Measurement of systemic carbon dioxide production during cardiopulmonary bypass: a comparison of Fick’s principle with oxygentor exhaust output

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Theoretically, systemic carbon dioxide (VCO₂) production should be an alternative means to systemic oxygen uptake (VO₂) for estimating the global efficacy of cardiopulmonary bypass (CPB). This study compared two methods of estimating VCO₂: Fick’s principle and oxygentor exhaust carbon dioxide (CO₂) output. Both of these estimates were then compared with VO₂. Fifty-one patients (39 male and 12 female) undergoing elective cardiac surgery requiring CPB were studied. Blood sampling was performed and measurements recorded during active cooling, environmental cooling/stable hypothermia and during rewarming. Blood samples were measured for CO₂ tension from which content was estimated. VCO₂ was calculated as the product of the arteriovenous difference in CO₂ content and pump flow rate (Fick’s principle), or the fresh gas flow rate and concentration of the oxygentor exhaust CO₂ (output technique). Over all measurements, method comparison analysis revealed a large mean bias of 41 (95% confidence intervals (CI) 32–50) mL/min with very wide limits of agreement (−23, 105 mL/min). Regression analysis found that the bias was also proportional to the size of measurement (β = 0.75 (95% CI 0.55, 0.95)). Although both methods of VCO₂ correlated significantly with VO₂ (p < 0.01), regression analysis found that the coefficients (β) of both techniques had wide CI (Fick’s principle: β = 1.37 (95% CI 1.20, 1.54); output technique: β = 0.58 (95% CI 0.44, 0.71)). In conclusion, both techniques of VCO₂ cannot be used interchangeably, and both are imprecisely related to VO₂ as estimated by Fick’s principle. Perfusion (2003) 18, 339–344.

Introduction

Since its introduction into clinical practice, systemic oxygen uptake (VO₂) has been the gold standard measure of the global efficacy of cardiopulmonary bypass (CPB). This standard for VO₂ estimation is based on Fick’s principle, and is the product of pump flow rate and the systemic arteriovenous difference in blood oxygen content (Appendix A). Over the years, many studies have investigated the relationship between pump flow rate and VO₂. As VO₂ is calculated from pump flow rate, this investigational approach is flawed as predictor and outcome variables are mathematically linked and, therefore, nonorthogonal, that is, not statistically independent. Moreover, the formula is error prone as it depends on the accuracy of the multiple component variables, each with its own measurement error and all the errors are compounded by each arithmetical calculation (Appendix A).

An alternative method of measuring the efficacy of CPB would be to examine the product of the metabolic pathway of respiration, that is, systemic carbon dioxide production (VCO₂). However, when calculated in a similar manner to VO₂ using Fick’s principle, it shares the same limitations. Additionally, blood carbon dioxide (CO₂) content is usually estimated indirectly from carbon tension using an algorithm based on the Kelman equation rather than measured directly (Appendix B).

An alternative to estimating VO₂ using Fick’s principle is the Haldane approach. VO₂ should be calculable from the product of fresh gas flow rate and the difference in the oxygen content between the fresh gas entering and the gas exhausting from...
the oxygenator. A major limitation to the application of this technique is the limited accuracy of oximeters that are used clinically to measure oxygen concentration. Commonly, the accuracy of such oximeters is in the range of plus or minus two percent and this range could often be greater than the difference that would be expected to occur between the fresh and exhaust gases. In contrast, clinical capnographs are usually ten times more precise in their measurement of CO₂ concentration. If the fresh sweep gas contains no CO₂, then VCO₂ should be calculable as the product of the fresh gas flow rate and the CO₂ content of the oxygenator’s exhaust gas (Appendix C).

If the oxygenator exhaust method of estimating VCO₂ proved to be reliable and accurate, then it would provide a simple, real-time method of assessing the metabolic efficacy of CPB that would be independent of pump flow rate and have minimal compound error. Such a method would not only be valuable for clinical monitoring of patients during CPB, but also as a powerful research tool.

Although some workers have used VCO₂ as predicted by the Fick’s principle,²⁷,⁸ we are unaware of any studies using oxygenator exhaust capnography nor of any that compare the two techniques or relate these methods to VO₂. The aim of this study was to compare the agreement between VCO₂ as predicted by Fick’s principle with that estimated by oxygenator exhaust CO₂ output, and to compare both methods of VCO₂ estimation with VO₂ as predicted by Fick’s principle.

Methods

The Lothian Research Ethics Committee approved the study (reference number: LREC/2000/4/165). Patients scheduled for any form of elective cardiac surgery in the Cardiothoracic Surgery Unit at the Royal Infirmary of Edinburgh who required CPB and who had given written informed consent were recruited.

Anaesthesia

Anaesthetic technique was dependent on individual consultant anaesthetists. Ninety min before surgery, patients were premedicated with lorazepam 1–2 mg or temazepam 20–40 mg by mouth alone or with intramuscular injections of atropine 0.3–0.6 mg and morphine 10–15 mg. Intravenous propofol 1–2 mg/kg, etomidate 0.1–0.2 mg/kg or thiopentone 1–3 mg/kg were used to induce anaesthesia, in addition to intravenous fentanyl 4–10 μg/kg or remifentanil 1–2 μg/kg. Neuromuscular blockade was obtained with pancuronium 0.1 mg/kg or rocuronium 0.9 mg/kg. Anaesthesia was maintained with intravenous propofol target-controlled infusion 2–3 μg/mL and remifentanil 0.02–0.1 μg/kg per min, isoflurane 1–2%, or morphine 0.25 mg/kg per hour and midazolam 0.004 mg/kg per hour.

Cardiopulmonary bypass

Heparin (300 units/kg) was administered before cannulation of the ascending aorta and right atrium. Once the activated clotting time was greater than 450 seconds, CPB was established. During CPB, an α-stat approach to acid–base management was used. The CPB circuit comprised of a solid membrane oxygenator (I3 3500-2A Integral Series, Medtronic, Minneapolis, USA) and a roller pump (S3 model, Stöckert Instruments GmbH, Munich, Germany). The circuit was primed with Ringer’s solution 2 L, heparin 8000 units, sodium bicarbonate 50 mmol, and, in most cases, mannitol 20% 150–200 mL, depending upon patient weight.

During the CPB, hypotension was corrected with boluses of intravenous methoxamine 2 mg or phenylephrine 0.5 mg. Hypertension was treated with intravenous phenolamine mesylate 1 mg or trimethaphan 5 mg. Hypovolaemia was treated with Ringer’s solution (haemoglobin concentration ≥ 60 g/L), or concentrated red blood cells (haemoglobin concentration < 60 g/L).

Measurements

Timing

Measurements were taken at three or four time points: one during active cooling, one or two during environmental cooling/stable hypothermia, depending upon duration, and one when the patient’s temperature reached 35°C during rewarming. These sampling times were chosen to allow comparison of the two methods across the range of thermal conditions experienced by patients during hypothermic CPB (Table 1).

Blood sampling

Samples of blood were aspirated from the CPB circuit at each time point into heparinized syringes (Arterial Blood Sampler, Bayer Diagnostics, Stoke Court, UK). First samples of arterial blood were taken from the miniductus of the oxygenator outflow, and then mixed-venous blood was aspirated.
from the venous inlet to the venous reservoir. Ten millilitres of blood was first drawn off through these connectors to ... analyser was routinely confirmed against tonometered samples supplied by the manufacturer. Samples were mea-

ered at 37°C and interpreted uncorrected for patient temperature.

Oxygenator exhaust gas capnography
The same capnograph (Normocap 2000, Datex-Ohmeda, Hatfield, UK), calibrated each morning before use according to the manufacturer’s specifications, was used to measure the CO₂ concentration of the oxygenator exhaust gas; FiO₂, oxygen fraction of the oxygenator sweep gas; MAP, mean arterial pressure; CVP, central venous pressure; VO₂, Fick, systemic oxygen uptake as predicted by Fick’s principle; VCO₂, Fick, carbon dioxide production as estimated by Fick’s principle; VCO₂, carbon dioxide production as predicted by oxygenator carbon dioxide output.

Other measurements
Pump flow, fresh gas flow, and venous and arterial temperatures were recorded at each time point from the digital pump display (S3 model, Stöckert Instruments). Pump and fresh gas flow meters were routinely calibrated and their accuracy confirmed. The manufacturer’s stated measuring error for gas flow is ±2%. Mean arterial pressure, central venous pressure and patient nasopharyngeal temperature were measured using a Kolormon Plus (Kontron Instruments, Watford, UK).

Statistical analysis
Data were analysed using SPSS v10.00 for Windows (SPSS Inc., Chicago, IL, USA). The Bland and Altman method comparison analysis was used to compare VCO₂ as estimated by Fick’s principle and oxygenator CO₂ output. The sample size of the population was based on Bland and Altman’s recommendation of 50 for this technique. Also based upon their recommendations, to overcome the problem of multiple, repeated measurements within patients that are not statistically independent, and to limit Type 2 error, all data for each patient was first meaned for initial statistical analysis. To determine whether the relationships between the techniques were influenced by thermal conditions, each time point was subsequently examined individually. Linear regression analysis was used to compare VO₂ as estimated by Fick’s principle with the two methods of VCO₂ estimation. Student’s paired t-test was used to compare means. The level of significance was taken to be 5%. Results are presented as mean followed by standard deviation unless otherwise indicated.

Table 1 Measured and calculated variables

<table>
<thead>
<tr>
<th>Time point</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period</td>
<td>Cooling</td>
<td>Stable hypothermia/environmental cooling</td>
<td>Rewarming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from start of CPB (min)</td>
<td>6–16</td>
<td>18–45</td>
<td>44–73</td>
<td>29–179</td>
<td>–</td>
</tr>
<tr>
<td>n</td>
<td>51</td>
<td>51</td>
<td>33</td>
<td>51</td>
<td>–</td>
</tr>
<tr>
<td>Art temperature (°C)</td>
<td>30.7 (3.9)</td>
<td>30.6 (3.2)</td>
<td>29.8 (3.8)</td>
<td>35.5 (3.8)</td>
<td>31.2 (4.3)</td>
</tr>
<tr>
<td>MV temperature (°C)</td>
<td>31.9 (1.3)</td>
<td>31 (1.9)</td>
<td>30.2 (2.3)</td>
<td>34.4 (1.0)</td>
<td>31.4 (2.2)</td>
</tr>
<tr>
<td>Capnograph CO₂ (%)</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.3)</td>
<td>2.1 (0.5)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>Fresh gas flow rate (L/min)</td>
<td>8.83 (0.9)</td>
<td>8.12 (1.2)</td>
<td>7.43 (1.6)</td>
<td>6.76 (1.8)</td>
<td>7.68 (1.6)</td>
</tr>
<tr>
<td>FiO₂ (%)</td>
<td>0.67 (0.07)</td>
<td>0.61 (0.06)</td>
<td>0.6 (0.07)</td>
<td>0.69 (0.08)</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>Pump flow rate (L/min)</td>
<td>4.38 (0.52)</td>
<td>4.38 (0.5)</td>
<td>4.29 (0.44)</td>
<td>4.35 (0.47)</td>
<td>4.27 (0.48)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>67 (3.7)</td>
<td>71 (15)</td>
<td>77 (14)</td>
<td>77 (40)</td>
<td>72 (28)</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>1.8 (3.7)</td>
<td>2.1 (4.1)</td>
<td>1.9 (3.5)</td>
<td>1.9 (3.5)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>VO₂ Fick (mL/min)</td>
<td>122 (38)</td>
<td>114 (43)</td>
<td>120 (41)</td>
<td>167 (35)</td>
<td>131 (45)</td>
</tr>
<tr>
<td>VCO₂ Fick (mL/min)</td>
<td>181 (49)</td>
<td>158 (50)</td>
<td>148 (69)</td>
<td>173 (60)</td>
<td>165 (57)</td>
</tr>
<tr>
<td>VCO₂ output (mL/min)</td>
<td>128 (22)</td>
<td>118 (26)</td>
<td>106 (23)</td>
<td>135 (28)</td>
<td>121 (27)</td>
</tr>
</tbody>
</table>

Values are presented as mean with standard deviation in parentheses except where indicated. Time from start of CPB, time from start of cardiopulmonary bypass (range); mean, averages of the data collected from all patients at all time points; MV, mixed venous capnograph CO₂, carbon dioxide concentration of the oxygenator exhaust gas; FiO₂, oxygen fraction of the oxygenator sweep gas; MAP, mean arterial pressure; CVP, central venous pressure; VO₂ Fick, systemic oxygen uptake as predicted by Fick’s principle; VCO₂, Fick, carbon dioxide production as estimated by Fick’s principle; VCO₂, carbon dioxide production as predicted by oxygenator carbon dioxide output.
Results

Fifty-three patients (40 male and 13 female) undergoing elective cardiac surgery requiring CPB were admitted to the study. One male and one female patient had to be excluded later due to a failure to sample blood at the final time point. Patients had a mean age of 65 (10) years; height of 1.67 m (0.09); weight of 78 (13) kg; body mass index of 28 (4) kg/m²; body surface of 1.87 (0.18) m². Blood sampling was performed, and measurements recorded during active cooling, environmental cooling/stable hypothermia and during rewarming in all cases (n = 51). In 18 cases, the duration of stable hypothermia/environmental cooling was too short to obtain a second sample.

When the data from all sampling points were averaged for each patient, VCO₂, as estimated by Fick’s principle, correlated significantly with that predicted by oxygenator CO₂ output (r = 0.7333, p < 0.001). Method comparison analysis of this meaned data for each of the 51 patients found a significant bias and very wide limits of agreement (Table 2). Regression of the difference in values upon their means found a significantly nonhorizontal trend (Table 2), indicating the bias was proportional to the size of VCO₂ being measured. Significant biases and wide limits of agreement were also found at each of the four time points along with significant nonhorizontal trends (Table 2).

A significant correlation (r = 0.765, p < 0.001) was found between VO₂ and VCO₂, as estimated using Fick’s principle. Regression analysis of VO₂ against VCO₂, as predicted by Fick’s principle, gave a constant of 36 (95% CI 12, 60) mL/min, and a coefficient of 0.575 (95% CI 0.44-0.71). VO₂, as estimated by Fick’s principle, and VCO₂, as predicted by oxygenator CO₂ output, were also found to correlate significantly (p < 0.01, r = 0.92). Regression analysis of these values gave a constant of −41 (95% CI: −63 to −19) mL/min, and a coefficient of 1.37 (95% CI 1.2–1.54).

Discussion

This study found a significant correlation between VCO₂, as estimated using Fick’s principle, and that by oxygenator exhaust output. Whilst the correlation coefficient gives a measure of the strength of the relationship between two variables, it provides no indication of agreement. Perfect agreement will only exist if all points lie on the line of equality; perfect correlation requires only that all points lie on a straight line. Indeed, a poor agreement was revealed by method comparison analysis, which found the limits of agreement to be extremely wide. Moreover, not only was there a significant mean bias between the two methods that was of considerable magnitude, but the bias was proportional to the size of VCO₂. Together, these findings indicate that the two methods of VCO₂ estimation should not be used interchangeably.

The method comparison technique makes no assumption regarding the accuracy of either technique. Therefore, the extremely wide limits of agreement and the proportional bias observed could reflect the inaccuracy of either, or both techniques. As with the estimation of VO₂, the calculation of VCO₂ using Fick’s principle is also associated with compounding of error as it is calculated from multiple measurements; pump flow rate and the CO₂ content of arterial and mixed venous blood. Variability in pump flow rate could also have contributed to error in VCO₂ measurement using Fick’s principle. However, any error from this source should have been minimal as regular volumetric calibration of the pump head was performed daily to minimize this source of error. However, even when calibrated, the device is only accurate to ±0.2% and, given the small range of measured concentrations, this limited accuracy may have been a source

Table 2 Method comparison analysis of VCO₂ production as estimated using Fick’s principle and by oxygenator exhaust CO₂ production

<table>
<thead>
<tr>
<th>Time point</th>
<th>Bias (mL/min)</th>
<th>95% CI of bias</th>
<th>Limits of agreement (mL/min)</th>
<th>Regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td>53</td>
<td>65–41</td>
<td>138</td>
<td>−33</td>
</tr>
<tr>
<td>Stable hypothermia</td>
<td>41</td>
<td>52–30</td>
<td>122</td>
<td>−40</td>
</tr>
<tr>
<td>Stable hypothermia</td>
<td>43</td>
<td>62–23</td>
<td>155</td>
<td>−70</td>
</tr>
<tr>
<td>Rewarming</td>
<td>37</td>
<td>50–25</td>
<td>129</td>
<td>−54</td>
</tr>
<tr>
<td>Mean</td>
<td>41</td>
<td>50–32</td>
<td>105</td>
<td>−23</td>
</tr>
</tbody>
</table>

Bias, mean difference between VCO₂ as estimated by the Fick principle and that predicted by oxygenator CO₂ output; 95% CI of bias, 95% confidence intervals for the bias as given by ±2 standard errors of the mean; limits of agreement, ±2 standard deviations of the bias; β, regression coefficient.
of error. Using a capnograph that has a greater degree of accuracy would have overcome this problem. However, such equipment would unlikely be available clinically and so would greatly limit the application of the technique.

Aerobic metabolism results in a smaller amount of CO₂ being produced to that of oxygen taken up, so less gas will be exhausted than is supplied to the oxygenator. The actual size of this effect will depend on the respiratory quotient, but whatever its size, gas outflow at a stable body temperature will always be less than the inflow to the oxygenator. However, given that high sweep gas flow rates are normal, this effect will only produce small differences in the volumes of gas entering and leaving the oxygenator and so will not have had an important influence on the accuracy of this technique. One way of overcoming this source of error would be to utilize the law of conservation of mass and use an inert marker such as helium to estimate such changes in volume.¹²

Another limitation of the exhaust output technique is that the actual flow rate of gas exhausted was not measured, but assumed to be equal to the flow rate of fresh gas entering the oxygenator. Possibly, this assumption is invalid. Thermal gradients across the oxygenator during systemic cooling and rewarming will, because of Charles Law, respectively reduce and increase the gas outflow from the oxygenator relative to the measured inflow. Direct measurement of gas outflow would eliminate this source of error, but would limit the clinical application of the technique.

Thermal gradients across the oxygenator may also be responsible for another source of error in the oxygenator exhaust production technique for estimation of VCO₂. During cooling, because of Henry’s Law, CO₂ will become more soluble and less will be eluted from the blood into the gaseous phase than is actually being produced systemically. Vice versa, more CO₂ will be released during rewarming than is being produced by the body because its solubility will decrease. This hypothesis would be supported by our work relating oxygenator exhaust CO₂ concentration to arterial CO₂ tension.¹³ In this work, we found a poor relationship between the two during cooling and rewarming, but a reasonable one during stable hypothermia.

When VCO₂ and VO₂ were both estimated by Fick’s principle, there was only moderate correlation between the measurements. A much greater correlation was found to exist between measurements of VCO₂ estimated by oxygenator CO₂ production and VO₂ estimated by Fick’s principle. However, analysis revealed wide confidence limits for the regression constants suggesting that both methods are very imprecise in their prediction of VO₂. For this reason, neither of the VCO₂ estimates should be used interchangeably with VO₂ estimation by Fick’s principle.

In conclusion, VCO₂ as calculated using Fick’s principle and using oxygenator exhaust CO₂ production cannot be used interchangeably and both techniques relate imprecisely with VO₂ as estimated by Fick’s principle.

References

Appendix A

**Fick’s principle for calculation of systemic oxygen uptake**

\[ \text{VO}_2 = \frac{\text{CaO}_2 - \text{CvO}_2}{Q} \]

where
- \( \text{VO}_2 \) = systemic oxygen uptake
- \( \text{CaO}_2 \) = arterial oxygen content
- \( \text{CvO}_2 \) = mixed venous oxygen content
- \( Q \) = pump flow rate

Appendix B

**Fick’s principle for calculation of systemic CO}_2 production**

\[ \text{VCO}_2 = \frac{\text{CvCO}_2 - \text{CaCO}_2}{Q} \]

where
- \( \text{VCO}_2 \) = systemic carbon dioxide production
- \( \text{CvCO}_2 \) = mixed venous carbon dioxide content
- \( \text{CaCO}_2 \) = arterial carbon dioxide content
- \( Q \) = pump flow rate

Appendix C

**Oxygenator exhaust CO}_2 production estimation of systemic CO}_2 production**

\[ \text{VCO}_2 = \text{FGF} \times \text{FeCO}_2 \]

where
- \( \text{VCO}_2 \) = systemic carbon dioxide production
- \( \text{FGF} \) = fresh gas flow rate to oxygenator
- \( \text{FeCO}_2 \) = fraction of carbon dioxide in the gas exhausting from the oxygenator
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