seen in anesthetized patients. These arise principally from alveolar dead space, associated with ventilation-perfusion inhomogeneity, which becomes more significant in critically ill patients and those with significant lung disease. The capnodynamic method awaits testing in patients, to determine whether these potential problems are significant, particularly in patients with serious lung pathology. However, the fluctuations in P\text{ETCO}_2 produced within each ventilatory cycle are between only 2 and 4 mmHg (fig. 2). Given that tidal volume oscillates by only 100 ml or so around the mean value, significant difficulties is achieving a useful ventilatory pattern are unlikely in the majority of patients.

In addition, the effect of anatomical dead space may contribute to error, because the equations assume that dead space is identical between breath pairs. A small increase in dead space with increased tidal volume is well described.31 Gedeon et al. chose to use a change in end-expiratory pause instead of tidal volume in their study for this reason, and current partial carbon dioxide rebreathing devices introduce a change in serial breathing system dead space instead.4,20 Although our data reveal no significant systematic error in cardiac output from the method we chose, investigation of the capnodynamic approach using continual cyclic opening and closing of a partial rebreathing valve would be of interest. Such a system may also allow breath-to-breath cardiac output measurement, achievable from a stand-alone device attached to an anesthetic breathing system. This contrasts to modulation of tidal volume or rate, as used in the current study, which requires integration into an existing anesthesia delivery platform.

The modeling data of Yem et al.28 predicted that the partial carbon dioxide rebreathing approach would underestimate deviations from normal cardiac output, and published clinical data generally support this prediction. A review of published studies comparing partial carbon dioxide rebreathing with thermodilution in animals and humans by Haryadi et al.4 found first-order regression coefficients varying between 0.27 and 1.04 (mean 0.83). The line of best fit through the correlation plot of our data (fig. 5) suggests that the capnodynamic method may do the same. However, much of this discrepancy in the current study may be explained by the inherent response lag of the system. Under the conditions of the study, with repeated sudden fluctuations in cardiac output, the effect of this lag is to cause the absolute magnitude of both sudden increases and decreases in Q\text{fp} to be temporarily underestimated on a breath by breath basis. This is supported by the observation that the slope of the relation between Q\text{fp} and Q\text{t} was closer to unity during the periods of cardiac output stability.

At high cardiac outputs, Yem et al.28 predicted that accuracy of partial carbon dioxide rebreathing may be impaired by carbon dioxide recirculation effects within the duration of a rebreathing period. Fluctuations in C\text{\bar{VCO}}_2 produced by the respiratory maneuver may produce similar errors in the method described here, and minimization of this is achieved by continuing alternation of alveolar ventilation at the highest frequency compatible with accurate results. In addition, during oscillating ventilation, the amplitude of the fluctuation in C\text{\bar{VCO}}_2 will be damped by passage of blood through the various vascular beds of the body, which have different time constants. We used a six-breath cycle to achieve a reasonably flat plateau in measured variables at the end of each half cycle under most conditions. However, the accuracy of a shorter cycle duration is worthy of future investigation, because smaller fluctuations in C\text{\bar{VCO}}_2 will be produced.

In the system described in this article, the continuity equation does not assume a constant C\text{\bar{VCO}}_2 between paired gas exchange measurements, but rather a constant metabolic carbon dioxide production. The robustness of this forcing function might be increased by simple adjustment for factors that may affect carbon dioxide production, such as changes in body temperature. Other factors that may prove problematic include sudden changes in the rate of carbon dioxide return to the lungs, such as after release of a limb tourniquet or during laparoscopic surgery. In general, frequent recalibration using the calibration equation is desirable to minimize errors due to this. Further in vivo clinical testing is
Appendix 1: Mass Balance Model of Lung Carbon Dioxide

An alveolar gas compartment is considered to be in equilibrium during expiration with lung tissue and pulmonary capillary blood. Mixed venous blood from the body tissues arrives at the compartment and, after achieving equilibrium with the alveolar gas mixture in the pulmonary capillaries, leaves as pulmonary end-capillary blood. This flow of blood, which engages in gas exchange with the inspired alveolar gas, is the “nonshunt” or “effective pulmonary capillary blood flow” Qc. In addition, mixed venous blood which bypasses the pulmonary end-capillary blood to form arterial blood, which issues as total pulmonary blood flow or cardiac output (Q˙t).

At any time, the volume of carbon dioxide present in the lung (VCO2) is given by

\[ V_{CO2} = \frac{P_{ACO2}}{P_B} \cdot Veff_{CO2}, \]  

(A1)

where P_{ACO2} is its alveolar partial pressure, P_B is ambient barometric pressure, and Veff_{CO2} is the effective lung volume for carbon dioxide.

Changes in VCO2 occur because of arrival of carbon dioxide in mixed venous blood and its removal in pulmonary end-capillary blood or expired alveolar gas. Therefore, the rate of change (dVCO2/dt) is given by

\[ \frac{dV_{CO2}}{dt} = Qc \cdot \Delta V_{CO2} + V_{CO2} - Qc \cdot S_{CO2} \cdot \frac{P_{ACO2}}{P_B}, \]  

(A2)

where ΔV_{CO2} is the rate of elimination of carbon dioxide by the lung (this will have a negative value) with any given breath, and S_{CO2} is the solubility coefficient of carbon dioxide in blood, for given conditions of temperature, hemoglobin, and oxygen saturation, is obtained from the equations of Kelman.13-15

Because, from equation A1,

\[ \frac{dV_{CO2}}{dt} = \frac{dP_{ACO2}}{dt} \cdot \frac{Veff_{CO2}}{P_B}, \]  

(A3)

then substituting in equation A2 and transposing

\[ \frac{dP_{ACO2}}{dt} \cdot \frac{Veff_{CO2}}{P_B} - V_{CO2} = Qc \cdot \Delta V_{CO2} + Qc \cdot S_{CO2} \cdot \frac{P_{ACO2}}{P_B}. \]  

(A4)

This equation contains three unknowns, Veff_{CO2}, ΔV_{CO2}, and Qc. In steady state, the terms on the right side of the equation equal metabolic production of carbon dioxide by the body (V_{CO2metabol}). The left-hand terms are measurable noninvasively if the end-tidal carbon dioxide partial pressure (P_{ETCO2}) is used as a noninvasive approximation for P_{ACO2}.

In this case, Veff_{CO2} includes alveolar dead space in the lung. Therefore,

\[ \frac{dP_{ACO2}}{dt} \cdot \frac{Veff_{CO2}}{P_B} - V_{CO2} = V_{CO2metabol} = Qc \cdot \Delta V_{CO2} + Qc \cdot S_{CO2} \cdot \frac{P_{ACO2}}{P_B}. \]

(A5)

Appendix 2: Derivation of the Capnodynamic Equations

1. The calibration equation:

Where S_{CO2} and Qc are assumed to be constant, Qc is calculated from two simultaneous equations of the form of equation A4. For two breaths i and j from the terminal breaths of two successive half cycles,

\[ \frac{S_{CO2} \cdot P_{ACO2}}{P_B} + \frac{dP_{ACO2}}{dt} \cdot \frac{Veff_{CO2}}{Qc \cdot P_B} - \frac{V_{CO2}}{Qc} \]  

(E6)

Transposing

\[ Qc = \frac{P_B \cdot [V_{CO2i} - V_{CO2j}] - Veff_{CO2} \cdot \left[ \frac{dP_{ACO2i}}{dt} - \frac{dP_{ACO2j}}{dt} \right]}{S_{CO2} \cdot [P_{ACO2i} - P_{ACO2j}]]. \]  

(E7)

Veff_{CO2} is determined on the following breath j + 1 by the capacitance equation.

2. The capacitance equation:

\[ Veff_{CO2} = Veff_{CO2} + \frac{1}{2} \cdot (V_i + V_j). \]

Using an assumed V_i of one third of the V_T.

Mixed venous carbon dioxide content (S_{CO2}) is now calculated for breath i (or j) by transposing equation A4:

\[ S_{CO2} = \frac{S_{CO2} \cdot P_{ACO2}}{P_B} + \frac{dP_{ACO2}}{dt} \cdot \frac{Veff_{CO2}}{Qc \cdot P_B} - \frac{V_{CO2}}{Qc} \]  

(E8)

Because dP_{ETCO2}/dt approaches zero at the end of the half cycle, Qc becomes largely independent of Veff_{CO2} in equation E1. Similarly, Veff_{CO2} is largely independent of Qc in equation E2 when calculated at the start of each half cycle, because the difference between P_{ETCO2} at breaths i + 1 and j + 1 tends to be relatively small. dP_{ETCO2}/dt is greatest at this point in the half cycle (fig. 1).

\[ \Delta V_{CO2} \]  

and Qc are interdependent, and a change in Qc will induce a change in ΔV_{CO2}. Where stable ΔV_{CO2} and Qc cannot be assumed, the continuity equations are used.

3. The continuity equations:

If Qc and ΔV_{CO2} at breath i (Qc_i and ΔV_{CO2i}) have been previously determined from equation E1-E3, we can calculate Qc on a subsequent breath k (Qc_k). From equation E3, for breath i,
\[ C_{\text{VCO}_2} = \text{SC}_{\text{O}_2} \cdot \frac{P_{\text{CO}_2}}{P_n} + \frac{dP_{\text{CO}_2}}{dt} \cdot \frac{V_{\text{effCO}_2}}{P_{\text{CO}_2} - P_n} \cdot \frac{\dot{V}_{\text{CO}_2}}{Q_c} \]  

(E3)

and similarly for breath \( k \).

\[ C_{\text{VCO}_2} = \text{SC}_{\text{O}_2} \cdot \frac{P_{\text{CO}_2}}{P_n} + \frac{dP_{\text{CO}_2}}{dt} \cdot \frac{V_{\text{effCO}_2}}{P_{\text{CO}_2} - P_n} \cdot \frac{\dot{V}_{\text{CO}_2}}{Q_c} \]  

(E3k)

Combining equations E3\( i \) and E3\( k \) to solve for \( Q_c \) in terms of \( Q_c \).

\[
\frac{d}{dt} \left( \frac{\dot{V}_{\text{CO}_2}}{P_{\text{CO}_2} - P_n} - \frac{V_{\text{CO}_2}}{Q_c} \cdot \frac{Q_c}{Q_c} \right) = \frac{dP_{\text{CO}_2}}{dt} \cdot \frac{V_{\text{effCO}_2}}{P_{\text{CO}_2} - P_n} \cdot \frac{\dot{V}_{\text{CO}_2}}{Q_c}.
\]

(E4)

Equation E4 is called the continuity equation. From equation A5, for breath \( i \),

\[
\frac{dP_{\text{CO}_2}}{dt} = \frac{V_{\text{CO}_2}}{P_{\text{CO}_2} - P_n}.
\]

If we assume that production of carbon dioxide by body tissues is constant from breaths \( i \) to \( k \), then from equation A5 again, \( C_{\text{VCO}_2} \) for breath \( k \) is a function of

\[
C_{\text{VCO}_2} = \text{SC}_{\text{O}_2} \cdot \frac{P_{\text{CO}_2}}{P_n} + \frac{V_{\text{CO}_2}}{P_{\text{CO}_2} - P_n} = \text{SC}_{\text{O}_2} \cdot \frac{P_{\text{CO}_2}}{P_n} + \frac{dP_{\text{CO}_2}}{dt} \cdot \frac{V_{\text{effCO}_2}}{P_{\text{CO}_2} - P_n} \cdot \frac{\dot{V}_{\text{CO}_2}}{Q_c}.
\]

(E5)

Equations E4 and E5 are interdependent functions of each other, which can be solved using an appropriate iterative method. The solution gives a value for \( Q_c \) and \( C_{\text{VCO}_2} \), which represent the point of balance in the interdependent relation between cardiac output and mixed venous gas content, using the assumption of a stable metabolic production of carbon dioxide by body tissues as the forcing function.

This allows for changes in \( Q_c \) to be followed on a breath-by-breath basis from a series of other terms, all of which can be readily measured noninvasively.

It should be noted that \( V_{\text{effCO}_2} \) will be altered slightly by a change in expired tidal volume \( (V_t) \) as it alters alveolar gas volume, and a correction for this can be incorporated into the continuity equation, although the effect on calculated \( Q_c \) is small.

References