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NON-INVASIVE AUTOMATED MEASUREMENT OF CARDIAC OUTPUT DURING STABLE CARDIAC SURGERY USING A FULLY INTEGRATED DIFFERENTIAL CO_2 FICK METHOD

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ABSTRACT. Objectives. To re-evaluate the accuracy and precision of a non-invasive method for measurement of cardiac output based on the differential CO_2 Fick approach using an automated change in respiratory rate delivered by a ventilator under control by a prototype measurement system. **Methods.** Twenty-four patients during coronary artery bypass surgery, pre- and postcardiopulmonary bypass were recruited. After routine cannulation including pulmonary artery catheter, relaxant general anesthesia was induced. After hemodynamic and ventilatory stability were achieved, simultaneous paired measurements were made by the differential Fick method and by bolus thermodilution. Measurements were generated by inducing a change in respiratory rate by the ventilator under computer control. In Group 1, this involved an increase in respiratory rate from 8 to 12 breaths/min. In Group 2, this involved a decrease from 12 to 6 breaths/min. **Results.** Nineteen measurements were made in each Group, 12 pre-CPB and 7 post-CPB. In Group 1 mean bias was −0.06 l/min, with a precision of agreement of 0.87 l/min, $r = 0.91$. In Group 2 (excluding one outlier) mean bias was −0.07 l/min, with a precision of 1.12 l/min, $r = 0.71$. **Conclusions.** Acceptable agreement with thermodilution during surgery was found, particularly where the ventilatory change involved an increase in respiratory rate from a lower baseline. This approach has potential to be readily integrated into modern anesthesia delivery platforms, allowing routine non-invasive cardiac output measurement.

KEY WORDS. carbon dioxide, pulmonary capillary blood flow.

INTRODUCTION

Development of techniques for less-invasive measurement of cardiac output in patients during surgery and critical care has attracted considerable interest and activity [1]. Methods based on pulmonary gas exchange measurement [2] using the differential Fick principle [3–5], pulse contour analysis and transpulmonary thermodilution [6], and esophageal or external Doppler [7, 8], have all generated recently published validation studies.

The differential Fick method using measurement of CO_2 elimination by the lungs has become accepted as a practical non-invasive means for measuring cardiac output in ventilated patients [9]. It has achieved clinical use in the form of the partial CO_2 rebreathing method, which uses an automated partial rebreathing valve and loop inserted proximal to the endotracheal tube. After making baseline measurements of CO_2 elimination by the lungs ($\dot{V}_{CO_2}$)

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and alveolar (end-tidal) CO_2 partial pressure ($P_{E'_{CO_2}}$), activation of the valve produces an acute change in alveolar ventilation and repeat measurements of these variables are then made prior to systemic recirculation time. These paired sets of measurements allow calculation of non-shunt pulmonary capillary blood flow ($\dot{Q}c$), without the need for prior estimation of mixed venous CO_2 content. This method was pioneered by Blomqvist et al. and Capek and Roy and is the basis for the NICO™ (Respironics USA) [9–11].

However, the earliest study to employ the differential CO_2 Fick approach was by Gedeon et al. and simply employed a change in respiratory rate delivered by the ventilator (accompanied by a change in I:E ratio) to produce the required change in alveolar ventilation [12]. Comparison of $\dot{Q}c$ determined in this way against thermodilution gave encouraging results in dogs, but the authors presented no results from humans and only one subsequent study into clinical use in patients has been published, which produced disappointing results [13]. Contributing factors to this possibly included changes in alveolar deadspace during the ventilatory manoeuvre, and technical limitations to the achievable precision of measurement of the relevant variables and to the transfer of the technology to available clinical equipment.

Major changes in the available ventilator technology have occurred over recent years, and software controlled ventilators are becoming routine equipment for patient care on modern anesthesia workstations. These devices present a renewed possibility for the approach pioneered by Gedeon and colleagues to be employed routinely for non-invasive cardiac output measurement in ventilated patients. Such a system could conceivably be fully integrated into an existing anesthesia delivery platform and be fully automated.

We conducted an exploratory study of an automated system employing a modification of this method in which a number of strategies were employed to optimize the precision of measurement of the relevant variables and of the calculated cardiac output. We compared measurements of cardiac output obtained this way against thermodilution in ventilated surgical patients.

METHODS

Ventilator control

An Ohmeda 7800 anesthesia ventilator (Datex-Ohmeda, Helsinki, Finland) was modified by replacing the existing analog potentiometer inputs for tidal volume, respiratory rate and I:E ratio with digitally controllable potentiometers (MCP42010, Microchip Technology Inc. Arizona USA). The MCP42010 was controlled by an ATMEGA8535 microcontroller (Atmel Corporation, San Jose, CA USA) which relayed user parameters communicated over a USB connector from the user input on a Macintosh Powerbook notebook computer (Apple Corp, California, USA). The user input consisted of a custom designed Graphical User Interface using *LabView* 7.01 (National Instruments, Austin, Texas, USA) software for Macintosh which accepted inputs in real time and transmitted data on user command. The microcontroller and digital potentiometer were external to the ventilator and drew power from the computer via the USB. This allowed independent manipulation of rate and I:E ratio by the computer using serial output.

When the ventilation rate was changed for a cardiac output measurement, a simultaneous change in I:E ratio was selected such that the duration of inspiration remained as stable as possible before and during the manoeuvre. This minimized any changes in respiratory mechanics and pulmonary deadspace. that might affect the difference between the measured end-tidal CO_2 and pulmonary capillary CO_2 partial pressures, before and during the change. In similar fashion to the original study by Gedeon et al. [12], this effectively altered only the duration of the end-expiratory pause.

Measurement system

With each breath, both $\dot{V}_{CO_2}$ and $P_{E'_{CO_2}}$ were measured as follows and corrected to body temperature and pressure saturated. $P_{E'_{CO_2}}$ was measured from a ½ s segment of the expiratory plateau of the capnograph obtained from sidestream gas sampling by a Datex *Capnomac Ultima* infrared gas analyzer (Datex-Ohmeda, Helsinki, Finland), calibrated using the manufacturer's proprietary calibration gas. The segment was taken at the same point of the curve both before and during the ventilatory change. $\dot{V}_{CO_2}$ for each breath *i* prior to the ventilatory change ($\dot{V}_{CO_2 i}$) was measured using a calibrated gas exchange measurement system consisting of a Fleisch pneumotachograph (Hans Rudolph Inc, Kansas, USA) attached to a differential pressure transducer (Validyne Corp, California, USA) for measurement of expired tidal flow, and the gas analyzer. Analog data from these devices was downloaded continuously at a sampling rate of 200 Hz via a USB analog-digital converter card (USB 6009, National Instruments, Austin, Texas, USA), to the computer for computation with each breath. Design of the software system for data download and computation, and instrument control, was done using *LabView* 7.01. Figure 1 shows a schematic diagram of the system. $\dot{V}_{CO_2}$ at the alveolar-capillary

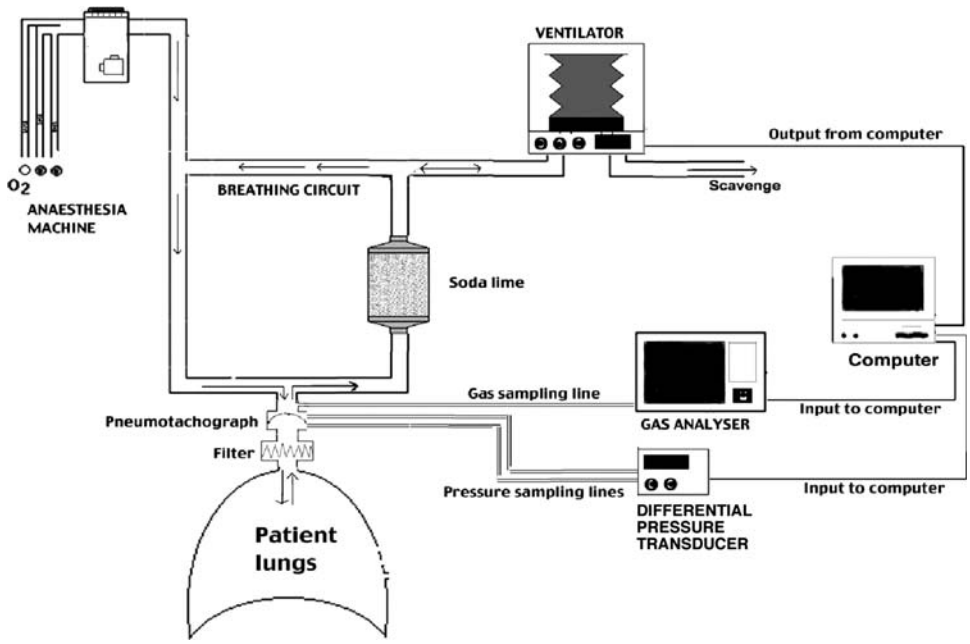

Fig. 1. Schematic diagram of the anesthesia delivery and measurement system.

level with each breath was calculated by multiplication and integration of expired flow and carbon dioxide concentration waveforms with respect to time, with appropriate compensation in software for sidestream sampling transport time delay and for the response time of the gas analyzer [14], as well as for breath to breath changes in lung volume and washin/washout of CO_2 from the lung [15, 16]. The accuracy of the device in measurement of gas flows and volumes was verified to within 1% by comparison of expired tidal volume (VT), calculated by integration of expired tidal flow versus time, against a 1 l dry gas syringe across a range of flow rates, and additional calibration was made to compensate for the effect of static pressure within the breathing system, as well as variations in viscosity of the sampled gas mixture during tidal variations in gas composition. $\dot{V}_{CO_2}$ measurement was secondarily calibrated against a volumetrically measured flow of pure carbon dioxide fed into a tidally ventilated gas exchange simulator (TTL type 1600 hinged bellows test lung, Michigan Instruments, USA), and found to be within 3% of the target value within the range of ventilator rate settings employed.

Clinical protocol

With approval by the local institutional human research ethics committee, adult patients undergoing elective coronary artery bypass surgery were approached and informed consent obtained for recruitment to the study. Patients were excluded who were morbidly obese (Body Mass Index over 35 kg/m^2), had severely impaired ventricular systolic dysfunction, or severe lung disease on the basis of history, examination or spirometry. Routine anesthetic management and monitoring was undertaken including insertion of an arterial line and pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA). Relaxant general anesthesia was induced and, following endotracheal intubation, maintained by intravenous fentanyl and propofol with or without inspired isoflurane or sevoflurane, titrated according clinical indication and bi-spectral index. The endotracheal tube was attached via a breathing filter to a circle absorber system attached to an Aestiva anesthetic machine (Datex-Ohmeda, GE Healthcare). The patient was ventilated with oxygen/air at an FIO_2 of approximately 70% and a fresh gas flow of 3 l/min at a minute ventilation adjusted to achieve a $P_{E'_{CO_2}}$ of approximately 27–30 mmHg. After several minutes, when the patient's blood pressure and ventilatory status had been stabilized, the gas exchange measurement system (pneumotachograph and gas sampling port) was attached to breathing system just proximal to the breathing filter, and the measurement process was commenced.

The software protocol stipulated that a change in ventilation for cardiac output measurement should be activated automatically when the standard error of the measured baseline $\dot{V}_{CO_2}$ ($\dot{V}_{CO_2 i}$) was less than 1.5% of the average value and that of the baseline $P_{E'_{CO_2}}$ ($P_{E'_{CO_2 i}}$) was less than 0.1 mmHg for a minimum of five consecutive breaths. The

duration of the change was approximately 50 s. Two patterns of ventilatory change were investigated. Patients in Group 1 had a change from a baseline rate of 8 breaths/min to 12 breaths/min, and those in Group 2 from a baseline rate of 12 breaths/min to 6 breaths/min.

Non-shunt pulmonary capillary blood flow ($\dot{Q}_c$) was calculated according to standard theory of the differential CO_2 Fick method [3, 11] by

$$\dot{Q}c = \frac{P_B \cdot \left[\dot{V}_{CO_2 i} - \dot{V}_{CO_2 j}\right]}{S_{CO_2} \cdot \left[P_{E'_{CO_2 i}} - P_{E'_{CO_2 j}}\right]} \quad (1)$$

where i and j represent, respectively, breaths prior to and during the induced change in alveolar ventilation. P_B is the measured barometric pressure and S_{CO_2} is the slope of the solubility curve of carbon dioxide in blood at a given partial pressure, obtained from the equations of Kelman [17, 18], using a previously published algorithm employing a measured hemoglobin, body temperature, arterial oxygen saturation and base excess obtained from an arterial blood gas sample at the time of measurement [19]. $P_{E'_{CO_2}}$ during the ventilatory change ($P_{E'_{CO_2 j}}$) was averaged from breaths from the last 30 s of the period of change.

Maintenance of the stability of pulmonary mechanics and deadspace during the measurement manoeuvre allowed a mathematical simplification to be adopted for the measurement of the numerator of Equation 1, since the change induced in alveolar ventilation ($\dot{V}_A$) can be assumed to be solely dependent on the change made in respiratory rate (RR). Thus

$$\dot{V}_{A_i} = \dot{V}_{A_j} \cdot \frac{RR_j}{RR_i} \quad (2)$$

where $\dot{V}_{A_i}$ and $\dot{V}_{A_j}$ are $\dot{V}_A$ prior to and during the change, respectively.

$\dot{V}_{A_i}$ was estimated from $\dot{V}_{CO_2 i}$ and $P_{E'_{CO_2 i}}$ according to

$$\dot{V}_{A_i} = \frac{P_B \cdot \dot{V}_{CO_2 i}}{P_{E'_{CO_2 i}}} \quad (3)$$

and likewise for $\dot{V}_{A_j}$

$$\dot{V}_{A_j} = \frac{P_B \cdot \dot{V}_{CO_2 j}}{P_{E'_{CO_2 j}}} \quad (4)$$

Combining Equations 2–4

$$\dot{V}_{CO_2 i} - \dot{V}_{CO_2 j} = \dot{V}_{CO_2 i}\left(1 - \frac{P_{E'_{CO_2 j}}}{P_{E'_{CO_2 i}}} \cdot \frac{RR_j}{RR_i}\right) \quad (5)$$

This term replaced the numerator of Equation 1. This was found to significantly improve the precision of measurement of $\dot{Q}_c$, because precision of measurement of $P_{E'_{CO_2}}$ is generally better than that of $\dot{V}_{CO_2}$, particularly during the ventilatory change.

$\dot{Q}_c$ was corrected using a non-invasive estimate of pulmonary shunt fraction ($\dot{Q}_s/\dot{Q}_t$) obtained from a pulse oximetry saturation measurement ($S_{p_{O_2}}$) and an assumed mixed venous saturation ($S_{\bar{v}_{O_2}}$) of 70% according to

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{100 - S_{p_{O_2}}}{100 - S_{\bar{v}_{O_2}}} \quad (6)$$

Finally, to obtain total pulmonary blood flow (cardiac output) $\dot{Q}_t$:

$$\dot{Q}_t = \dot{Q}_c + \dot{Q}_s \quad (7)$$

One $\dot{Q}_t$ measurement was made in the pre-cardiopulmonary bypass period and, where logistic and time demands permitted, a second measurement was made in the post-cardiopulmonary bypass (CPB) period as well. This was treated as an independent measurement for statistical purposes. With each measurement, a blinded measurement was simultaneously made by bolus thermodilution using an average of 3 boluses with room temperature saline.

Agreement between the differential Fick method ($\dot{Q}_t$) and thermodilution ($\dot{Q}_{Td}$) was determined using the method of Bland and Altman [20], by calculation of mean bias and standard deviation of the difference between paired measurements by the two techniques, and by calculation of correlation coefficient r.

RESULTS

Twenty-four patients were recruited to the study, 12 in each Group. Mean age was 63.1 years (range 37–77 years) and mean weight was 79.4 kg (range 53–107 kg). Nineteen measurements were made in each Group, 12 pre-CPB and 7 post-CPB.

Results are summarized in Table 1. In Group 1, where the ventilatory manoeuvre involved an increase in respiratory rate from 8 to 12 breaths/min, mean bias ($\dot{Q}_t - \dot{Q}_{Td}$) was −0.06 l/min, with a standard deviation of the difference of 0.87 l/min. The correlation coefficient r was 0.91. Results are displayed in Figure 2a (Bland and Altman plot) and Figure 3a (correlation plot).

In Group 2, where the ventilatory manoeuvre involved a decrease in respiratory rate from 12 to 6 breaths/min, mean bias ($\dot{Q}_t - \dot{Q}_{Td}$) was −0.07 l/min, with a standard deviation of the difference of 1.12 l/min. r was 0.71. One outlier was excluded from the analysis in this group where the calculated $\dot{Q}_t$ was in excess of three standard deviations

Table 1. Agreement of the differential CO_2 Fick method with simultaneous measurements by the reference method (bolus thermodilution) in measurement of cardiac output

Group	Ventilatory rate change	*n*	Mean bias (l/min)	Standard deviation of difference (l/min)	*r*
1	8 → 12/min	19	−0.06	0.87	0.91
2	12 → 6/min	18	−0.07	1.12	0.71

Mean bias, and standard deviation of the difference between measurements by the two methods, and correlation coefficient (*r*) are given.

higher than $\dot{Q}_{Td}$. Results are displayed in Figure 2b (Bland and Altman plot) and Figure 3b (correlation plot).

DISCUSSION

The differential Fick approach to pulmonary blood flow measurement using CO_2 elimination by the lungs has been well validated in ventilated patients as a means for measuring cardiac output, in the form of the partial CO_2 rebreathing method [5, 9, 13, 21, 22]. The method has significant advantages, being entirely non-invasive and adaptable to use as a stand-alone device that requires no modification of the function of the anesthesia delivery system or ventilator. Interposing a partial rebreathing loop and valve into the breathing system has the drawback of introducing some physical bulk and complexity just proximal to the patient's airway, and adds the costs of this disposable equipment item to the anesthetic.

The approach previously demonstrated by Gedeon et al. [12] promised the most seamless and fully integrated alternative means for achieving this outcome, but subsequently received little published clinical investigation. This might be partly explained by the limitations of the technology then available for translating this approach into clinical practice. Ventilators were generally stand-alone devices, often with mechanical analog controls. However, advances in the field have now provided a new generation of clinical ventilators as standard equipment for both anesthesia and critical care, which allow easy digital manipulation of multiple ventilatory settings, including rate, volume and I:E ratio. This technology makes the approach proposed by Gedeon et al. a more realistic possibility.

In their original study in animals, these authors made an important modification to their ventilator settings, by simultaneously altering the I:E ratio, allowing respiratory rate to be altered without changing the duration or pattern of inspiration, thus avoiding changes in inspiratory pressure or flow rates which might affect pulmonary alveolar deadspace and arterial-alveolar CO_2 difference before and during the ventilatory manoeuvre. This was important in assuring that the difference in measured $P_{E'_{CO_2}}$ produced by the manoeuvre reflected as closely as possible the real difference in arterial CO_2 partial pressure.

In the only subsequent study of this approach published, Bosman et al. compared results using a ventilatory manoeuvre consisting of a 30 s period of increased rate followed by a 45 s period of reduced rate, against bolus thermodilution in patients after cardiac surgery.13 They did not modify their I:E ratio settings in similar fashion to Gedeon et al., and noted significant differences in inspiratory pressure during these two periods in their patients. Their results were described as disappointing, with a low correlation value with thermodilution. This primarily arose from a relatively flat response on their method to differences in cardiac output measured by thermodilution. They achieved better correlation with thermodilution using a partial rebreathing valve. Interestingly however, the scatter (standard deviation) in agreement with thermodilution was similar using the two differential CO_2 methods.

In the current study, we found acceptable agreement with thermodilution during surgery, particularly where the ventilatory change involved an increase in respiratory rate from a lower baseline. Our better correlation probably is due to the fact that we emulated the original methodology of Gedeon et al. and altered the I:E ratio as well to keep the inspiratory phase of the tidal respiratory cycle unaffected by the manoeuvre. The poorer results we found with the opposite change in respiratory rate, including the presence of an outlier in this Group, are partly due to the fewer breaths available during the change from which to derive an average $P_{E'_{CO_2 j}}$ Breath-to-breath scatter in $P_{E'_{CO_2}}$ is typically up to 1 mmHg so that the accuracy of the denominator of Equation 1 is dependent upon minimising the standard error in its calculation. Seven or eight breaths were available for averaging during the period of increased ventilatory rate to 12 breaths/min in Group 1, before recirculation begins to alter the mixed venous CO_2 content. This is assisted by the faster achievement of new equilibrium CO_2 concentrations in

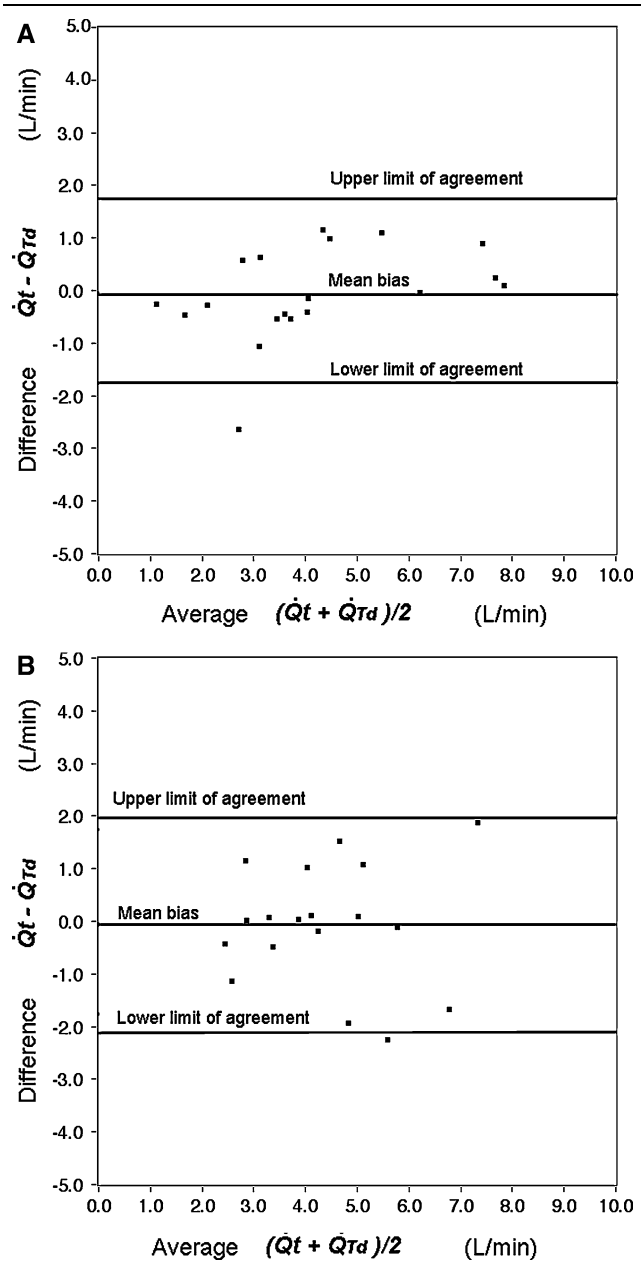

Fig. 2. Bland and Altman plot of the agreement between the differential CO_2 Fick method and simultaneous measurements by bolus thermodilution in measurement of cardiac output. (a) Data from Group 1, where the ventilatory manoeuvre involved a change in respiratory rate from 8 to 12 breaths/min. (b) Data from Group 2, where the ventilatory manoeuvre involved the opposite change.

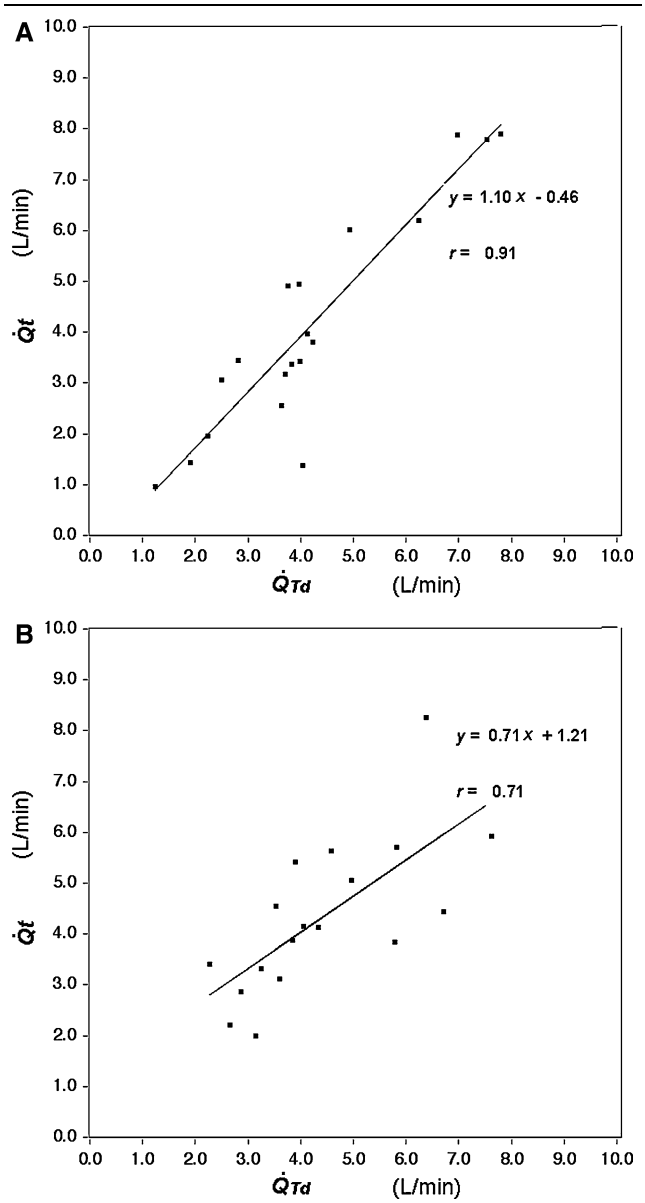

Fig. 3. Correlation plot of the agreement between the differential CO_2 Fick method and simultaneous measurements by bolus thermodilution in measurement of cardiac output. (a) Data from Group 1, where the ventilatory manoeuvre involved a change in respiratory rate from 8 to 12 breaths/min. (b) Data from Group 2, where the ventilatory manoeuvre involved the opposite change. Regression equations for each are included.

the lung during the change where ventilation is increased, rather than reduced.

Other strategies we employed to optimize the precision of measurement of the cardiac output included automating the measurement manoeuvre so that it was triggered under software control by the achievement of a high level of precision in the breath-by-breath measurement of baseline $\dot{V}_{CO_2}$. In addition, the numerator obtained from Equation 5 improved the precision of measurement, because accurate measurement of $P_{E'_{CO_2}}$ from a rapid gas analyzer is a technically simpler process than measurement of $\dot{V}_{CO_2}$ at the mouthpiece, which requires sophisticated integration of data from several component devices and is

prone to compounding error. Improved precision in calculation of cardiac output may also be obtained from larger changes in alveolar ventilation, which produces larger changes in alveolar and arterial CO_2 partial pressure. The magnitude of the change in rate in our study was roughly half that used by Bosman et al. and produced a change in $P_{E'_{CO_2}}$ of typically 2–3 mmHg.

The precision in agreement with thermodilution we found is similar to that in a number of recent clinical studies investigating the accuracy and precision of minimally invasive techniques for cardiac output measurement. Gueret et al. recently found a standard deviation in agreement of the NICO^{TM} with pulmonary artery thermodilution of approximately 1.1 l/min in patients undergoing hip surgery [21]. Thermodilution has limitations as a standard for assessment of the precision of less invasive methods, but is frequently used because of its availability and the technical difficulties of clinical use of more accurate invasive technologies, such as transit time flow probes. Botero et al. found comparable or better scatter in agreement with an ultrasonic aortic flow probe for NICO^{TM} than for either bolus or continuous pulmonary thermodilution in patients undergoing cardiac surgery [22]. Two recent studies investigating agreement of a commercially available pulse contour device with bolus thermodilution found precision of agreement of 0.87 l/min and 0.98 l/min in patients during and after coronary artery surgery [23, 24].

The method we studied shares some of the limitations of the partial CO_2 rebreathing method, including the assumption of steady cardiac output and mixed venous CO_2 content during the measurement period [9]. In addition, the method will not measure pulmonary shunt flow and an estimate of this is required for comparison with other methods of cardiac output measurement. This correction was small in our study (less than 7% in all patients). The automated algorithm we used ensured that $\dot{V}_{CO_2}$ and $P_{E'_{CO_2}}$ were in steady state prior to the ventilatory change, but sudden interference with smooth ventilation or hemodynamics during the manoeuvre may produce artefacts in the cardiac output calculated. The method was found to give poor agreement with thermodilution in the immediate post-CPB period, when instability in hemodynamics was very common. This may be because of concurrent instability in gas exchange, but also may reflect errors in thermodilution due to thermal fluctuations in the central circulation during this time [25]. Disequilibrium between body CO_2 production and minute ventilation can produce error. For example, early washout of CO_2 following instigation of mechanical ventilation with anesthetic induction will cause a steady fall in $P_{E'_{CO_2}}$ which will lead to error in Equation 1 if it continues into the period of the ventilatory manoeuvre for the cardiac output measurement. While compensation for this can be introduced into the algorithm, accuracy of measurement is best served by waiting for a few minutes after commencement of ventilation before attempting a measurement.

Partial CO_2 rebreathing using a rebreathing valve and loop awaits validation of its accuracy in patients with severe lung disease. In these patients, it may perform better than the method described in the current study since activation of the partial rebreathing manoeuvre does not alter the ventilatory pattern or mechanics. In contrast, changes to respiratory rate and I:E ratio may cause paradoxical alterations to alveolar ventilation in patients with some element of gas trapping during mechanical ventilation. In our experience, this is only a limiting factor in the presence of very severe airflow obstruction.

In conclusion, a pilot study of an automated system employing a differential CO_2 Fick method based on that originally described by Gedeon et al. [12] found that accuracy and precision in measurement of cardiac output can be achieved which is comparable to other more invasive methods for measurement of cardiac output. The advantage of this approach is its potential to be fully and seamlessly integrated using appropriate software-based algorithms into modern anesthesia delivery platforms of the type now widely used for patient care. Such a development would allow non-invasive cardiac output measurement to be made a routine part of perioperative monitoring for ventilated patients undergoing major surgery, and warrants further investigation.

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