Indirect Calorimetry has Better Reproducibility than the Reverse Fick Method in Measurement of Oxygen Uptake

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Abstract: *Purpose*: To compare the reproducibility of measurement of oxygen uptake made using the reverse Fick and indirect calorimetry methods.

Methods: A custom designed system was constructed for the measurement of oxygen uptake from an anaesthetic breathing system using indirect calorimetry based on the Haldane transformation. In a series of 42 patients undergoing coronary artery surgery in the pre-cardiopulmonary bypass period, two reverse Fick measurements were made using bolus thermodilution and paired arterial and mixed venous blood sampling. Simultaneous measurements of oxygen uptake by the Haldane-based method were made. The within-patient standard deviation (WPSD) and variance (WPV) of repeat measurement by each method was determined using 1-way ANOVA for repeated measures.

Results: The median WPSD for the reverse Fick method was 12.5 mL/min and for indirect calorimetry was 8.5 mL/min, giving a WPV of 157.0 mL/min and 72.4 mL/min respectively. The difference between the two methods was significant using the Wilcoxon signed rank test in both WPV ($p < 0.01$) and WPSD ($p < 0.02$).

Conclusions: The reproducibility of measurement of O_2 uptake in patients during cardiac surgery is clinically and statistically superior using indirect calorimetry to that obtainable by the reverse Fick method.

Keywords: Gas exchange, oxygen consumption, metabolic monitoring, anaesthesia.

INTRODUCTION

Metabolic monitoring by measurement of oxygen uptake ($\dot{V}_{O_2}$) may be a useful tool in patient care during critical illness or the peri-operative period. Measurement of $\dot{V}_{O_2}$ assists in assessment and optimisation of oxygen delivery to the tissues and cardio-respiratory function, in association with other physiological variables such as arterial and mixed venous blood gases, F_iO_2 and cardiac output. It has been suggested as a useful monitor of cardiovascular dysfunction [1] and as a useful end-point for resuscitation [2]. During anaesthesia $\dot{V}_{O_2}$ measurement may be useful for assessment and early intervention in acute metabolic, cardiovascular and respiratory disturbances.

$\dot{V}_{O_2}$ measurement is performed using one of two principal techniques, indirect calorimetry and the reverse Fick method. The reverse Fick method, while being an invasive technique, involving arterial and mixed venous blood gas sampling and cardiac output measurement, is a well established method. Indirect calorimetry, which generally uses the Haldane transformation to achieve acceptable accuracy [3], and thus requires administration of an insoluble gas such as nitrogen in the inspired gas mixture, is non-invasive and can be adapted to provide continuous monitoring [4, 5].

Commentators have suggested that indirect calorimetry in fact provides more reproducible and precise $\dot{V}_{O_2}$ measurement than the reverse Fick method [6-10]. This is an important hypothesis, as it supports the use of the safer, less invasive technique in clinical care. These authors have compared the reproducibility of $\dot{V}_{O_2}$ measurements made in patients simultaneously using the two methods. However their data, while demonstrating trends consistent with this hypothesis, was not accompanied by proof of statistical significance. Thus the question as to which technique is superior remains essentially unresolved.

We hypothesised that the precision of $\dot{V}_{O_2}$ measurements made by indirect calorimetry was superior to that achievable by the reverse Fick method. To test this, we compared the reproducibility of repeated $\dot{V}_{O_2}$ measurements made simultaneously using the two methods, in a series of patients during cardiac surgery.

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MATERIALS AND METHODOLOGY

45 patients undergoing elective coronary artery bypass graft surgery at The Alfred hospital and the Austin hospital, Melbourne, Australia were recruited to the study. Patients with severely impaired left ventricular function or American Society of Anesthesiologists (ASA) Grade 4 patients were excluded. Ethical approval was obtained from both institutions' human research ethics committees and informed written consent was obtained from each patient at the time of surgical admission.

Prior to surgery patients were cannulated in accordance with routine anaesthetic management with a peripheral arterial line and pulmonary artery catheter (Edwards Lifesciences, California, USA). Following pre-oxygenation, anaesthesia was induced with a mixture of fentanyl, a benzodiazepine, propofol and a neuromuscular blocker. Maintenance of anaesthesia was achieved using an infusion of propofol with or without volatile anaesthetic agent (AA) titrated according to depth of anaesthesia with the assistance of bispectral index monitoring. Following endotracheal intubation, controlled ventilation commenced with tidal volumes of approximately 7-10 mL.kg^{-1} at a rate of 9 – 12 breaths/min. The fresh gas flow was set to at least 5 L.min^{-1} with a fresh gas O_2 concentration of 40-50%, which remained unchanged throughout the experimental period. The balance gas mixture was N_2 in medical air, although in 9 patients at one of the centres, 30% nitrous oxide (N_2O) was administered as well. No continuous inotropic infusions were administered.

Continuous measurement of oxygen uptake by indirect calorimetry was commenced, as described below. During surgery, at a period of stability in haemodynamics and ventilation during the pre-cardiopulmonary bypass period, simultaneous measurements were done by the reverse Fick method. This process was then repeated to obtain a second set of measurements by both techniques in each patient. Heart rate, mean arterial pressure, pulmonary capillary wedge pressure, end-tidal CO_2 concentration, room and patient temperature measured by nasopharyngeal probe were also noted at the time of each set of measurements.

Indirect Calorimetry Measurements

Measurement of oxygen uptake by indirect calorimetry ($\dot{V}_{O_2}$ *Haldane*) was done according to the principle of mass balance of O_2 and N_2 between fresh gas and mixed exhaust gas streams within the breathing circuit:

$$\dot{V}_{O_2}\ Haldane = \dot{V}_{F_T} \cdot F_{F_{O_2}} - \dot{V}_{\bar{X}_T} \cdot F_{\bar{x}_{O_2}} \qquad (1)$$

where $\dot{V}_{F_T}$ is total fresh gas flow rate, $\dot{V}_{\bar{X}_T}$ is total mixed exhaust gas flow rate, and $F_{F_{O_2}}$ and $F_{\bar{x}_{O_2}}$ are fractional concentrations of O_2 in fresh gas and mixed exhaust gas respectively. According to the Haldane transformation

$$\dot{V}_{\bar{X}_T} = \dot{V}_{F_T} \cdot \frac{F_{F_{N_2}}}{F_{\bar{x}_{N_2}}} \qquad (2)$$

then

$$\dot{V}_{O_2}\ Haldane = \dot{V}_{F_T} \cdot \left(F_{F_{O_2}} - \frac{F_{F_{N_2}}}{F_{\bar{x}_{N_2}}} \cdot F_{\bar{x}_{O_2}} \right) \qquad (3)$$

The measurement system for the indirect calorimetry measurement consisted of a rapid gas analyser and personal computer with analogue-digital converter card. Values for fresh gas flow were set visually on the anaesthetic machine rotameters and this value was entered into the computer. Rotameter flows were calibrated using the 1 Litre dry gas syringe, and were found to be able to be accurately set visually to within 1%. Fresh gas air was obtained from an 'E' sized cylinder of medical air attached to the anaesthetic machine, instead of using the hospital's wall supply, as this was found to vary significantly in pressure over a period of time, causing variation in fresh gas air flow rates. Cylinder air supply pressure however was computer-monitored throughout the experimentation period *via* a transducer and provided stable air flow.

Having thus set stable fresh gas flows, continuous monitoring of $\dot{V}_{O_2}$ from measurement of mixed exhaust gas concentrations is performed. Gas concentration measurements in mixed exhaust gas were made downstream of the ventilator's bellows ensuring full mixing of gas, which was further assisted by the addition of a length of exhaust gas tubing upstream of the ventilator. Gas concentration measurements were made by sidestream sampling by a Datex-Ohmeda Capnomac *Ultima* rapid gas analyzer (Datex-Ohmeda, Helsinki, Finland) calibrated according to the manufacturer's specifications using their proprietary calibration gas mixture (Quickcal, Datex-Ohmeda). The gas analyzer measured O_2 concentration paramagnetically, with an observed standard deviation under steady state conditions of 0.1%. CO_2, N_2O and anaesthetic agent were measured by infrared spectroscopy. N_2 concentration was calculated by subtraction of the concentration of all other measured gases from 100%. Analogue data was downloaded from the analyzer to the computer every 100 msec *via* the analogue-digital converter card (12-bit Burr-Brown, Arizona, USA). Computations were made in real time using Borland C++ programming language. Gas concentration samples were averaged and reported values for $\dot{V}_{O_2}$ *Haldane* were updated every 15 seconds, and then further averaged over a 3 minute period surrounding the collection of blood samples and cardiac output measurements for the corresponding reverse Fick measurement. All measurements were corrected to BTPS (body temperature and pressure saturated) at 37°C for comparison purposes. The configuration of the system is shown schematically in Fig. (**1**).

Prior to commencement of anaesthesia, a dynamic system calibration was performed at the chosen fresh gas flows and concentrations by ventilation of a pair of silicon bags of suitable compliance in place of the patient in the circuit. This test determined the value of any significant zero offset for $\dot{V}_{O_2}$ *Haldane* in the system. This value was used to correct all measurements made during the operation. To compensate for analyzer drift, periodic (not greater than half
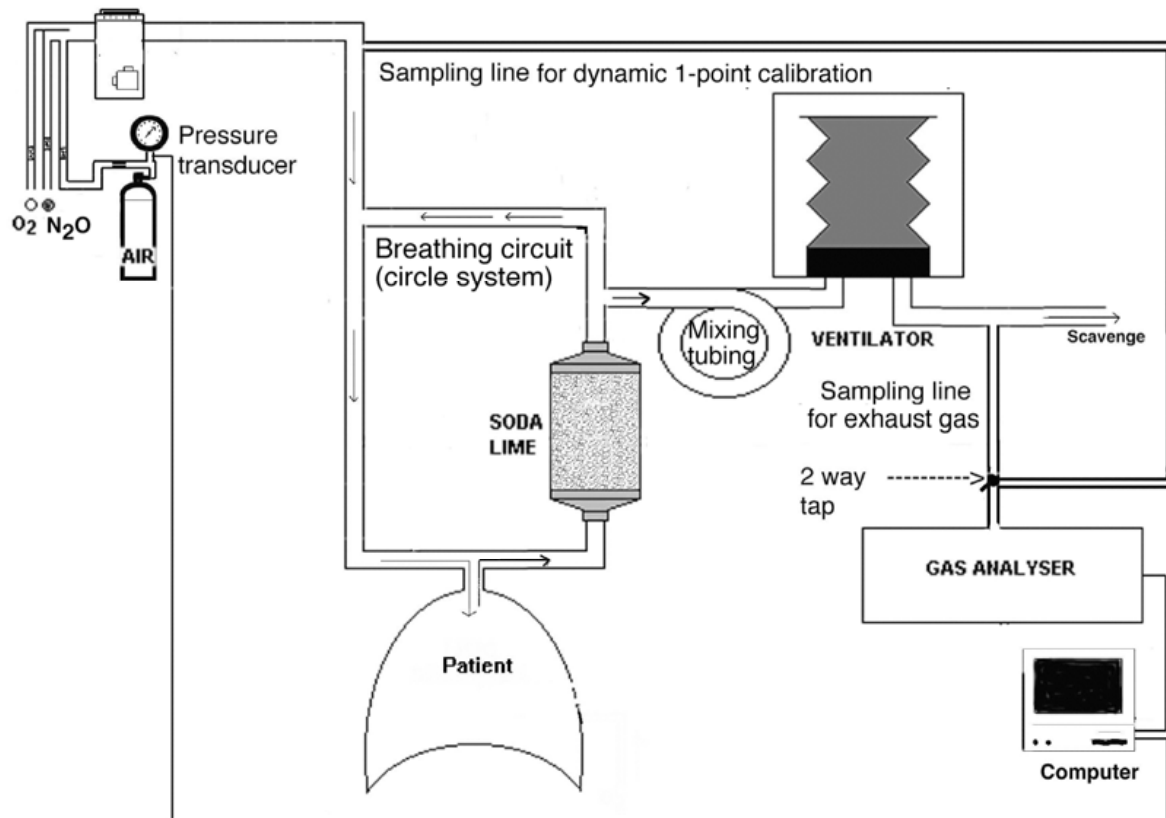
Fig. (1). Schematic diagram of the system for continuous measurement of oxygen uptake within the anaesthetic breathing circuit by indirect calorimetry.

hourly) recalibration of the system was performed by brief sampling of fresh gas, as follows. The fresh gas O_2 concentration calculated from the rotameter flow of air and oxygen was compared to an average value measured by the analyzer over a period of 15 seconds at the beginning of the measurement process and again after each automatic recalibration (or 'zero') of the analyzer which occurred every half hour. The measured difference (*delta FO_2*) was used to correct all subsequent $\dot{V}o_2$ *Haldane* measurements until the next recalibration. This effectively calibrated the O_2 concentrations measured by the analyzer against the rotameter settings. The accuracy and precision of the system was previously validated using a benchtop simulator of lung gas exchange [11].

Reverse Fick Measurement

At the same time, as the data was being collected for the indirect calorimetry measurement, simultaneous paired blood samples were drawn from the arterial line and the distal lumen of the pulmonary artery catheter. Blood samples were analysed immediately at point of care for oxygen saturation, partial pressure and hemoglobin content on the operating suite's blood gas analyser (Alfred: Rapidlab 1265, Bayer Diagnostics, Sudbury, UK; Austin: Radiometer ABL625, Odense, Denmark). Both devices employ a co-oximeter to determine O_2 saturation. During the measurement period a set of five cardiac output measurements were made by thermodilution using a 10mL bolus of room temperature saline over a three minute period, and the results averaged.

Results were excluded if they were found to lie more than ± 10 percent outside of the mean value. Oxygen content of both the arterial and mixed venous samples were obtained by calculation using equation (4) below. Values for saturation and partial pressure made by the blood gas analyser were corrected to 37°C before calculation of oxygen content was made

$$Co_2 = 1.34 \cdot \left[Hb \cdot \left(\frac{So_2}{100} \right) \right] + \left(0.003 \cdot Po_2 \right) \qquad (4)$$

where Co_2 is the oxygen content of the sample (mL.100mL^{-1}) being either mixed venous or arterial, 1.34 is Hüffner's constant, Hb is the hemoglobin content (g.dL^{-1}), So_2 is the measured percentage saturation of oxygen and Po_2 is the partial pressure of oxygen (mmHg).

Using the cardiac output measurement in conjunction with the calculated arteriovenous oxygen content difference, oxygen uptake ($\dot{V}o_2$ *rFick*) was determined by the reverse Fick method.

$$\dot{V}o_2 \ rFick = \left[\left(\frac{Ca_{O_2} - C\bar{v}_{O_2}}{100} \right) \cdot \dot{Q}_{Thermo} \right] \cdot 1000 \qquad (5)$$

where Ca_{O_2} is the calculated arterial oxygen content of the sample, $C\bar{v}_{O_2}$ is the mixed venous oxygen content and $\dot{Q}_{Thermo}$ is the cardiac output measured by thermodilution.

Indirect Calorimetry Measurements

Statistics

For both methods, the standard deviation and variance of the difference between the first and second measurements of $\dot{V}o_2$ in each patient (within-patient standard deviation, WPSD) was calculated using 1-way ANOVA with repeated measures. The within-patient variance (WPV, the square of the WPSD) of each of the two methods was compared to determine the method with the lowest variance. Statistical significance of the comparison was determined using the *t*-test after examination of the data for normal distribution, with log transformation of the data and use of a non-parametric test (the Wilcoxon signed rank test) if necessary. The correlation coefficient was also calculated.

In addition, the overall agreement between $\dot{V}o_2$ *Haldane* and $\dot{V}o_2$ *rFick* was assessed by determining the mean difference between the methods (bias, $\dot{V}o_2$ *Haldane* - $\dot{V}o_2$ *rFick*) and the standard deviation of the difference and limits of agreement (bias $\pm$ 2 standard deviations) and applying a paired *t*-test. A similar comparison was made between first and second measurements for both methods.

RESULTS

Of the 45 patients recruited, repeat measurements of $\dot{V}o_2$ by both methods were unable to be obtained during the pre-cardiopulmonary bypass period of the operation in 3 patients, due to technical or logistic reasons or time constraints, so that reproducibility of $\dot{V}o_2$ was able to assessed in a total of 42 patients (27 from one centre and 15 from the other).

Demographic data for this group is shown in Table **1**. Table **2** shows observational data at the first and second measurement points for respiratory rate (RR), tidal volume (V_T), peak inspiratory pressure (PIP), heart rate (HR), inspired oxygen concentration (F_iO_2), mean arterial pressure (MAP), cardiac output ($\dot{Q}$) and nasopharyngeal temperature (T). The only statistically significant differences found were that MAP and temperature fell slightly between the first and second measurement points by 5.8 mmHg and 0.2 ^oC respectively.

Table 1. Patient Demographic Data Showing the Details of the Population of Patients Undergoing Cardio-Pulmonary Bypass Grafting

Age (Years)	69.8 (7.9 [49 - 85])
Gender (M/F)	32/10
Height (cm)	169.3 (9.2 [146 -185.5])
Weight (kg)	81.1 (14.9 [51.4 - 123])
BSA(m²)	1.9 (0.2 [1.5 – 2.5])

Data is presents as mean (standard deviation [range]).

Table 2. Hemodynamic and Other Measurements Made at the Time of $\dot{V}o_2$ Measurement

Variable	Measurement 1	Measurement 2	*p* Value
RR (/min)	10.9 (1.6)	11.0 (1.6)	$p = 0.68$
V_T (mL)	608.1 (123)	587 (149)	$p = 0.073$
PIP (cmH_2O)	21 (3.7)	20.4 (4.3)	$p = 0.10$
HR (/min)	64.9 (15.4)	64.2 (14.2)	$p = 0.74$
F_iO_2	0.47 (0.07)	0.47 (0.07)	$p = 0.59$
MAP (mmHg)	82.2 (15.7)	76.4 (15.6)	$p = 0.015$
$\dot{Q}$ (L/min)	3.8 (1.2)	3.92 (1.2)	$p = 0.38$
T (^oC)	35.2 (0.6)	34.9 (0.6)	$p < 0.001$
BIS	28.3 (5.7)	29.5 (8.6)	$p = 0.62$

Data shown here is presented as mean (standard deviation). *p* values comparing the data sets at both measurement points were calculated using a paired, two tailed *t*-test. Respiratory rate (RR), tidal volume (V_T), peak inspiratory pressure (PIP), heart rate (HR), inspired oxygen concentration (F_iO_2), mean arterial pressure (MAP), cardiac output ($\dot{Q}$), nasopharyngeal temperature (T), and bispectral index (BIS).

The mean [standard deviation] of $\dot{V}o_2$ *rFick* was 151.3 [33.1] mL/min and the $\dot{V}o_2$ *Haldane* was 175.3 [39.1] mL/min, with a bias [standard deviation of the difference] between the methods of 23.5 [27.0] mL/min. The correlation coefficient *r* was 0.73 (p <0.01). There was no statistically significant difference between the mean values for the first and second measurements for either method. This data is summarised in Table **3**.

Table 3. Data Summarising the Measurement of $\dot{V}o_2$ by the Reverse Fick (*rFick*) and Indirect Calorimetry (*Haldane*) Methods and their Reproducibility, as Given by the Within-Patient Standard Deviation (WPSD) and Variance (WPV)

Method	*rFick*	*Haldane*	*p* Value
$\dot{V}o_2$ mL/min mean [SD]			
Overall	151.3 [33.1]	175.3 [39.1]	$p < 0.001$ *
Measurement 1	148.1 [29.7]	173.3 [39.1]	
Measurement 2	154.5 [33.1]	176.3 [39.2]	
p value	ns *	ns *	
$\dot{V}o_2$ WPSD mL/min median	12.5	8.5	$p < 0.02$ **
$\dot{V}o_2$ WPV (mL/min)² median	157.0	72.4	$p < 0.01$ **

ns = not significant * Paired *t*-test ** Wilcoxon signed rank test.

WPSD and WPV were calculated. Inspection of the relationship of the differences between methods in WPV to their mean WPV revealed that this was not normally distributed and this was not rectified by log transformation

of the data, making use of the *t*-test inappropriate. Non-parametric analysis of the data was performed. The median WPSD for $\dot{V}_{O_2}\,rFick$ was 12.5 mL/min and for $\dot{V}_{O_2}\,Haldane$ was 8.5mL/min, giving a WPV of 157.0 mL/min and 72.4 mL/min respectively. Using a Wilcoxon signed rank test showed that the difference between the two methods was significant in both WPSD ($p < 0.02$) and WPV ($p < 0.01$).

DISCUSSION

Determination of the most reliable means for measurement of $\dot{V}_{O_2}$ may promote its more widespread use in the clinical assessment of patients during critical care and major surgery. In our series we were able to demonstrate a statistically and clinically significant difference in the reproducibility of $\dot{V}_{O_2}$ measurement between indirect calorimetry and the reverse Fick method, confirming the suggestion that indirect calorimetry is the more reproducible method.

Smithies *et al.* found in a group of 8 intensive care patients that there was a trend for WPSD from the reverse Fick method to be substantially greater than that achieved by a spirometric measurement system designed by them [6]. Hanique *et al.* found that it was 1.4 times greater than that for indirect calorimetry in a large series of 171 intensive care patients [7]. Bizouarn *et al.* found a similar trend in 9 patients after cardiac surgery [12], and Walsh *et al.* in a group of 17 patients with fulminant liver failure found this ratio to be greater (2.14) [8]. Brandi *et al.* found that the coefficient of variation of repeated measurements in 22 surgical patients by the reverse Fick method was considerably greater than that for indirect calorimetry, which was very low (3.1%) in their study using a commercially produced device (Nellcor-Puritan-Bennett 7250) [13].

However, statistical analysis of the comparison of these differences in intra-patient dispersion of $\dot{V}_{O_2}$ measurement was not presented by any of these authors and their significance remains unclear for this reason. Measurements of dispersion in data such as variances are not normally distributed, making their comparison using parametric methods such as the *t*-test hazardous, and as we found, log transformation may not be helpful, so that weaker non-parametric tests are required.

The ratio of median WPSD for $\dot{V}_{O_2}\,rFick$ to $\dot{V}_{O_2}\,Haldane$ was 1.47, which is intermediate in magnitude to the trends suggested by the data of these previous authors. The WPSD for both methods was higher in the nine patients where nitrous oxide was administered, but exclusion from the analysis of these patients did not alter the statistical significance of our results, despite the smaller number of participants and the lower overall WPSD for both methods ($n = 33$, WPSD for $\dot{V}_{O_2}\,rFick$ = 18.3 mL/min, $\dot{V}_{O_2}\,Haldane$ = 10.7 mL/min, $p < 0.05$). There were no statistically or clinically significant differences between measurements from the two centres (for $\dot{V}_{O_2}\,rFick$: Alfred = 151.9 mL/min, Austin = 150.2 mL/min, $p = 0.58$, for $\dot{V}_{O_2}\,Haldane$: Alfred = 179.1 mL/min, Austin = 167.1 mL/min, $p = 0.89$).

A possible limitation of the current study relative to previous studies is that it was conducted intra-operatively on a group of surgical patients, as opposed to a group of critical care patients which would more directly represent the category of patient in which measurement of $\dot{V}_{O_2}$ would be of most clinical interest. However, the advantage of conducting the study in this group, involving patients undergoing coronary artery graft harvesting in the pre-cardiopulmonary bypass period, is that relatively stable hemodynamics typically characterise this period, with stable $\dot{V}_{O_2}$ expected. By thus minimising the real variation in $\dot{V}_{O_2}$, this improves the focus of the study on the reproducibility of $\dot{V}_{O_2}$ measurement itself, and may have consequently increased the power of the study to demonstrate a statistically significant difference in reproducibility of $\dot{V}_{O_2}$ measurement. Any instability in $\dot{V}_{O_2}$ that may have been induced by, for instance, surgical activity between measurements, will be reflected in the WPSD of each method. However, there is no *a priori* reason to suspect that this should affect one method differently from the other. The lower WPSD of the indirect calorimetry measurement reflects its intrinsically better reproducibility.

Another significant difference between our study and the previous studies is that most of these were conducted using a commercially produced device, the Deltatrac (Datex-Ohmeda, Helsinki) which had been previously tested by other workers [14]. In contrast, our study was conducted using a custom-made prototype measurement system specifically designed to deliver continuous monitoring of gas exchange in an anaesthetic breathing system, which had been previously validated by us [11, 15]. Despite these methodological differences, our results reflect some of the previously observed differences between $\dot{V}_{O_2}$ measured by indirect calorimetry and the reverse Fick method. The overall bias [standard deviation] of agreement between paired measurements of $\dot{V}_{O_2}\,Haldane$ and $\dot{V}_{O_2}\,rFick$ was 23.5 [27.0] mL/min in our study. This mean bias and scatter in agreement between the two methods is consistent with previously published work in the field [1, 7, 8, 12]. This bias has been attributed to lung tissue O_2 uptake or intracardiac shunting, which is not measured by the reverse Fick method [12, 16, 17]. The consistency of our results with those of the previous studies are therefore of note, and suggest that our findings are robust and generalizable, even though further work would be required to demonstrate similar findings using other devices for measurement of oxygen uptake.

The reasons for the poorer repeatability of the reverse Fick method have been discussed by previous commentators, and include the cumulative imprecision in the measurement of the input variables to Equations (4) and (5), in particular the measurement of cardiac output and the methodology of determination of blood O_2 content [8, 10, 18]. In our study,

which was conducted across two centres, cardiac output was measured using similar technique and equipment at each location, but the blood gas O_2 content data were generated by two different commercial blood gas analysers. However, the WPSD of $\dot{V}_{O_2}\ rFick$ measurements from these two centres was very similar (18.9 and 20.9 mL/min) suggesting that our findings could not be attributed to the performance of individual measurement devices, but are generic to the methods tested themselves.

The better reproducibility of measurement of O_2 uptake by indirect calorimetry is a useful finding. The system employed here has the advantage of delivering continuous measurement from a variety of breathing system designs, although changes in ventilatory settings or fresh gas flows will cause temporary interruption of the system until steady state gas uptake from the breathing circuit is achieved. deBloisblanc *et al.* have questioned the value of $\dot{V}_{O_2}$ measurement in the care of critically patients [7]. However, the non-invasiveness of indirect calorimetry makes it a more appealing alternative, and this is reinforced by the firm evidence of its accuracy and precision achieved by our study.

CONCLUSION

In summary, in a series of patients during cardiac surgery, we provide statistical proof that the reproducibility of measurement of O_2 uptake is clinically superior using indirect calorimetry to that obtainable by the reverse Fick method.

CONFLICT OF INTEREST

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