ESTIMATES OF ARTERIAL $P_{CO_2}$ AND THEIR EFFECT ON THE CALCULATED VALUES OF CARDIAC OUTPUT AND DEAD SPACE ON EXERCISE

S. GODFREY AND C. T. M. DAVIES

Department of Paediatrics, Institute of Diseases of the Chest, London and MRC Environmental Physiology Research Unit, London

(Received 30 April 1970)

SUMMARY

1. A study of exercise physiology in 117 children aged 6–16 is described including the measurement of cardiac output by the Indirect ($CO_2$) Fick Principle.
2. Computer produced graphs enabled various alternative values for arterial $P_{CO_2}$ ($Pa_{CO_2}$) to be inserted simultaneously into the Fick equation for cardiac output and the Bohr equation for dead space.
3. Dead space could be estimated with reasonable accuracy using end-tidal $P_{CO_2}$.
4. Cardiac output determination was unreliable at rest due to the small veno-arterial $P_{CO_2}$ difference but it was very good on exercise when this difference is much larger.
5. The $Pa_{CO_2}$ used for the calculation of cardiac output could be derived either from ear lobe $P_{CO_2}$ or end-tidal $P_{CO_2}$. However, the best estimate of cardiac output was that using the $Pa_{CO_2}$ implied by assuming a normal dead space.

Interest in the Indirect ($CO_2$) Fick method of measuring cardiac output has been revived by the studies of Campbell and his colleagues (Jones, Campbell, McHardy, Higgs & Clode, 1967; Higgs, Clode, McHardy, Jones & Campbell, 1967). The use of a rebreathing technique for estimating mixed venous $P_{CO_2}$ ($Pv_{CO_2}$) renders this method simple, safe and acceptable even to children (Gadhoke & Jones, 1969), and it has been found valid compared with independent estimates of cardiac output (Higgs et al., 1967; Ferguson, Faulkner, Julius & Conway, 1968).

McHardy, Jones & Campbell (1967) have pointed out that the transport of $CO_2$ from tissues to expired gas provided certain interrelationships between cardiac output and physiological dead space. This can be seen from the following versions of the equations of Fick (1870) and Bohr (1891):

Correspondence: Dr S. Godfrey, Institute of Diseases of the Chest, Fulham Road, London, S.W.3.
\[ \dot{Q} = \frac{\dot{V}_{CO_2}}{f(PV,CO_2 - Pa,CO_2)} \]  
\[ V_D = V_T \times \frac{(Pa,CO_2 - Pe,CO_2)}{Pa,CO_2} \]  

(where \( \dot{Q} \) = cardiac output, \( \dot{V}_{CO_2} \) = CO_2 production, \( f \) = slope of CO_2 dissociation curve, \( PV,CO_2 \) = mixed venous \( PCO_2 \), \( Pa,CO_2 \) = arterial \( PCO_2 \), \( V_D \) = dead space, \( V_T \) = tidal volume, \( Pe,CO_2 \) = mixed expired \( PCO_2 \)). All the values on the right hand side of these equations are easily determined without blood sampling, except for arterial \( PCO_2 \). However, if a value of arterial \( PCO_2 \) is substituted into the equations, simultaneous solutions for \( \dot{Q} \) and \( V_D \) are obtained. In other words \( \dot{Q}, \ V_D \) and \( Pa,CO_2 \) are intimately linked together once the other variables are known. Use has been made of this fact to construct a digital computer program (Godfrey, 1970) to solve the simultaneous equations for any number of alternative estimates of \( Pa,CO_2 \).

In the present study we have explored the extent to which various alternative estimates of \( Pa,CO_2 \) affected the derived values for \( \dot{Q} \) and \( V_D \). This is of particular importance in order to interpret the response to exercise in subjects such as normal children in whom it is unjustifiable and often impractical to perform arterial catheterization.

**MATERIALS AND METHODS**

The study was carried out on a total of 117 children (fifty-seven boys and sixty girls) aged 6-16 years. They were all healthy volunteers from local schools. Each child was examined clinically before the study in order to exclude significant disease. Informed parental consent was obtained in writing for every child. Their physical details are reported elsewhere (Godfrey, Davies & Wozniak, unpublished observations).

Each child reported to the laboratory after a light breakfast or lunch and was studied at rest and \( \frac{1}{2} \) and \( \frac{3}{4} \) of its previously determined maximum working capacity. All measurements were taken when in the steady state, usually during the third to fifth min of exercise. Expired gas was collected for 1 min in a Tissot spirometer and immediately analysed for \( O_2 \) and \( CO_2 \). During the collection, or immediately afterwards in the more timid child, a sample of arterial-ized ear lobe blood was collected by the method of Godfrey, Wozniak, Courtenay Evans & Samuels (1970). This was followed by determination of the mixed venous \( PCO_2 \) (PV,CO_2), using essentially the method of Jones et al. (1967), except that the rebreathing bag was primed with \( CO_2 \) in \( O_2 \) mixtures from premixed gas cylinders which facilitated the selection of a suitable gas to achieve a plateau. The \( PV,CO_2 \) was taken to equal the plateau \( PCO_2 \) on the rebreathing record if it fulfilled the criteria of Ashton & McHardy (1963) and Jones et al. (1967). If not, the geometrical extrapolation procedure of Denison, Edwards, Jones & Pope (1969) was used. The next work level was begun immediately after completion of the rebreathing procedure.

Throughout the experiments \( O_2 \) was analysed with a paramagnetic analyser (Servomex O.A.150) and \( CO_2 \) with an infra-red analyser (URAS-4). These instruments were calibrated with four gas mixtures after every two or three patients. Ear lobe blood was analysed for \( PCO_2 \), \( PO_2 \) and pH with microelectrodes (Eschweiler) which were calibrated with three gas
Estimates of $P_{CO_2}$ and exercise calculations

mixtures and two standard buffers between each single sample. All calibrating gases were analysed in duplicate with a Lloyd-Haldane apparatus. The SD of the difference between duplicate estimates on the same sample of blood was 0.3 mmHg for $P_{CO_2}$, 0.9 mmHg for $P_{O_2}$ and 0.005 units for pH. Correction for the difference between ear blood and arterial blood was made after the method of Godfrey et al. (1970).

Calculations

Analysis of mixed expired gas enabled the computer to calculate ventilation and gas exchange from the raw data for each subject at each work load. These calculations provided the variables $\dot{V}_{CO_2}$ and $P_{E,CO_2}$ while $P_{V,CO_2}$ was measured from the rebreathing record and fed into the computer. The program then used these three constants together with stepwise increments of possible values for $P_{A,CO_2}$ to produce a series of alternative solutions of the Fick and Bohr equations for the work load in question. In fact the relationship between $Q$ and $V_D$ is a smooth curve, each point on the curve representing the solution for a different selected value of $P_{A,CO_2}$. A curve for one work load in a subject constructed by the computer is shown in Fig. 1. A similar curve was obtained for the other work loads performed by the subject and a separate set of curves was obtained for each subject. At each stage in the calculations, corrections were applied by the computer for the haemoglobin, arterial saturation, pH and base excess of the subject at the work load in question.

A graph, such as Fig. 1, produced for a subject at one work load makes it possible to insert any one of the three variables $Q$, $V_D$ and $P_{A,CO_2}$ and then read off the other two. For example, if the likely value for $V_D$ is known, the point on the curved line corresponding to this value of $P_{A,CO_2}$:
$V_D$ indicates the $P_{a,CO_2}$ which must have been present to satisfy the Bohr equation and the $Q$ which is calculated by inserting this $P_{a,CO_2}$ into the Fick equation. A similar argument could be applied if $P_{a,CO_2}$ or $Q$ were known instead of $V_D$.

In the present study, we used the graphs produced by the computer to read off two of the three variables $Q$, $V_D$ and $P_{a,CO_2}$ when the third was known as described above. For each work load in each subject five solutions were obtained from the graph using the following expected values as the known variable:

(a) Arterialized ear lobe blood $P_{CO_2}$ fully corrected by the method of Godfrey et al. (1970).
(b) End-tidal $P_{CO_2}$ uncorrected as an alternative to $P_{a,CO_2}$.
(c) End-tidal $P_{CO_2}$ corrected by the formula of Jones, McHardy, Naimark & Campbell (1966) as an alternative to $P_{a,CO_2}$.

(d) $Q$ appropriate to the oxygen consumption ($\dot{V}O_2$) of the work load in question from the relationship obtained by Bevegard, Holmgren & Jonsson (1960) for sitting bicycle exercise.

(e) $V_D$ appropriate to body weight according to the relationship of Radford (1954) with our own modification for the effect of tidal volume (Fig. 2).

The five alternative solutions to the Fick and Bohr equations and the $P_{a,CO_2}$ which they implied for each work load in each subject were used to construct a series of regression equations in which the derived values were compared with the likely solutions. The likely solution for $P_{a,CO_2}$ was taken as the corrected ear lobe $P_{CO_2}$ and used as the independent variable ($X$).
Estimates of $P_{CO_2}$ and exercise calculations

against which the four remaining estimates of $P_{a,CO_2}$ were each regressed as dependent variables ($Y$). The regression coefficient ($B$), the intercept on the $Y$ axis ($M$), the correlation coefficient ($r$) and its significance ($P$) are all given for each of these equations in Tables 1 and 2.

Table 1. Regression equations for rest for arterial $P_{CO_2}$, dead space and cardiac output. $Y$ is the dependent variable which is the parameter in the first column derived graphically from a normal dead space ($V_D$), a normal cardiac output ($\dot{Q}$), end-tidal $P_{CO_2}$ (ET), corrected end-tidal $P_{CO_2}$ after Jones et al. (1966)—(JET), or from ear lobe blood (Blood). $X$ is the independent variable which is the assumed normal value for $P_{a,CO_2}$ based on ear lobe blood $P_{CO_2}$ (Blood), the assumed normal value for dead space ($V_D$), or the assumed normal value for cardiac output based on oxygen consumption ($\dot{Q}$). The symbols are explained in the text.

<table>
<thead>
<tr>
<th>$Y$</th>
<th>$X$</th>
<th>$B$</th>
<th>$M$</th>
<th>$r$</th>
<th>$P$</th>
<th>$n$</th>
<th>SE $Y$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$V_D$ Blood</td>
<td>0.42</td>
<td>19.9</td>
<td>0.29</td>
<td>&lt;0.0250</td>
<td>52</td>
<td>3.7</td>
</tr>
<tr>
<td>Arterial 2</td>
<td>$\dot{Q}$ Blood</td>
<td>0.30</td>
<td>24.9</td>
<td>0.24</td>
<td>&lt;0.0500</td>
<td>51</td>
<td>3.3</td>
</tr>
<tr>
<td>$P_{CO_2}$ 3</td>
<td>ET Blood</td>
<td>0.32</td>
<td>22.1</td>
<td>0.28</td>
<td>&lt;0.0250</td>
<td>52</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>JET Blood</td>
<td>0.40</td>
<td>20.5</td>
<td>0.33</td>
<td>&lt;0.0100</td>
<td>52</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>Blood $V_D$</td>
<td>1.57</td>
<td>-41.9</td>
<td>0.79</td>
<td>&lt;0.0005</td>
<td>69</td>
<td>32.4</td>
</tr>
<tr>
<td>Dead 6</td>
<td>$\dot{Q}$ VD</td>
<td>0.74</td>
<td>21.4</td>
<td>0.55</td>
<td>&lt;0.0005</td>
<td>84</td>
<td>29.3</td>
</tr>
<tr>
<td>space 7</td>
<td>ET VD</td>
<td>0.96</td>
<td>-4.1</td>
<td>0.78</td>
<td>&lt;0.0005</td>
<td>87</td>
<td>20.2</td>
</tr>
<tr>
<td>8</td>
<td>JET VD</td>
<td>0.90</td>
<td>7.1</td>
<td>0.75</td>
<td>&lt;0.0005</td>
<td>87</td>
<td>21.1</td>
</tr>
<tr>
<td>9</td>
<td>Blood $Q$</td>
<td>2.67</td>
<td>-8.1</td>
<td>0.49</td>
<td>&lt;0.0005</td>
<td>66</td>
<td>1.8</td>
</tr>
<tr>
<td>Cardiac 10</td>
<td>$V_D$ Q</td>
<td>1.99</td>
<td>-4.7</td>
<td>0.50</td>
<td>&lt;0.0005</td>
<td>84</td>
<td>1.4</td>
</tr>
<tr>
<td>output 11</td>
<td>ET Q</td>
<td>1.80</td>
<td>-4.4</td>
<td>0.67</td>
<td>&lt;0.0005</td>
<td>84</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>JET Q</td>
<td>1.76</td>
<td>-3.8</td>
<td>0.57</td>
<td>&lt;0.0005</td>
<td>84</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 2. Regression equations for exercise with the same nomenclature as Table 1.

<table>
<thead>
<tr>
<th>$Y$</th>
<th>$X$</th>
<th>$B$</th>
<th>$M$</th>
<th>$r$</th>
<th>$P$</th>
<th>$n$</th>
<th>SE $Y$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$V_D$ Blood</td>
<td>0.75</td>
<td>9.7</td>
<td>0.58</td>
<td>&lt;0.0005</td>
<td>121</td>
<td>3.1</td>
</tr>
<tr>
<td>Arterial 2</td>
<td>$\dot{Q}$ Blood</td>
<td>0.59</td>
<td>16.6</td>
<td>0.44</td>
<td>&lt;0.0005</td>
<td>116</td>
<td>3.6</td>
</tr>
<tr>
<td>$P_{CO_2}$ 3</td>
<td>ET Blood</td>
<td>0.86</td>
<td>3.7</td>
<td>0.61</td>
<td>&lt;0.0005</td>
<td>121</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>JET Blood</td>
<td>0.54</td>
<td>15.3</td>
<td>0.48</td>
<td>&lt;0.0005</td>
<td>121</td>
<td>2.9</td>
</tr>
<tr>
<td>5</td>
<td>Blood $V_D$</td>
<td>0.56</td>
<td>22.1</td>
<td>0.34</td>
<td>&lt;0.0005</td>
<td>153</td>
<td>54.9</td>
</tr>
<tr>
<td>Dead 6</td>
<td>$\dot{Q}$ VD</td>
<td>0.81</td>
<td>37.4</td>
<td>0.45</td>
<td>&lt;0.0005</td>
<td>181</td>
<td>57.3</td>
</tr>
<tr>
<td>space 7</td>
<td>ET VD</td>
<td>0.81</td>
<td>-20.7</td>
<td>0.66</td>
<td>&lt;0.0005</td>
<td>193</td>
<td>31.7</td>
</tr>
<tr>
<td>8</td>
<td>JET VD</td>
<td>-0.42</td>
<td>92.8</td>
<td>-0.31</td>
<td>&lt;0.0005</td>
<td>193</td>
<td>44.5</td>
</tr>
<tr>
<td>9</td>
<td>Blood $Q$</td>
<td>0.97</td>
<td>0.4</td>
<td>0.92</td>
<td>&lt;0.0005</td>
<td>144</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiac 10</td>
<td>$V_D$ Q</td>
<td>0.99</td>
<td>0.2</td>
<td>0.94</td>
<td>&lt;0.0005</td>
<td>182</td>
<td>0.9</td>
</tr>
<tr>
<td>output 11</td>
<td>ET Q</td>
<td>0.97</td>
<td>0.6</td>
<td>0.94</td>
<td>&lt;0.0005</td>
<td>182</td>
<td>0.9</td>
</tr>
<tr>
<td>12</td>
<td>JET Q</td>
<td>0.81</td>
<td>1.1</td>
<td>0.92</td>
<td>&lt;0.0005</td>
<td>182</td>
<td>0.8</td>
</tr>
</tbody>
</table>

In addition the number of points ($n$) from which the data was constructed is given together with the standard error of the estimate of $Y$ about the line (SE $Y$). The same procedure was used for dead space in which case the likely value for $V_D$ used as the independent variable ($X$) was that based on body weight and tidal volume, and for cardiac output the likely value used ($X$) was that based on $V_{O_2}$ as described above. The four regression equations for $V_D$ and for $\dot{Q}$ are also given in Tables 1 and 2.
RESULTS

Using Table 1 (for rest) and Table 2 (for exercise) it was possible to make certain observations about the various alternative methods of calculating $V_D$, $Q$, and $P_{a,CO_2}$.

Dead space

The highest correlation with the likely $V_D$ based on weight was obtained by using the $V_D$ calculated from ear blood $P_{CO_2}$ ($r = 0.79$) or from uncorrected end-tidal $P_{CO_2}$ ($r = 0.78$) at rest (Equations 5 and 7, Table 1). The simplest regression equation was that based on end-tidal $P_{CO_2}$ ($B = 0.96$, $M = -4.1$) implying that the value of $V_D$ calculated from uncorrected end-tidal $P_{CO_2}$ at rest agreed closely with what is predicted from body size (Fig. 3). The error of all estimates of $V_D$ (SE $Y$) was large. As far as exercise was concerned, the correlation coefficients were generally smaller than those at rest and the SE $Y$ were larger, but again the estimate based on uncorrected end-tidal $P_{CO_2}$ was the best (Equation 7, Table 2).

Cardiac output

Unlike $V_D$, the estimations of $Q$ on exercise showed much greater agreement with the expected values than the estimations at rest (Equations 9–12, Tables 1 and 2). Indeed all the correlation coefficients were extremely high on exercise (0.92–0.94) with little to choose
Estimates of $P_{CO_2}$ and exercise calculations

between the four alternative equations and all the SE $Y$ values were between 0.8 and 1.0 l/min. It is particularly important to note the excellent agreement between the $\dot{Q}$ calculated from ear lobe $P_{CO_2}$ or from the $P_{CO_2}$ implied by a normal $V_D$ (Equations 9 and 10, Table 2) with the expected $\dot{Q}$ based on $V_O_2$. The latter relationship is shown in Fig. 4.

![Fig. 4. The relationship between cardiac output calculated from the arterial $P_{CO_2}$ implied by a normal dead space ($\dot{Q}_{emp}$) and the expected cardiac output predicted from oxygen consumption ($\dot{Q}_{expected}$). These results are for exercise.](image)

Arterial $P_{CO_2}$

The comparison between various forms of arterial $P_{CO_2}$ ($Y$) derived from end-tidal $P_{CO_2}$ or implied by the assumption of a normal $\dot{Q}$ or $V_D$, with the measured (and corrected) ear lobe $P_{CO_2}$ ($X$), was poor both at rest and on exercise (Equations 1–4, Tables 1 and 2). Like the equations for $\dot{Q}$ however, the exercise values were rather better than those at rest, the best equations being those based on an assumed normal $V_D$ and on uncorrected end-tidal $P_{CO_2}$ (Equations 1 and 3, Table 2), but even so the SE $Y$ was of the order of 3 mmHg.

DISCUSSION

In order to investigate the various methods of deriving $\dot{Q}$ and $V_D$ from the possible alternatives available in the $CO_2$ transport method of analysis a large number of calculations were necessary. The use of a digital computer to perform these calculations and to draw the graphs not only made the comparisons of this study possible, but also reduced mathematical errors to a minimum and vastly reduced the time spent on calculations.
The difference between the results at rest and on exercise for $V_D$ and $Q$ can be explained by the fact that the arterio–expired $PCO_2$ difference changes relatively little from rest to exercise, while the veno–arterial $PCO_2$ difference widens considerably. The former difference governs the calculation of $V_D$ and being normally small (of the order of 10–15 mmHg), is hence susceptible to analytical errors both at rest and on exercise. The veno–arterial $PCO_2$ difference governing the calculation of $Q$ enlarges from some 6–8 mmHg at rest to some 25–35 mmHg on exercise. Thus $Q$ is highly susceptible to any analytical error at rest but relatively insensitive on exercise.

The above reasoning also explains the somewhat poor results obtained for $V_D$ based on ear blood $PCO_2$ since an error of 2 SD of the difference between true $Pa_{CO_2}$ and ear blood $PCO_2$ (2.6 mmHg) as found by Godfrey et al. (1970) would significantly affect calculations of $V_D$ at rest and on exercise. It also accounts for the poor resting values of $Q$ derived from ear blood $PCO_2$.

Our best results were obtained using end-tidal $PCO_2$ to calculate $V_D$ but we found that the correction factor of Jones et al. (1966) gave poorer correlations (Equation 8, Tables 1 and 2). This is not really surprising since it was derived from studies in adults under conditions rather different from ours—in particular their respiratory rate was lower. Gadhoke & Jones (1969) used this factor in their study but their resulting values for dead space can be shown to be very variable.

Our best results for $Q$ were based on a predicted normal $V_D$. This is helpful in children with normal lungs since $V_D$ increases with weight (Radford, 1954; Tenney & Bartlett, 1967; Levinson, personal communication) and can be predicted with reasonable certainty (Fig. 2). Our results for $Q$ will be discussed more fully later (Godfrey et al., 1970), but the agreement with the predicted $Q$ is encouraging. We did not apply the 'downstream correction' to $PvCO_2$ described by Jones et al. (1967) and Jones, Campbell, Edwards & Wilkoff (1969) but like Dennison et al. (1969) we found the uncorrected value to be more useful.

We conclude that the Indirect (CO$_2$) Fick method for $Q$ gives reliable results on exercise, even in quite small children, virtually independent of the method of estimating $Pa_{CO_2}$. The best method is to calculate $Pa_{CO_2}$ from the Bohr equation using a normal $V_D$ predicted from weight if the lungs are normal. Alternative results based on end-tidal or ear blood $PCO_2$ are acceptable. Calculations of $Q$ at rest are most unreliable. Calculation of $V_D$ from end-tidal or ear blood $PCO_2$ is moderately reliable.

REFERENCES


Estimates of \( \text{PCO}_2 \) and exercise calculations


