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Comparison of Methods to Calculate Cardiac Output Using the CO_2 Rebreathing Method*

Donald H. Paterson and David A. Cunningham

Faculty of Physical Education and Department of Physiology, University of Western Ontario,
London, Ontario N6A 5C1, Canada

Summary. A comparison was made of methods used to calculate cardiac output by the indirect (CO_2) Fick procedure (equilibrium method). Alternative methods for calculation of arterial PCO_2, mixed venous PCO_2, and conversion of gas tension to content were tested. Cardiac output values determined with a "corrected" equilibrium PCO_2, to approximate mixed venous PCO_2, were observed to be closest to cardiac output values determined on similar populations by the dye dilution method. Arterial PCO_2 was best estimated from the Bohr equation using a dead space in exercise from prediction equations in the literature applicable to the populations under study. CO_2 dissociation curves used to derive the veno-arterial CO_2 content difference, were shown to differ considerably. For the present, the curve by McHardy [25], as modified by Jones (personal communication), and similar to the standard Comroe curve [5], was chosen.

Key words: Cardiac output in exercise – Methods for approximating $P\bar{v}CO_2$ and $PaCO_2$ – Comparison of CO_2 dissociation curves.

CO_2 rebreathing methods for measurement of mixed venous PCO_2 allow an indirect, non-invasive method to estimate cardiac output in exercise. The essence of the method is that with rebreathing of an appropriate volume and concentration of CO_2 in O_2, in less than blood recirculation time, an equilibrium plateau of no net CO_2 exchange may be obtained for the CO_2 tension in the bag which is then equal to the alveolar and pulmonary capillary blood tensions, and in turn equal to the CO_2 tension of the mixed venous blood entering the lungs.

The purpose of this study was to detail and compare alternative methods in the calculation of cardiac output by the indirect (CO_2) Fick method. Varied methods and calculations have emerged in the estimation of cardiac output from rebreathing

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methods. $PaCO_2$ has been estimated from alveolar PCO_2 (P_ACO_2) from continuous end-tidal recordings, either without correction [3, 13] or with correction for alveolar-arterial (*A*-*a*) differences [20, 24, 26]. Alternatively, many have solved the Bohr equation for $PaCO_2$ using an assumed normal dead space from established prediction equations. Methods for $P\bar{v}CO_2$ measurement by the equilibrium method of Jones et al. [19] have recently been standardized [21]. However, Jones and others apply a "downstream correction" for the often observed gas to blood PCO_2 difference during rebreathing (the "downstream effect") [4, 7, 15, 16, 18, 19, 22], while Godfrey [14] (mostly working with children) and others [7] do not support this correction. Those estimating $P\bar{v}CO_2$ by the Defares' [6] method do not apply any correction; as this method does not involve the attainment of an equilibrium PCO_2, it is uncertain whether the downstream effect is present. The choice of the oxygenated CO_2 dissociation curve to convert gas tensions to content, also affects the calculated cardiac output. Jones and co-workers employ the McHardy [25] in vitro dissociation curve. Most authors [4, 11, 24] using the Defares' technique employ the Comroe [5] or other standard curves (as cited in [7]). Godfrey and co-workers employed a computer solution of the dissociation curve as described by Godfrey [12]. Rode and Shephard [26] have used an approximate 0.48 slope, assuming linearity of the dissociation curve in the range of interest.

Methods

Studies were made on nine girls, aged 12—13 years, and six adult females, aged 20—24.

Exercise tests were performed on a constant work load bicycle ergometer (Quinton 870), in the upright position, with cycling rates between 55 and 65 rpm. Prior to testing, each subject was familiarized with the procedures of the ergometer test and given experience with the CO_2 rebreathing procedure. Subjects were tested at four steady state work levels ranging from approximately 25—80% of the individual maximum aerobic capacity.

Subjects breathed through a modified Lloyd valve (dead space 38.1 ml). Inspired ventilation was recorded from a dry gas meter, and expired gas was collected in a Tissot (350 l) for subsequent analysis of CO_2 by a rapid response infrared CO_2 analyzer and O_2 by a paramagnetic O_2 analyzer. The gas analyzers were calibrated with known gas mixtures, as established by the micro-Scholander method. Expired gas was sampled continuously at the mouth (tidal gas-peak response of CO_2 analyzer in 0.9 s) for measurement of end-expiratory CO_2 from the mean concentration over the total number of breaths recorded during 1 min (range 13—64). Heart rate was continuously monitored from a bipolar chest lead (CM5). Inspired volumes, cardiac frequency, mixed expired CO_2 and O_2, and end-tidal CO_2 were continuously recorded on an eight channel recorder.

Oxygen consumption and carbon dioxide output were calculated and expressed at STPD. $PaCO_2$ was estimated from corrected mean end-tidal concentrations [Eq. (1)], or from prediction formulae for respiratory dead space with derivation of $PaCO_2$ ($= P_ACO_2$) from the Bohr equation, [adults, Eq. (2), children Eq. (2)–(5)]. Each method of calculation, as shown below, is designated by the author's initial.

(1) Corrected end-tidal (*J* (*ET*)). Mean end-tidal CO_2 concentrations during the 1-min collection were corrected as follows:

$PaCO_2$ (mm Hg) = end-tidal (alveolar) PCO_2 (mm Hg) + 4.43 + 0.034 f − 0.00226 V_T (ml) − 0.085 P_ECO_2 (mm Hg) (Jones, personal communication, 1971) where $PaCO_2$ = arterial PCO_2; V_T = tidal volume; f = respiratory frequency; and P_ECO_2 = mixed expired PCO_2.

(2) Jones dead space prediction (*J* (*VD*)).

V_D (ml) = 138.4 + 0.077 V_T (ml) [20] where V_D = personal dead space.

(3) Godfrey dead space prediction (*G* (*VD*)).

V_D (ml) = 1.54 weight (kg) + 0.049 V_T (ml) + 2.0 [13].

(4) Andrew dead space prediction (A (VD)).
V_D (ml) = $-21.8 + 0.77$ height (cm) + $0.11\ V_T$ (ml)
(Andrew, personal communication, 1970).

(5) Shephard dead space prediction (S (VD)).
V_D (ml) = $0.285\ V_T$ (ml) -64.0 [27].

The latter three equations were derived from studies in children. The end-tidal correction and dead space prediction of Jones were developed with adult subjects.

$P\bar{v}CO_2$ was estimated and analyzed according to the methods described by Jones et al. [19, 21]. At the end of a normal expiration subjects rebreathed from a five litre bag filled with an appropriate volume ($1\frac{1}{2}$ times tidal volume) and concentration of CO_2 (range 8–15%) in balance O_2. The subject rebreathed from the bag for 10–15 s. With suitable gas mixtures [19, 21], and a respiratory frequency of one cycle per second, an equilibrium PCO_2 between lung and bag is observed as early as 6 s with the equilibrium plateau breaking with recirculation at 10–12 s. For calculations of cardiac output $P\bar{v}CO_2$ was calculated either with the downstream correction (D.C.): $P\bar{v}CO_2$ (mm Hg) = rebreathe PCO_2 (mm Hg) – (0.24 rebreathe PCO_2 (mm Hg) – 11.0) (Jones, personal communication, 1971), or with the downstream correction omitted (no D.C.).

The veno-arterial CO_2 content difference was calculated from the arterial and venous gas tensions by both of the following descriptions of the oxygenated CO_2 dissociation curve:

(1) Solving the following equation to determine arterial and venous contents separately
$\log_e CCO_2$ (ml/100 ml) = $0.396 \log_e PCO_2$ (mm Hg) + 2.4
(Jones, personal communication, 1971). This method is designated by J; or

(2) Solving the mathematical description of the McHardy [25] relationships as presented by Godfrey [12]. This method of calculation is designated by G. The calculations are described as follows:

$C\bar{v}\text{-}a\ CO_2 = CaCO_2 \times (10.0^{(S \times \log_{10}\ (P\bar{v}CO_2/PaCO_2))} - 1)$ where: (1) S corrects for acid base status and the effect of Hb on the slope of the dissociation curve, and (2) $CaCO_2$ is derived from plasma CO_2, CCO_2 (plasma) = $2.226 \times 0.0307 \times PCO_2 \times (1.0 + (1.0 + 10.0^{(pH-pK)})$ and $CaCO_2$ (blood) = CCO_2 (plasma) $\times (1.0 - (K_1 \times K_2 \times K_3))$, where K_1, K_2 and K_3 are factors related to Hb, saturation and pH.

Appropriate corrections for individual haemoglobin were made and arterial oxygen saturation assumed to be 97%.

Cardiac output ($\dot{Q}$) was then calcuted from the CO_2 output ($\dot{V}CO_2$) and a value for the veno-arterial CO_2 content difference by application of the Fick principle. Results were calculated with a digital computer program adapted from Godfrey [12], (and personal communication, 1971).

Results

Cardiac outputs calculated with the downstream correction were 13–16% higher than results with the downstream correction omitted. This difference applied to both children and adults for the entire work range studied (Table 1).

Use of the Godfrey expressions [12] for conversion of partial pressures to veno-arterial content difference resulted in cardiac outputs 7–9% higher than those calculated using the CO_2 dissociation curve provided by Jones (personal communication, 1971). This difference existed for both children and adult data, throughout the work range studied (Table 1).

The method of $PaCO_2$ determination also considerably influenced the derived cardiac outputs. In children cardiac output differed by as much as 15–20% depending on which of the five $PaCO_2$ estimates was used. $PaCO_2$ from the G (VD) prediction equation yielded the lowest cardiac outputs throughout the work range studied. The S (VD) equation for $PaCO_2$ estimation resulted in the highest cardiac outputs for moderate and heavy work. The J (ET), J (VD) and A (VD) equations for $PaCO_2$

Table 1. Cardiac output by different methods of calculation with comparison data from previous dye dilution studies

Method of calculation		Children			Adults		
		O_2 uptake level (l/min)			O_2 uptake level (l/min)		
		1.0	1.5	2.0	1.0	1.5	2.0
G No D.C.	*J* (*ET*)	8.6	10.5	12.5	9.5	11.5	13.4
	J (*VD*)	8.6	10.6	12.5	9.0	11.3	13.5
	G (*VD*)	7.7	10.0	12.4			
	A (*VD*)	8.4	10.5	12.7			
	S (*VD*)	8.2	10.8	13.4			
G D.C.	*J* (*ET*)	9.8	12.1	14.3	10.8	13.2	15.5
	J (*VD*)	10.0	12.2	14.5	10.2	13.1	16.0
	G (*VD*)	8.6	11.5	14.3			
	A (*VD*)	9.6	12.2	14.9			
	S (*VD*)	9.5	12.8	16.0			
J No D.C.	*J* (*ET*)	8.2	9.8	11.4	9.0	10.6	12.1
	J (*VD*)	8.3	9.9	11.4	8.3	10.5	12.8
	G (*VD*)	6.8	8.9	10.9			
	A (*VD*)	7.9	9.9	11.8			
	S (*VD*)	7.8	10.6	13.3			
J D.C.	*J* (*ET*)	9.3	11.2	13.1	10.2	12.1	14.0
	J (*VD*)	9.5	11.3	13.1	9.3	12.1	14.9
	G (*VD*)	7.5	10.0	12.5			
	A (*VD*)	9.0	11.3	13.6			
	S (*VD*)	8.9	12.2	15.6			
Dye dilution studies							
Eriksson et al. [9]		9.8	12.8	15.2			
Eriksson and Koch (training study) [10]		9.3 to 9.6	11.6 to 12.4	13.4 to 14.6			
Åstrand et al. [2]					10.5	12.3	14.1
Ekelund et al. [8]					10.8	13.4	16.6
Kilbom and Åstrand [23]					9.6	12.0	14.6
Stenberg et al. [28]					11.5	13.9	16.3

Cardiac outputs at each of the given oxygen consumption levels were calculated by prediction from linear regression equations of $\dot{Q}$ to $\dot{V}O_2$, for each of the methods of calculation in children and adults. The standard deviation of a predicted cardiac output averaged 2.3 (range 1.7 to 3.3) for children, and 2.5 (range 1.8 to 3.1) for adults. The coefficient of correlation for $\dot{Q}$ to $\dot{V}O_2$ averaged 0.87 for children, and 0.89 for adults

estimation resulted in cardiac output estimations which differed from each other by less than 5% on average (Table 1). In adults, the *J* (*VD*) and *J* (*ET*) methods for $Pa\mathrm{CO}_2$ estimation resulted in slightly different slopes for the $\dot{Q}$ to $\dot{V}O_2$ line. In light work cardiac output was 7.6% higher using the end-tidal $Pa\mathrm{CO}_2$ estimation. In moderate and heavy work the choice of $Pa\mathrm{CO}_2$ estimate resulted in cardiac outputs differing from each other by less than 4% (Table 1).

Discussion

Estimates of CO_2 rebreathing cardiac outputs were largely influenced by the methods of calculation of $PaCO_2$, $P\bar{v}CO_2$, and conversion of these partial pressures to a veno-arterial content difference. Thus, careful attention to the methods used in estimating cardiac output is required for meaningful data comparisons or physiological interpretation.

Present data were compared to dye dilution cardiac outputs published for similar sample groups. For children, cardiac outputs reported by Eriksson and associates [9, 10] were used. Adult results were compared to dye dilution data reported for young females exercising in the upright posture [2, 8, 23, 28] (Table 1).

Ignoring differences in the method of $PaCO_2$ estimation, and tension to content conversion, all data calculated without the downstream correction (no D.C.) were consistently lower than the reference cardiac outputs (Table 1). The necessity of the downstream correction for estimation of $P\bar{v}CO_2$ in both children and adults was not surprising. The downstream effect has been shown to exist in children in similar magnitude to that found in adults [15], and the existence of the downstream factor has been supported by a number of independent authors seeking its explanation [4, 7, 15, 16, 18, 19, 22].

The differences in calculated cardiac output which resulted from the method used for conversion of tension to content were unexpected. Although the dissociation curves at "normal" $PaCO_2$ (40 mm Hg) were found quite similar, at $PaCO_2$

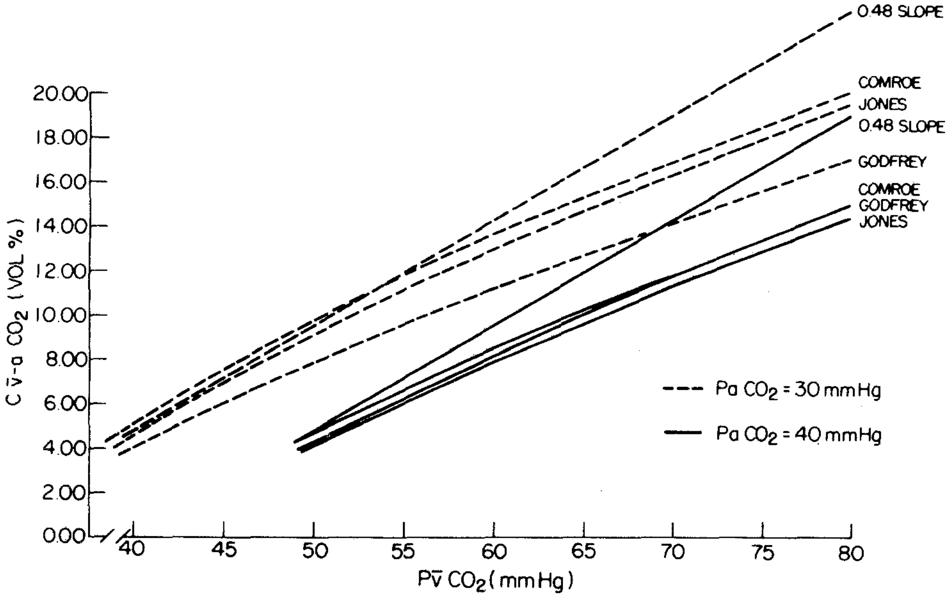

Fig. 1. $C\bar{v}\text{-}aCO_2$ difference plotted for a given mixed venous PCO_2 with an arterial PCO_2 of 30 mm Hg (dashed lines) or arterial PCO_2 of 40 mm Hg (solid lines). The curves from Comroe [7], equations of Godfrey [15] and Jones (personal communication, 1971), and curves of 0.48 slope are labelled. All curves were calculated for an arterial saturation of 97% and haemoglobin of 15 g/100 ml

30 mm Hg the Godfrey [12] curve gives a content difference 20 ml/l lower than the Jones or Comroe curves, producing higher cardiac outputs (Fig. 1). The difference in the CO_2 dissociation curve derived by Godfrey [12] from rearrangement of the McHardy equation was not explained. Therefore, we have preferred to use the standard Comroe curve [5], or the McHardy [25] curve as described by Jones. Possibly Godfrey and associates in applying the Godfrey dissociation curve to calculations in children have raised their cardiac outputs, and for this reason, the use of the downstream correction which further raises cardiac output has not been employed by these workers. The use of a 0.48 slope [26], which relates the CO_2-partial pressure changes (mm Hg) to content (in vol-%), is approximately valid for the range of 30–55 mm Hg (Fig. 1). In the normal range of exercise $P\bar{v}CO_2$ a 0.48 slope produces high content differences and low cardiac outputs.

Compared to Eriksson's data [9, 10], $PaCO_2$ in the young girls was best estimated from the *A* (*VD*), *J* (*VD*) or *J* (*ET*) predictions (Table 1). The *A* (*VD*) equation was derived in studies of children aged 9–17 years and for this reason was accepted as the "best overall" dead space equation to estimate $PaCO_2$. The *J* (*VD*) equation (derived in an adult sample) appeared acceptable in the children studied, who were slightly taller than subjects investigated by Godfrey et al. [13]. These authors reported poor results for cardiac output when the *J* (*VD*) equation was applied in their children.

The *J* (*VD*) prediction produced acceptable results in adults compared with the reference range (Table 1). The Jones dead space prediction approximates the Asmussen-Nielsen [1] data of a 7 ml increase in dead space per 100 ml tidal volume increase. Thus, in contrast to the suggestion of others [3, 13] the Asmussen-Nielsen [1] data, as used by many authors, would apparently give cardiac output results in the expected range for the populations studied.

The use of a corrected end-tidal estimate for $PaCO_2$ deserves comment. The end-tidal sampling system employed in the present study may not have allowed for complete breath to breath separation of the expired CO_2 especially where breathing rates were high. Thus, during heavy work, end-tidal PCO_2 may be underestimated and cardiac outputs too low. Several authors who studied women [21] and children [4, 17] have supported the use of corrected end-tidal PCO_2 estimates in the calculation of cardiac output. Our experience with a narrow short sampling line supports the validity (though greater variance) of corrected end-tidals.

In conclusion, the calculations producing most reasonable cardiac outputs were those estimating $PaCO_2$ from the Andrew dead space equation (*A* (*VD*)) for children and Jones dead space prediction (*J* (*VD*)) for adults, with $P\bar{v}CO_2$ corrected for the downstream effect (D.C.), and veno-arterial content difference calculated from the modified McHardy relations (*J*). The regression equations for $\dot{Q}$ to $\dot{V}O_2$ from these calculations were as follows:

children: $\dot{Q} = 4.66\ \dot{V}O_2 + 4.32 \pm 2.30, r = 0.87$
adults: $\dot{Q} = 5.63\ \dot{V}O_2 + 3.64 \pm 2.49, r = 0.89.$

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