A COMPARISON OF METHODS FOR THE MEASUREMENT OF CARDIAC OUTPUT AND BLOOD OXYGEN CONTENT

I. H. S. DOUGLAS, J. A. E. MACDONALD, G. F. MILLIGAN, ANNE MELLON AND I. MCA. LEDINGHAM

SUMMARY
A comparison has been made between the recently introduced thermal dilution method for measurement of cardiac output and the standard dye dilution technique. Two relatively new methods of measurement of blood oxygen content, one involving the measurement of oxygen tension after release of oxygen by carbon monoxide, and the other the measurement of current flow upon reduction of oxygen in a galvanic cell, have been compared with a standard indirect method of measurement of blood oxygen content. All three new methods fulfilled the criteria of accuracy and simplicity and compared favourably with the standard methods. Of the two new methods for measurement of oxygen content, that involving reduction of oxygen in a galvanic cell was superior by virtue of compactness and speed of operation.

The standard techniques for measuring cardiac output and blood oxygen content are limited to the clinical laboratory as a result of the high degree of technical expertise necessary for their performance. By virtue of their compactness and ease of use, newer methods have enabled these measurements to be made at the bedside.

This study was designed to compare the thermal dilution technique for measurement of cardiac output with the standard dye dilution method and to compare two relatively simple methods for the direct measurement of blood oxygen content with an established method for the derivation of this value. Using two of these techniques, total body oxygen consumption has been calculated and the results compared with the direct measurement of oxygen consumption by collection of expired air.

MATERIALS AND METHODS
Thirty-two greyhounds (weight 20-30 kg) were studied. Anaesthesia was induced with sodium thiopentone 15 mg/kg and maintained with halothane, nitrous oxide and oxygen; when measuring oxygen consumption by collection of expired gas into a Douglas bag, anaesthesia was maintained with sodium pentobarbitone i.p. An endotracheal tube was passed in each animal. Thirty of the animals breathed spontaneously, but to obtain lower levels of oxygen consumption, two were paralysed with suxamethonium chloride i.m. and ventilated artificially.

Catheters were inserted into the descending aorta, right atrium and pulmonary artery for measurement of pressures and sampling of blood. Core temperature was recorded from the midoesophagus using a direct recording thermocouple (Ellab, Copenhagen).

Cardiac Output

Dye dilution method.
A known quantity of indocyanine green (2.5 mg) was injected into the right atrium and blood was withdrawn from the aorta through a Waters densitometer (X P-302, Waters Company, Rochester, Minnesota) using a syringe pump with a constant rate of withdrawal (Harvard Apparatus Co. Inc., Dover, Mass.). The resulting change in optical density was recorded on a potentiometer recorder (Servoscribe, Smiths Instruments, London). Three samples of blood having dye concentrations of 5, 10 and 15 mg/litre were prepared; these calibration mixtures were drawn through the densitometer cuvette and the recorder deflections plotted against dye concentrations. The line of best fit through these points was drawn, and the slope (m) and y intercept (c) measured.

Cardiac output was calculated from the dye dilution curve as follows: the recorder deflection for each second was converted to dye concentration,
using the calibration line, and the concentrations were summed. When the descending slope of the curve was judged to be exponential, the decay constant of the curve was calculated from the succeeding three points on the curve. To eliminate the error resulting from recirculation of dye, the remainder of the curve was assumed to decay at this rate. Since the curve is integrated from optical density values converted to dye concentrations at intervals of 1 sec, the Stewart-Hamilton equation (Stewart, 1921; Hamilton et al., 1928) reduces to:

Cardiac output (litre/min) = (60 × I)/s.c.

where I = mass of dye injected (mg)

s.c. = sum of concentrations (mg/litre).

All calculations were performed on a desk calculator (Hewlett-Packard 9100B) programmed to convert deflection measurements to dye concentrations and to allow for the calculation of the decay constant.

Thermal dilution method.

This method utilized a fine catheter bearing a thermistor at the tip, connected to a cardiac output computer, Type 3750 (Devices Instruments Ltd, Welwyn Garden City, Herts). The catheter was passed by flotation into the pulmonary artery via the external jugular vein and its position was verified by pressure recordings. Under fluoroscopic control, a separate injection catheter (4 FG) was passed into the right atrium, and through it was injected 10 ml of 5% dextrose at room temperature. The resulting reduction in temperature in the pulmonary artery was detected by the thermistor. Syringes charged with this solution were stored in a Thermos container, the temperature of which was sensed by a second thermistor mounted on a probe. The temperature difference between the injectate and the pulmonary artery blood was measured automatically and the reduction in temperature in the pulmonary artery was integrated with respect to time. A meter provided a direct reading of cardiac output (CO) after evaluation by an analogue computer, of the expression:

\[ \text{CO (litre/min)} = \left[ \frac{\text{AV}(T_i - T_b)D_iS_i}{\int \Delta T_b \, dt \times D_iS_i} \right] - B \]

Where A and B are constants, the suffices i and b refer to injectate and blood, and:
- \( V \) = injectate volume (litre)
- \( T \) = temperature (°C)
- \( \Delta T \) = incremental temperature (°C)
- \( D \) = density (g/ml)

In practice, \( V = 0.00975 \) litre (10 ml less the volume of the injectate catheter)

\[ S_i = 0.964 \text{ cal/g°C} \]

\[ S_b = 0.87 \text{ cal/g°C} \]

\[ D_i = 1.018 \text{ g/ml} \]

\[ D_b = 1.057 \text{ g/ml} \]

\[ A = 0.96 \] from the thermal dilution/\( B = 0.20 \) Fick regression equation.

Oxygen Content

Derived method.

Blood oxygen tension (\( P_{O_2} \)), carbon dioxide tension (\( P_{CO_2} \)) and pH were measured using appropriately calibrated electrode systems (Radiometer, Copenhagen). To allow for the difference in the measurement of \( P_{O_2} \) in gas, used for calibrations, and blood, a blood-gas factor was derived for each experiment, using blood tonometered in a rotating syringe (McDowall, Ledingham and Tindal, 1968). Blood-gas tensions and pH were corrected for any temperature difference between the electrodes and the mid-oesophagus using the Radiometer blood-gas calculator (Severinghaus, 1966). Oxygen content was calculated from the formula:

\[ \text{O}_2 \text{ content (ml/100 ml) = } \left[ \frac{\text{Hb (g) \times 1.39 \times Hb saturation (\%)}{100}} \right] + \left[ \frac{P_{O_2} (\text{mm Hg}) \times 0.0031}{100} \right] \]

assuming that 1g haemoglobin (Hb) combines with 1.39 ml oxygen at standard temperature and pressure (Sykes et al., 1970). In this study Hb measurements were made by the cyanmethaemoglobin method.

There is a good correlation between this method and simultaneous determinations using the Van Slyke apparatus \( (\gamma = 0.37 + 1.06x; r = 0.983); \text{Ledingham et al., 1970} \).

Direct methods.

Carbon monoxide. Blood oxygen content may be calculated by measurement of oxygen tension following the release of oxygen from haemoglobin by carbon monoxide (Klingenmaier, Behar and Smith, 1969). Using a 5-port, 2-bore stopcock (National Glass Industry (Tottenham) Ltd, London) and a volume limited syringe, an accurately known volume of blood was diluted to another accurately known volume with deoxygenated car-
bon monoxide-saturated physiological saline. The oxygen is released from haemoglobin without cell lysis thus increasing the oxygen tension in the mixture by an amount proportional to the oxygen content. The measuring electrode (Radiometer E5036) was maintained at 21°C. Although the solubility coefficient of oxygen in saline at this temperature is not well documented, the value for oxygen in 0.6% ferricyanide solution has been measured recently (Solymar, Rucklidge and Prys-Roberts, 1971) and this value has been used. The desk calculator was programmed to perform the calculation:

\[ O_3 \text{ content (ml/100 ml)} = \frac{(100/v) \cdot (\lambda/760) \cdot [P_2 \cdot V - P_1 \cdot (V - v)]}{P_1} \]

where \( P_1 \) = partial pressure of oxygen in CO-saline (mm Hg)
\( P_2 \) = partial pressure of oxygen in diluting syringe (mm Hg)
\( v \) = volume of stopcock bore (ml)
\( V \) = volume of diluting syringe (ml)
\( \lambda \) = solubility coefficient of oxygen in saline at 21°C (vol O₂/vol liquid/atm).

"Lex O₂ Con". With this instrument (Lexington Instruments, Waltham, Mass.) a slow flow (40 ml/min) of carrier gas (97% nitrogen, 2% carbon monoxide, 1% hydrogen) was passed over a catalyst to remove traces of oxygen. The gas was then passed into a scrubber filled with distilled water into which an accurately measured volume of blood (0.02 ml) was injected using a Hamilton syringe. Following its release in the scrubber, the oxygen was swept by the carrier gas into a galvanic cell which, in reducing the oxygen, produced a corresponding flow of current.

The current was integrated and displayed on a digital counter calibrated as ml/100 ml of oxygen. The instrument was calibrated before use by injection of a sample of air, dried by passage through silica gel, using the same Hamilton syringe.

The Lex O₂ Con apparatus was used by a single operator on any one day to ensure uniformity of technique in calibration and measurement. Different operators on different days achieved a similar standard of efficiency.

**Oxygen Consumption**

**Derived method.**

Measurements were made of cardiac output and of the oxygen content of arterial and mixed venous blood samples. Oxygen consumption \((\text{VO}_2)\) was derived using the formula:

\[ \text{VO}_2 \text{ (ml/min)} = \text{CO} \times \Delta(A - V)O_2 \times 10 \]

where \( \text{CO} \) = cardiac output (litre/min)
\( \Delta(A - V)O_2 \) = arteriovenous oxygen content difference (ml/100 ml).

In this study cardiac output and oxygen content were measured by thermal dilution and Lex O₃ Con methods respectively.

**Direct method.**

Oxygen consumption may be measured directly by analysis of the mixed expired gas. The animals breathed room air through a non-rebreathing valve, the expiratory part of which was connected to a Douglas bag of 100-litre capacity, washed out with expired gas before commencing collection. Expired gas was collected during a 10-min period, and an aliquot of the collection was transferred to an evacuated sample bag and analysed immediately using Lloyd's modified Haldane apparatus. The volume of gas in the Douglas bag was then measured by evacuation through a dry gas meter, the temperature of which was measured also. The measured gas volume was converted to STPD from the formula:

\[ V \text{ (ml STPD)} = \frac{V_m \cdot 273 \cdot (P_b - WVP)}{760 \cdot T_m} \]

where \( V_m \) = measured volume (ml)
\( P_b \) = barometric pressure (mm Hg)
\( T_m \) = meter temperature (°C)
\( WVP \) = saturated water vapour pressure at meter temperature (mm Hg).

Using the measured values of \( F_{E_O_2} \) and \( F_{E_CO_2} \), to derive \( F_{E_N_2} \), and assuming \( F_{I_N_2} \) to be 0.7907, oxygen consumption is calculated as:

\[ \text{VO}_2 \text{ (ml/min)} = \frac{[(V_E \cdot F_{E_N_2})/F_{I_N_2}](F_{I_O_2} - F_{E_O_2})V_E}{V_E} \]

where \( V_E \) = volume of expired gas (ml)
\( F_E \) = fractional concentration of expired gas
\( F_I \) = fractional concentration of inspired gas.

In order to obtain a range of values of oxygen consumption for the purpose of correlation analysis, the core temperature of six animals was varied by surface warming or cooling. The lowest values were obtained in two animals using muscle relaxants and artificial ventilation, in addition to cooling.

**RESULTS**

**Duplicates.** Each method, with the exception of the direct measurement of oxygen consumption, was tested separately for reproducibility, by correlation of duplicate measurements. Using the thermal dilution method, the time interval between duplicates was minimal; with the dye dilution
method, the delay was necessarily longer to permit reinjection of the first volume of blood withdrawn. In the oxygen content methods, duplicate measurements were performed on the same sample, which was stored anaerobically in iced water between measurements.

In all instances, correlation between duplicate measurements was of a satisfactorily high order (table I).

**Cardiac Output**

Since it was believed that the very small volume of indocyanine green which could be accommodated by the fine-bore thermal dilution injectate catheter would compromise the dye-dilution method, simultaneous measurements of cardiac output by the two methods were not attempted. The methods were applied separately, therefore, with as little delay as possible and in a randomized sequence. Figure 1 shows the high degree of correlation between dye (x) and thermal dilution (y) methods in 160 consecutive measurements \((r=0.96)\). Details of the regression analysis are given in table II.

**Oxygen Content**

The carbon monoxide and Lex O\(_3\) Con methods \((y)\) were each compared separately with the derived method \((x)\) on different occasions. In each case, measurements were made on the same blood sample, divided into two aliquots. Both methods correlated well with the derived method (figs. 2 and 3; table II), the Lex O\(_3\) Con method providing slightly better correlation than the carbon monoxide method.

**Oxygen Consumption**

Oxygen consumption was measured on 30 occasions over a range of values from 92 to 277 ml/min. In each instance the value derived from cardiac output and arteriovenous oxygen content difference was obtained at the midpoint of the direct measurement (fig. 4). There was a fairly wide scatter, with an overall tendency for the derived value \((x)\) to exceed the directly measured value \((y)\) by \(19\pm5\) ml/min (mean difference±SEM). However, the correlation was still good \((r=0.74; P<0.001)\).

Details of the regression analysis are shown in table III.

**DISCUSSION**

**Cardiac Output Methods**

Although the dye dilution technique is a well-proven and widely accepted method of measuring cardiac output, it has several disadvantages which

---

**Table I. Correlations of duplicate measurements of cardiac outputs (2 methods) and oxygen contents (3 methods).**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac output</td>
<td>Oxygen content</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dye</td>
<td>Thermal</td>
<td>Derived</td>
<td>CO</td>
</tr>
<tr>
<td>Number of samples</td>
<td>45</td>
<td>139</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Range (litre/min; ml/100 ml)</td>
<td>0.4–7.3</td>
<td>0.7–7.5</td>
<td>3.2–27.8</td>
<td>2.6–31.1</td>
</tr>
<tr>
<td>Correlation coefficient ((r))</td>
<td>0.989</td>
<td>0.983</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>Regression equation ((y=0.97x+0.06))</td>
<td>(y=0.998x–0.05)</td>
<td>(y=0.996x+0.082)</td>
<td>(y=0.979x+0.206)</td>
<td>(y=1.014x–0.19)</td>
</tr>
<tr>
<td>(Sy)</td>
<td>0.25</td>
<td>0.24</td>
<td>0.27</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean (\Delta) ((litre/min; ml/100ml))</td>
<td>–0.04</td>
<td>–0.06</td>
<td>0.03</td>
<td>–0.12</td>
</tr>
<tr>
<td>SD of mean (\Delta)</td>
<td>±0.24</td>
<td>±0.25</td>
<td>±0.27</td>
<td>±0.48</td>
</tr>
</tbody>
</table>

\(Sy=\) standard error of the estimate of \(y\); Mean \(\Delta=\) mean difference between duplicates; SD of mean \(\Delta=\) standard deviation of mean difference.
MEASUREMENT OF CARDIAC OUTPUT AND BLOOD OXYGEN

TABLE II. Comparisons of cardiac output measurements by thermal dilution and dye-dilution techniques and of blood oxygen content measurements by the Lex O₃ Con and carbon monoxide (CO) direct methods against a derived method.

<table>
<thead>
<tr>
<th></th>
<th>Cardiac output</th>
<th>Oxygen content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thermal v. dye dilution</td>
<td>CO v. derived</td>
</tr>
<tr>
<td>Number of samples</td>
<td>161</td>
<td>72</td>
</tr>
<tr>
<td>Range (litre/min; ml/100 ml)</td>
<td>0.7-6.9</td>
<td>2.7-31.1</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.960</td>
<td>0.988</td>
</tr>
<tr>
<td>Regression equation</td>
<td>y=1.02x+0.01</td>
<td>y=1.04x-0.919</td>
</tr>
<tr>
<td>Sy</td>
<td>0.40</td>
<td>1.08</td>
</tr>
<tr>
<td>Mean Δ (litre/min; ml/100 ml)</td>
<td>0.06</td>
<td>-0.21</td>
</tr>
<tr>
<td>SD of mean Δ</td>
<td>±0.4</td>
<td>±1.12</td>
</tr>
</tbody>
</table>

Sy=standard error of the estimate of y; Mean Δ=mean difference between methods; SD of mean Δ=standard deviation of mean difference.

Fig. 2. Correlation between carbon monoxide and derived methods of measuring oxygen content. Dotted lines indicate 95% confidence limits.

Fig. 3. Correlation between Lex O₃ Con and derived methods of measuring oxygen content. Dotted lines indicate 95% confidence limits.

Table II shows comparisons of cardiac output measurements by thermal dilution and dye-dilution techniques and of blood oxygen content measurements by the Lex O₃ Con and carbon monoxide (CO) direct methods against a derived method. The table includes the number of samples, range, correlation coefficient, regression equation, and mean difference for each method. The thermal dilution technique is described as offering an attractive alternative to dye-dilution methods, being compact, self-contained, and rapid. It also avoids the problems associated with recirculation of indicator and does not involve withdrawal of blood from the subject.

The main theoretical objection to the method, recognized by earlier workers using iced saline as injectate (Fegler, 1954; Goodyer et al., 1959) is the possible loss of thermal indicator by heat gain from the adjacent tissues during the passage of the injectate through the pulmonary circuit. This source of error is minimized by the use of indicator at room temperature (Evonuk et al., 1961).

The present study has shown that in terms of accuracy, the method compares favourably with the standard method of dye-dilution and would, in practice, limit its routine use as a clinical tool. In practice, the technique is time-consuming, and its accuracy depends to a large extent on the skill of the operator. The indicator is an expensive dye with limitations of dosage. In low output states, errors resulting from recirculation of indicator may cause problems, although these may be minimized by using the Dow formula for the calculation (Dow, 1955).
Oxygen Consumption

Correlation between direct and derived methods of measuring oxygen consumption. Dotted lines indicate 95% confidence limits.

Fig. 4. Correlation between direct and derived methods of measuring oxygen consumption. Dotted lines indicate 95% confidence limits.

Table III. Comparison of oxygen consumptions measured directly (y) by collection of expired gas with those obtained indirectly (x) utilizing the Fick principle.

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (ml/min)</td>
<td>92-277</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.74</td>
</tr>
<tr>
<td>Regression equation</td>
<td>y=0.89x-0.13</td>
</tr>
<tr>
<td>Sy</td>
<td>30.4</td>
</tr>
<tr>
<td>Mean Δ (ml/min)</td>
<td>-19</td>
</tr>
<tr>
<td>SD of mean Δ</td>
<td>±30</td>
</tr>
</tbody>
</table>

Sy = standard error of the estimate of y; Mean Δ = mean difference between methods; SD of mean Δ = standard deviation of mean difference.

therefore, seem to be ideally suited to a clinical role. The practical disadvantage in this respect is the relative invasiveness of the method as it entails the flotation of a catheter into the pulmonary artery. However, in none of these animal studies has positioning of the catheter presented any technical problems. Transient arrhythmias produced by coiling of the catheter in the right atrium during insertion have been observed occasionally, but these resolved promptly on temporarily withdrawing the catheter.

The value of cardiac output measurements is not confined to the haemodynamic data obtained. In conjunction with measurements of blood oxygen content, information may be obtained regarding tissue oxygen utilization. In view of the importance of tissue hypoxia as a lethal factor in shock (Goodyer, 1967) there is a need to determine oxygen content simply and accurately in the clinical situation.

Oxygen Content Methods

The method of Van Slyke and Neill (1924) is the accepted standard for the measurement of blood oxygen content. The procedure is time-consuming and demands a standard of specialized technical skill which is not widely available. In the present study we have adopted as our standard a method which has been tested previously in this laboratory against the Van Slyke method (Ledingham et al., 1970). This derived method, although considerably less demanding, still requires a high standard of technical assistance and this renders it less suitable for routine clinical use. Two simpler methods of directly measuring blood oxygen content were found to correlate well with the derived method.

The carbon monoxide method was first proposed by Baumberger in 1940, but was not sufficiently accurate until Mayers and Forster (1966) suggested the use of stopcocks as a precision sampling device. The apparatus used in the present study incorporates the modification of Klingenmaier, Behar and Smith (1969) of a single 5-port double-bore stopcock replacing the two of Mayers and Forster. This technique, which can be learned easily, offers a high degree of accuracy, as the results of this study show. However, the apparatus is not commercially available.

The Lex O3 Con apparatus provided a slightly better correlation with the control method and has the additional advantage of being completely self-contained and portable. The role of the operator is confined to the injection of the blood sample into the apparatus, which may then be left unattended whilst the sample is analysed automatically. In the clinical situation, where the operator may be the attending clinician, this feature is of some importance.

Oxygen Consumption

The correlation between directly measured and derived values for total body oxygen consumption was, not surprisingly, of a lower order (r=0.74). Although every effort was made to ensure haemodynamic and respiratory stability during the collection of expired gas, it is possible that the instantaneous oxygen consumption, based on cardiac out-
put and arteriovenous oxygen content difference, may not be representative of the whole 10-min period with which it was compared. Furthermore, sizeable errors in derived oxygen consumption may arise from relatively small errors in sampling. These errors may be unavoidable, particularly those involving the sampling of mixed venous samples in which there may be variability in oxygen content due to intermittent "wedging" of the catheter in the pulmonary artery (McGuinness et al., 1972). The mean difference between methods of 19 ml/min, significant at the 1% level, raises the possibility of a systematic error. The degree of scatter, however, is more in keeping with a random error than a true systematic error.

ACKNOWLEDGEMENT

We are grateful to Mr K. Gorman of the Department of Surgery, Western Infirmary, for his able technical assistance.

REFERENCES


COMPARACION DE LOS METODOS PARA MEDICION DE POTENCIA CARDIACA Y CONTENIDO EN OXIGENO DE LA SANGRE

SUMARIO
Se compararon el método, recientemente introducido, por disolución térmica para medición de potencia cardíaca y la técnica normal de disolución de colorante. Se compararon con un método normal indirecto de medición del contenido en oxígeno de la sangre dos métodos, relativamente nuevos, de medición del contenido en oxígeno de la sangre, uno envolviendo la medición de la tensión de oxígeno después de liberación de oxígeno por el monóxido de carbono, y el otro la medición del flujo actual por reducción del oxígeno en una célula galvánica. Los tres nuevos métodos cumplieron los criterios de precisión y simplicidad y se compararon favorablemente con los métodos normales. De los dos nuevos métodos de medición de contenido en oxígeno, el que consiste en la reducción de oxígeno en una célula galvánica fue superior en cuanto a tamaño reducido y rapidez de operación.