Pulmonary Carbon Dioxide Elimination for Cardiac Output Monitoring in Peri-operative and Critical Care Patients: History and Current Status

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ABSTRACT

Minimally invasive measurement of cardiac output as a central component of advanced haemodynamic monitoring has been increasingly recognised as a potential means of improving perioperative outcomes in patients undergoing major surgery. Methods based upon pulmonary carbon dioxide elimination are among the oldest techniques in this field, with comparable accuracy and precision to other techniques. Modern adaptations of these techniques suitable for use in the perioperative and critical care environment are based on the differential Fick approach, and include the partial carbon dioxide rebreathing method. The accuracy and precision of this approach to cardiac output measurement has been shown to be similar to other minimally invasive techniques. This paper reviews the underlying principles and evolution of the method, and future directions including recent adaptations designed to deliver continuous breath-by-breath monitoring of cardiac output.

Keywords: pulmonary blood flow, carbon dioxide, Fick principle, gas exchange

1. INTRODUCTION

In recent years there have been major shifts in thinking concerning optimal management of fluid resuscitation and haemodynamics in patients undergoing major surgery [1-4]. Central to this process has been the wider availability of monitors that can provide essential information to the clinician about cardiovascular status by less invasive means than those previously available, allowing their readier application for peri-operative and critical care patient management. Among the most important of these monitors are those designed to provide minimally invasive measurement of cardiac output (pulmonary blood flow). A growing number of studies and reviews have suggested that improved patient outcomes will accompany advanced haemodynamic monitoring incorporating measurement of blood flow or perfusion [5-10].

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The invasive clinical standard for measurement of cardiac output in the peri-operative and critical care setting for many years has been the pulmonary artery catheter (PAC), which allows cardiac output measurement by several means, principally by right heart thermodilution. Due to its uncertain risk-benefit profile however, the place of the PAC has become increasingly controversial and has remained largely restricted to a limited number of clinical situations: high risk cardiac surgery and management of septic shock in the intensive care unit being among the most common examples [11–13]. The development of less invasive techniques and devices promises to extend the potential benefits of advanced haemodynamic monitoring to a much wider surgical and critical care population.

A wide variety of techniques and devices for cardiac output measurement, using vastly different physical and physiological principles, have become available for peri-operative and critical care applications in recent years [14]. Measurement of pulmonary blood flow from the uptake or elimination of soluble gases by the lungs is the oldest methodology for this purpose [15–17]. Methods based on carbon dioxide (CO₂) elimination by the lungs have been among the most well established of these approaches and have continued to attract interest from researchers and clinicians because of their non-invasiveness and adaptability to various clinical environments. This paper reviews this approach, its underlying principles, evolution and limitations and its performance in terms of accuracy and precision, relative to other methods for cardiac output measurement.

2. PHYSIOLOGICAL PRINCIPLES

2.1. The Fick Principle

Methods utilizing carbon dioxide (CO₂) elimination by the lungs are based on the principle of conservation of mass during lung gas exchange embodied in the classical Fick equation. Applied to CO₂ elimination by the lungs, the Fick equation states

$$\dot{Q}_t = \frac{\dot{V}_{CO_2}}{C_{aCO_2} - C_{\bar{v}CO_2}} \quad (1)$$

where $\dot{V}_{CO_2}$ is measured volumetric flow rate of CO₂ elimination (L/min), $C_{\bar{v}CO_2}$ and C_{aCO_2} are the fractional concentrations of CO₂ in mixed venous and systemic arterial blood, respectively, and $\dot{Q}_t$ is pulmonary volumetric blood flow rate (L/min). Direct measurement of mixed venous blood gas content is impossible without pulmonary artery catheterization, which makes the direct Fick approach impractical for routine clinical use.

Early methods used breath holding or rebreathing manoeuvres to estimate $C_{\bar{v}CO_2}$ and methods for pulmonary blood flow measurement based on CO₂ rebreathing continue to attract interest and innovation in the fields of exercise and sports physiology and in preoperative stress testing [18–24]. However, this approach was not readily adapted to use in the peri-operative or critical care setting. Nevertheless, pulmonary blood flow estimation based on CO₂ measurement continued to attract interest. Arterial CO₂ partial pressure could be approximated by measurement of end-expired CO₂ partial pressure

($P_{E'CO_2}$) and the development of capnography for routine clinical monitoring in anaesthesia made this readily accessible. Furthermore, while accurate and reproducible measurement of $\dot{V}_{CO_2}$ on a breath-by-breath basis is technically challenging, requiring real-time integration of gas flow and concentration waveforms, it is much easier to do accurately than measurement of gas uptake, which requires measurement of gas inflow as well as outflow from the patient [25–27].

2.2. The Differential Fick Approach

The problem posed by the inaccessibility of mixed venous measurement was elegantly solved by the development of what has been subsequently referred to as the differential Fick approach [28]. Originally proposed by Gedeon *et al.*, measurements of $\dot{V}_{CO_2}$ and $P_{E'CO_2}$ are made at two different levels of alveolar ventilation [29]. If done prior to one recirculation time after the change in ventilation, $C_{\bar{V}CO_2}$ can be considered to remain constant for the purposes of the measurement. Two simultaneous Fick equations are obtained, allowing for the unknown pulmonary blood flow to be solved.

To be technically correct, because the method uses $P_{E'CO_2}$ which is an estimate of pulmonary end-capillary (not arterial) blood, only that part of the pulmonary blood flow engaging in gas exchange, non-shunt pulmonary capillary blood flow $\dot{Q}_c$, is measured.

$$\dot{Q}_c = \frac{\dot{V}_{CO_{2i}} - \dot{V}_{CO_{2j}}}{S_{CO_2} (P_{E'CO_{2i}} - P_{E'CO_{2j}})} \quad (2)$$

where i and j are the two measurement points, i prior to, and j during the change in alveolar ventilation. S_{CO_2} is the solubility coefficient of CO_2 in blood, a function of the CO_2 dissociation curve which requires an estimate of the patient's haemoglobin concentration and oxygen saturation SpO_2 obtained from pulse oximetry [30,31].

To obtain total pulmonary blood flow, equivalent to the cardiac output $\dot{Q}_t$, an estimate of shunt fraction $\dot{Q}_s/\dot{Q}_t$ is required, which can be made from the SpO_2 and computerized reference to published nomograms such as the “iso-shunt diagram” for example [32], so that

$$\dot{Q}_t = \dot{Q}_c / (1 - \dot{Q}_s/\dot{Q}_t) \quad (3)$$

In a patient whose lungs are ventilated, the method is non-invasive. In the original study by Gedeon *et al.* [29] in an animal model, the change in alveolar ventilation required was made by simply changing the respiratory rate delivered by the ventilator in such a way that, by also changing the inspiratory:expiratory (I:E) ratio, the duration and pattern of inspiration was unaltered by the manoeuvre, in effect only the duration of the end-expiratory pause being increased. The authors identified this as important, because it minimized physiological sources of error with the method, by avoiding any changes in pulmonary inflation pressures or lung mechanics which might influence alveolar deadspace and the relationship between end-capillary and end-expired CO_2

partial pressures [29]. Despite encouraging agreement with an invasive standard in the form of bolus thermodilution via a pulmonary artery catheter, this precise approach was not pursued further in human studies [33]. This was possibly because of the difficulty in those days of developing an automated means of controlling a standard anaesthesia ventilator in the way needed to make the method convenient for the clinician in everyday practice.

2.3. Partial CO₂ Rebreathing

The differential Fick approach using CO₂ elimination was instead pursued using the partial rebreathing method, where a rebreathing loop of variable volume was inserted into the breathing circuit near the mouthpiece [33–35]. After obtaining baseline measurements of $\dot{V}_{CO_2}$ and $P_{E'CO_2}$ the loop was opened using a valve which could be readily automated, producing a sudden increase in serial deadspace in the breathing system and a reduction in alveolar ventilation. The manoeuvre was terminated after a partial rebreathing period of 30–50 seconds when the second set of measurements of $\dot{V}_{CO_2}$ and $P_{E'CO_2}$ had been captured. Figure 1 shows the acute change in these variables produced by the rebreathing manoeuvre.

Alternative approaches to the measurement of the inputs into the differential Fick equation were also reported. Parkin *et al.* [36,37] tested a system in ventilated patients in the intensive care unit with valve-activated diversion of inspired gas through a known volume of the expired line of the breathing circuit, with or without a fast mixing box, instead of the variable volume loop used previously. This allowed the numerator of Equation 2 to be calculated from the volume of the deadspace tubing multiplied by $P_{E'CO_2}$ within the tubing and the respiratory rate. This simplified approach avoided many of the technical difficulties with accurate breath-by-breath measurement of $\dot{V}_{CO_2}$ during the rebreathing manoeuvre, with good results in terms of accuracy and precision of measurement.

Figure 1. The partial CO₂ rebreathing manoeuvre for measurement of pulmonary blood flow by the differential Fick method. Typical patterns of change are shown in CO₂ elimination rate ($\dot{V}_{CO_2}$) and end-expired CO₂ partial pressure ($P_{E'CO_2}$) from the baseline period *i* and over the partial rebreathing period *j*.

The advantage of the partial rebreathing approach was that it lent itself readily to application as a stand-alone system, with disposable single-use rebreathing loop and valve, and theoretically could be used in spontaneously breathing subject. Brought to the marketplace by Novamatrix (later Respironics/Philips) it became available for clinical use in the form of the NICO® [38]. The accuracy and precision of this device has been studied in a number of publications and this technology is now becoming available as an option on the NM3 metabolic monitor (Respironics/Philips) [39-56]. These devices are shown in Figure 2.

2.4. Back to the Future

Over the intervening years, electronically controlled ventilators which are fully integrated into the anaesthesia delivery and monitoring system have become standard equipment in modern platforms for use in anaesthesia and critical care. This has

Figure 2. (a) The partial rebreathing loop developed for the Novamatrix (later Respironics/Philips) NICO® monitor. (b) The Respironics/Philips NM3 metabolic monitor which incorporates the partial CO₂ rebreathing cardiac output measurement capability.

raised again the potential for the original approach of Gedeon *et al.* [29] to provide an automated non-invasive means of delivering cardiac output measurement in ventilated patients undergoing surgery or critical care. Peyton *et al.* developed and tested a system employing a computer algorithm with software control of an electronic anaesthesia ventilator to obtain fully automated measurements of pulmonary blood flow [57]. They ensured that the original method of Gedeon *et al.* [29] was followed in which both respiratory rate (RR) and I:E ratio were changed so as not to alter the duration of the inspiratory phase of the respiratory cycle or alveolar deadspace during the ventilatory manoeuvre. This allowed a modified form of the differential Fick equation to be used which simplified the measurement of change in $\dot{V}_{CO_2}$ in the numerator of the equation, by assuming no change in the relationship between $\dot{V}_{CO_2}$ and $P_{E'CO_2}$:

$$\dot{V}_{CO_{2i}} - \dot{V}_{CO_{2j}} = \dot{V}_{CO_{2i}} \left(1 - \frac{P_{E'CO_{2j}}}{P_{E'CO_{2i}}} \times \frac{RR_j}{RR_i} \right) \quad (4)$$

They tested the system in a pilot study against simultaneous measurements by bolus thermodilution in patients undergoing cardiac surgery and found similar agreement with thermodilution regardless of whether the alveolar ventilation was increased or decreased by the ventilatory manoeuvre employed [57].

This methodology was subsequently used to provide baseline and repeated calibration, performed during a brief period of stability in $\dot{V}_{CO_2}$ and $P_{E'CO_2}$, for a technique for continuous monitoring of cardiac output in ventilated patients, called the Capnotracking method [58]. The relationship between cardiac output changes and $\dot{V}_{CO_2}$ have been previously explored by Breen and Isserles using computer modeling and patient measurement [59, 60]. In the Capnotracking algorithm, after each automated calibration, breath-by-breath monitoring of acute changes cardiac output was done using a continuity equation which assumes equal and opposite change in the numerator and denominator of Equation (1) in response to changes in $\dot{Q}_t$. This results in a simple relationship between change in measured $\dot{V}_{CO_2}$ and $\dot{Q}_t$

$$\dot{Q}_{tk} = \dot{Q}_{ti} \cdot \left(\frac{\dot{V}_{CO_{2k}}}{\dot{V}_{CO_{2i}}} \right)^2 \quad (5)$$

where i is the baseline calibration measurement and k is any measurement made on a subsequent breath k . With automated recalibration performed every 30 minutes, this was found to deliver useful real-time tracking of dramatic changes in cardiac output in both an animal model and in patients undergoing cardiac surgery or liver transplantation, and was potentially seamless and hands-free in its implementation, requiring attachment of no peripheral devices to the patient [58].

3. ACCURACY AND PRECISION

3.1. Theoretical Analysis of Accuracy

In a series of papers by Yem *et al.* some of the theoretical issues with the accuracy of the partial CO₂ rebreathing method were explored using a computer model of simulated body and lung CO₂ elimination [61]. They identified that systematic errors in measurement of cardiac output could arise from a number of physiological factors. These factors are summarized in Table 1. These included recirculation of mixed venous blood prior to the termination of the rebreathing manoeuvre at high simulated cardiac outputs, and inadequate rebreathing time at low cardiac outputs due to incomplete equilibration between alveolar gas and pulmonary blood compartments. An additional factor was the presence of arterial to end-expired CO₂ partial pressure differences due to the presence of significant ventilation-perfusion mismatch in the lung. This is universal in anaesthetized patients, and is the cause of the increased alveolar deadspace and pulmonary shunt that can be measured in these patients [62–64]. The common tendency of these factors was to “normalise” the calculated cardiac output, that is to overestimate low values and underestimate high values. The developers of NICO® pointed out in response that this modeling only simulated the basic theory of calculation of cardiac output, and that the algorithms employed in the device were more sophisticated than those tested in these simulations [65]. In patients with obstructive airways disease, a tendency to underestimate the cardiac output was predicted [66].

3.2. Animal Studies

Data from studies using animal models provide some support of the predictions of computer modeling. Haryadi *et al.* in dogs found good agreement of NICO® with bolus thermodilution during induced variations in haemodynamics [67]. Following earlier validation studies showing good agreement with thermodilution in a sheep model of a prototype partial CO₂ rebreathing measurement system, Gama de Abreu and colleagues showed that there was a systematic tendency to normalise the cardiac output measurement, and the presence of elevated alveolar deadspace led to cardiac output underestimation [68,69]. They demonstrated that during high cardiac output states, the

Table 1. Physiological and pathophysiological sources of error with the partial CO₂ rebreathing method and their effects on accuracy of measurement of cardiac output predicted from computer modelling. “Normalise” means to underestimate high cardiac outputs and/or overestimate low cardiac outputs [61, 66]

Source of error	Effect on measurement
Recirculation of mixed venous blood	Normalise high cardiac outputs
Inadequate rebreathing time	Normalise low cardiac outputs
Ventilation-perfusion mismatch	Normalise cardiac output
Obstructive lung disease	Underestimate cardiac output
Pulmonary embolism	Underestimate normal/high cardiac output

higher mixed venous CO_2 partial pressures reached at the end of the rebreathing manoeuvre contributed to higher $P_{E'\text{CO}_2}$ and therefore to underestimation of pulmonary capillary blood flow based on Equation (2). Other work in a swine model of blunt chest trauma found a 26% underestimate of continuous thermodilution measurements in extreme laboratory conditions of trauma-induced cardiopulmonary dysfunction [70]. Comparison of NICO® measurements with bolus thermodilution in anaesthetized pigs during induced ventricular fibrillation and external chest compression showed acceptable correlation with a tendency for NICO® measurements to underestimate thermodilution but this difference declined at low cardiac outputs [71].

3.3. Clinical Data

The accepted statistical method for assessment of accuracy (bias) and precision (scatter) of measurement of a variable such as cardiac output is by comparison with simultaneous paired measurements made by another, accepted reference technique, as described by Bland and Altman [72]. The standard deviation of the difference between paired measurements is calculated. The average of these is the mean bias of the test method, the precision of agreement is defined as 1 standard deviation of the difference between paired measurements, and ± 1.96 standard deviations of the difference between paired measurements are referred to as the limits of agreement with the reference method. By definition, 95% of measurements will lie between these limits. The limits of agreement divided by the mean cardiac output are commonly referred to as the percentage error.

Most published studies examining the accuracy and precision of measurement of cardiac output by a technique have used simultaneous measurements by bolus thermodilution via a PAC as the reference standard for comparison. Patients undergoing cardiac surgery or intensive care for critical illness represent a common population for these validation studies of accuracy and precision of measurement, because they have a PAC routinely placed for haemodynamic management as part of their normal clinical care.

A criterion for acceptability of precision of measurement of cardiac output by a test method was suggested by Critchley and Critchley in 1999 [73]. They stipulated that the percentage error of a method relative to thermodilution should be less than $\pm 30\%$, based on the statistical assumption that this equated to both methods being within approximately $\pm 20\%$ of the true cardiac output. Relatively few published data were available at that time to compare with this criterion. In the intervening decade the proliferation of new technologies and validation studies examining accuracy and precision has provided a great deal more data.

Peyton and Chong recently published a quantitative meta-analysis of data from 10 years of published studies comparing minimally invasive techniques for cardiac output measurement adapted to peri-operative and critical care use, where bolus thermodilution was the comparator [74,75]. Studies using continuous thermodilution were not included due to its documented poorer precision compared to bolus thermodilution in the perioperative situation [50]. They calculated a weighted average for both bias and precision for four different generic classes of technique: pulse contour techniques, oesophageal Doppler, partial CO_2 rebreathing and trans-thoracic bio-impedance. They found that the percentage errors for these four approaches were similar (ranging 42 – 45 %), which was considerably wider than the limits of acceptability suggested by Critchley and Critchley [76].

In Peyton and Peyton and Chong's analysis, the bias of the partial CO₂ rebreathing method, incorporating data from 8 studies, found a mean [95% confidence intervals] bias of -0.05 [0.17] L/min with a precision of 1.12 L/min, giving a percentage error of +/- 44.5 [6.0]%. The pooled coefficient of correlation with thermodilution was $r = 0.58$. Although data from another 7 papers were unable to be included in the pooled weighted calculation because of data quality (mainly uncontrolled inclusion of multiple measurements from subjects without statistical correction) there was no evidence from comparison of these data with the included data that there was any significant difference in the findings of the excluded studies (Figure 3) [74]. Data from these studies, obtained mostly from earlier or later software versions of NICO®, included a wide variety of surgery, including one lung ventilation for thoracic surgery, and a variety of ventilatory rates and settings. Overall the performance of the method was comparable to the other generic techniques studied. These studies are listed in Table 2.

Figure 3. Distribution of percentage error in measurement of cardiac output by the partial CO₂ rebreathing method (PCO₂RB), among studies where comparison to thermodilution was made, from lowest (first centile) to highest (hundredth centile). The heavy line represents 8 studies where a single measurement per patient was presented, included in a pooled weighted meta-analysis. The broken line represents all sets of measurements among all studies on the method (34 studies in 15 papers). Reproduced with permission [74].

Table 2. Bias and precision of agreement of cardiac output (L/min) with intermittent bolus thermodilution (ITD). Data included in the pooled weighted meta-analysis are indicated in bold. Reproduced with permission [74]

ICU = Intensive Care Unit, OP = Operative, PSV = pressure support ventilation, SIMV = Synchronized intermittent mandatory ventilation, VCV = volume controlled ventilation, NICO = NICO®

Reference	Year	Population	Device	Version	Reference	Data Points	Bias	Precision
Partial CO ₂ rebreathing (PCO ₂ RB) method								
Kotake <i>et al.</i>	2009	Aortic surgery (OP)	NICO (version 4.2)		ITD	182	0.18	0.88
Killick <i>et al.</i>	2008	Postoperative cardiac surgery (ICU)	NICO (version 5.0)		ITD	194	0.18	0.83
Peyton <i>et al.</i>	2008	Cardiac surgery (OP) Group 1 (increase in respiratory rate)			ITD	113	-0.60	0.86
		Group 2 (decrease in respiratory rate)			ITD		-0.06	0.87
Ng <i>et al.</i>	2007	Thoracic surgery (OP)	NICO		ITD	12	0.25	0.86
Tachibana <i>et al.</i>	2005	Postoperative cardiac surgery (ICU)	NICO		ITD	76	-0.29	0.76
		35 s rebreathing system				13	0.02	1.06
		50 s rebreathing system					-0.34	1.08
Rocco <i>et al.</i>	2004	ICU	NICO		ITD	36	-1.20	1.50
Tachibana <i>et al.</i>	2003	Postoperative cardiac surgery (ICU)	NICO		ITD			
		Tidal volume 12 ml/kg, RR 10				25	0.09	1.00
		Tidal volume 6 ml/kg, RR 20					-0.67	0.73
		Tidal volume 6 ml/kg, RR 10					-1.73	1.27
		SIMV/PSV ventilation					0.18	1.41
		PSV/long loop ventilation					0.80	1.26
		PSV/short loop ventilation					1.20	1.80
Mielck <i>et al.</i>	2003	Postoperative cardiac surgery (ICU)	NICO		ITD	33	-0.64	1.39

(Continued)

Table 2. Bias and precision of agreement of cardiac output (L/min) with intermittent bolus thermodilution (ITD). Data included in the pooled weighted meta-analysis are indicated in bold. Reproduced with permission [74] (*Continued*)

ICU = Intensive Care Unit, OP = Operative, PSV = pressure support ventilation, SIMV = Synchronized intermittent mandatory ventilation, VCV = volume controlled ventilation, NICO = NICO®

Reference	Year	Population	Device	Version	Reference	Data Points	Bias	Precision
Kotake <i>et al.</i>	2003	Aortic surgery (OP)	NICO	ITD	ITD	28	-0.10	0.61
		After induction					-0.52	0.95
		During aortic cross-clamping					-0.99	0.86
Tachibana <i>et al.</i>	2002	At reperfusion of unilateral iliac artery	NICO	ITD	ITD	25	-0.72	0.97
		Dunnig peritoneal closure					0.18	1.04
		Postoperative cardiac surgery (ICU)					-1.67	1.06
		VCV large tidal volume					0.37	1.17
		VCV small tidal volume					-1.64	1.19
		PCV large tidal volume					0.19	1.12
		PCV small tidal volume					0.37	0.81
		VCV F 10 ₂ = 1					0.48	1.27
		VCVhigh PEEP					1.30	1.15
		VCV long loop					0.52	1.02
Murias <i>et al.</i> Odenstedt <i>et al.</i> Binder <i>et al.</i> Nilsson <i>et al.</i> van Heerden <i>et al.</i>	2002	VCV short loop	NICO	ITD	ITD	22	0.18	1.39
		PSV					-0.05	0.96
		ICU					-0.05	0.70
		ICU					0.16	0.90
		Postoperative cardiac surgery (ICU)					-0.73	2.05
Binder <i>et al.</i> Nilsson <i>et al.</i> van Heerden <i>et al.</i>	2001	Postoperative cardiac surgery (ICU)	NICO	ITD	ITD	358	0.16	0.90
		Postoperative cardiac surgery (ICU)					-0.73	2.05
		Postoperative cardiac surgery (ICU)					-0.73	2.05

Similarly, data from a recent paper by Peyton [58] testing the Capnotracking method in comparison with bolus thermodilution in 77 patients undergoing cardiac or liver transplantation surgery found a bias of -0.1 L/min, with a percentage error $\pm 44.2\%$, $r = 0.92$. The higher correlation arose from the very wide range of cardiac output values present in the study population ($0.7 - 16.4$ L/min) and pointed to a high degree of linearity of response of the differential CO_2 Fick approach.

However, data from other publications suggest that some of the theoretical questions about accuracy and linearity of response raised by Yem *et al.* have not been resolved [61, 66]. Allardet-Servent *et al.* studied agreement of the partial CO_2 rebreathing method in the form of the later generation NICO₂® with continuous thermodilution in twenty patients with acute respiratory distress syndrome receiving lung protective ventilation and found a bias and percentage error of 0.8 L/min and 36% respectively [54]. The authors attributed this error to underestimation of pulmonary shunt fraction by the NICO₂® due to its use of a fixed value to estimate the arterio-venous O_2 content difference, which is directly related to shunt fraction in standard concepts of ventilation-perfusion maldistribution in the lung. They found a much closer agreement in measurement of non-shunt pulmonary capillary blood flow (using total pulmonary blood flow obtained from thermodilution corrected for measured shunt fraction as the reference) which was consistent with this assumption. Subsequent improvements in the algorithm incorporating reference to the iso-shunt diagram instead may improve this source of bias [32].

Earlier investigation of the partial CO_2 rebreathing method by Gama de Abreu *et al.* suggested that precision and reproducibility of measurement of cardiac output was significantly poorer in patients who were not undergoing controlled mechanical ventilation [77]. Data from the small number of patients in whom it has been tested during spontaneous ventilation with pressure support are not encouraging, with bias ranging from 0.18 to 1.2 L/min, and precision (standard deviation $1.26-1.8$ L/min) which is toward the upper end of the range seen among minimally invasive methods for perioperative cardiac output measurement [43, 45, 74, 77]. Tachibana and colleagues have investigated NICO® extensively in various modes of ventilation (pressure controlled, volume controlled and pressure support modes) with a specific focus on the effect of these on accuracy of measurement. They demonstrated that variations in the length of the rebreathing loop and extremes of tidal volume and rate selection could elicit significant changes in bias within a given patient group [43,45]. Linearity of agreement with thermodilution was best when the tidal volume was set at relatively higher levels (12mL/kg) with minute ventilation maintained at a sufficient level to achieve mild arterial hypcapnia.

Some commentators recommend that relatively low tidal volumes with accompanying higher respiratory rates, in accordance with a “lung protective” ventilation strategy, may be associated with improved postoperative lung function [78]. For this reason validation of the Capnotracking method was performed using baseline ventilation settings with a lower tidal volume and higher respiratory rate [58]. The most significant biases with NICO® measured in the studies listed in Table 2 were seen in the presence of hypercapnia, due to low tidal volume, rate or a combination of them,

regardless of mode of ventilation. Its accuracy in one lung ventilation for thoracic surgery is open to question, because of the substantial changes in ventilation-perfusion relationships in the lung that occur. However, a study by Ng *et al.* using the NICO® found relatively good preservation of accuracy with the change from two lung to one lung ventilation, with the biggest increase in bias seen early after the change and subsequently reducing [40, 79].

Peyton *et al.* have reported that the differential Fick CO₂ method based on the original method of Gedeon *et al.* [29] employed in their studies does not work reliably in that small proportion of patients with severe obstructive lung disease with chronic gas trapping [58]. This is because an increase in duration of the end-expiratory pause that accompanies the drop in respiratory rate may partly improve effective alveolar ventilation, particularly to lung regions with moderately low ventilation/perfusion ratios, where most pulmonary gas exchange takes place. This may paradoxically increase rather than decrease CO₂ clearance, or at least render the manoeuvre ineffective for measurement purposes. The partial rebreathing method using a rebreathing loop is more advantageous in this situation because the pattern of ventilatory mechanics does not change during the rebreathing manoeuvre. Gama de Abreu *et al.* found well preserved agreement with thermodilution in patients with acute lung injury using a partial rebreathing system [80]. The accuracy of NICO® is adversely affected by use of Xenon in the gas mixture, due to Xenon's different density and viscosity and their influence on the accuracy of gas flow rates by the device's pneumotachograph [55].

4. DISCUSSION

4.1. Limitations and Advantages

While effectively non-invasive in patients who are intubated and ventilated, the use of the differential Fick CO₂ approach to cardiac output monitoring is largely restricted to this patient population. For instance, patients undergoing major lower limb surgery under neuraxial block require an alternative method for cardiac output monitoring. This also makes it less adaptable than some other devices for transition of the postoperative patient to the high-dependency care unit, where ongoing advanced cardiovascular monitoring and goal directed haemodynamic management may be required. Other limitations of the partial CO₂ rebreathing method include the requirement for incorporation of the rebreathing loop into the breathing system near the patient's airway. This can be somewhat cumbersome and impractical in some situations, for example, during head and neck surgery.

When assessing these mixed results from a variety of clinical situations, it may be concluded that techniques based on lung gas exchange for the measurement of cardiac output are not an ideal choice in patients with severe lung disease, and methods based on pulmonary CO₂ elimination share the same limitation. This is because of the various sources of error that may accompany the measurement in this patient population. The variability in accuracy in different modes of ventilation documented in the studies quoted earlier makes its reliability during weaning from ventilatory support in critical care unproven. It should be pointed out, though, that there are relatively few published

validation data for the accuracy and precision of any of the generic methods for cardiac output monitoring in the non-ventilated patient, with most data being gathered in patients undergoing elective cardiac surgery due to the ready availability of measurements from the PAC in this group.

The usefulness of the differential Fick CO₂ approach in various other clinical situations requires examination. Formal validation of its accuracy and precision in the setting of laparoscopic surgery is also warranted, because of the significant changes in pulmonary CO₂ elimination that accompany its absorption from the peritoneal cavity. Despite encouraging data from case reports of its successful use in guiding haemodynamic management in laparoscopic surgery in the presence of substantial cardiovascular instability, formal comparison studies with reference standards such as thermodilution are still lacking in this surgical setting [81-83]. It has received US FDA approval for use with tidal volumes of more than 200 mL, but has been tested in a paediatric population in only one study by Levy *et al.* [56]. These authors found accuracy and precision of agreement with thermodilution which they deemed clinically acceptable in children with body surface area over 0.6 m² and where tidal volume was set at more than 300 mL.

The advantages of the differential Fick CO₂ method are firstly that it is effectively non-invasive in patients who are intubated and ventilated for surgery or critical care. In addition this technology provides continuous data on the patient's metabolic status, with ongoing capnography and monitoring of $\dot{V}_{CO_2}$, which is useful to inform nutritional and metabolic management in a septic or critically ill patient. The NICO® and NM3 monitors also provide measurements of pulmonary deadspace, functional residual capacity, and airway compliance and resistance. The methodology described by Gedeon *et al.* [29] and pursued by Peyton *et al.* [57,58], with automated modulation of respiratory rate and I:E ratio delivered by the ventilator, avoids additional peripheral equipment and can potentially be fully integrated into the anaesthesia delivery and monitoring platform.

Another advantage of methods based on lung CO₂ elimination may be their relative robustness in the face of sudden cardiovascular collapse. The animal study by Carretero and various case reports have demonstrated that NICO® delivers cardiac output measurements in ventilated subjects even in the presence of vigorous chest compressions and extreme haemodynamic instability which might present large technical challenges to measurement of input variables for the method [71]. These case reports show that many of the alternative devices available for continuous cardiac output monitoring have more prolonged response times than the NICO® or fail to provide a meaningful measurement at all during profound circulatory collapse [84,85]. A number of authors have investigated the utility of CO₂ elimination, in the form of $P_{E'CO_2}$ measurement, as an index of pulmonary blood flow during cardiopulmonary resuscitation [86-88]. Peyton [58] and Peyton *et al.* [98] demonstrated the ability of measured CO₂ elimination to successfully follow dramatic changes in pulmonary blood flow in real time in both an animal model and in patients undergoing major surgery, including episodes of cardiac arrest, and during run onto cardiopulmonary bypass.

4.2. Assessment of Techniques for Cardiac Output Monitoring

Arguably the theoretical critique made by Yem *et al.* on the accuracy of the partial CO₂ rebreathing method was the result of the transparency of the method, and its clear physiological basis, which opens it to detailed scrutiny [61,66]. This should not be seen as a weakness, and it stands in contrast to some other technologies in the cardiac output measurement field, and other areas of patient monitoring. In a 2005 editorial, Ruskin and Shelley pointed out the potential pitfalls and dangers that accompany the trend toward adoption of new monitoring technologies with complex “black box” algorithms [90]. These authors referred to this phenomenon as “patent medicine”. Ironically, however, publication under patent protection arguably presents a lesser obstacle to transparency than the intellectual property strategy based upon keeping these algorithms the proprietary secrets of their developers. Other commentators have spoken on the need for rigor in the regulatory framework for approval and licensing of new patient monitoring modalities, and the tension between this and the “black box” approach reinforces the need for thorough clinical testing of new devices and technologies, preferably with large clinical trials conducted independently of commercial support from developers [90,91].

There has been an explosion of interest in improved haemodynamic monitoring in the last decade, driven synergistically by suggestions that traditional approaches to maintenance of cardiovascular stability, such as liberal fluid maintenance and resuscitation strategies may be detrimental to patient outcomes. Indeed this has led some authorities to recommend that use of certain cardiac output monitoring devices as part of a “goal directed” management strategy should be made a standard of care in major surgery [92,93]. This has been criticized over the lack of data confirming these outcome benefits from large multicentre studies, despite expressions of support by many practitioners [94-97]. Such large studies should be a research priority so that any potential for advanced haemodynamic monitoring, including minimally invasive cardiac output monitors, to improve patient outcomes in routine practice can be confirmed.

5. CONCLUSION

Minimally invasive measurement of cardiac output as a central component of advanced haemodynamic monitoring has been increasingly recognised as a potential means of improving perioperative outcomes in patients undergoing major surgery. Techniques for monitoring of cardiac output based on lung gas exchange have a long pedigree in the field, and methods based on pulmonary CO₂ elimination are well adapted to use in ventilated patients with a track record of accuracy and precision equal to other devices suitable for peri-operative and critical care use. In the midst of the recent proliferation of devices and alternative techniques for cardiac output measurement, the CO₂ based approach warrants assessment in larger effectiveness trials to determine its ability to benefit patient management and outcomes in the peri-operative and critical care setting.

CONFLICT OF INTEREST

Philip Peyton is the inventor on a United States Patent Application No. 12/743224, 2010 in the name of Philip John Peyton, entitled: "System and method for monitoring cardiac output".

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