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The Consistency of Cardiac Output Measurement (CO_2 Rebreathe) in Children During Exercise*

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Summary. Exercise cardiac output ($\dot{Q}$) was determined using the CO_2 rebreathing equilibrium method. Five repeat tests in 12 boys and two tests over a 4 month interval in 47 boys were performed. Regression equations to predict $\dot{Q}$ from $\dot{V}_{O_2}$ were in close agreement with dye dilution studies in boys (Eriksson and Koch 1973). Group mean data were reproducible from trial to trial. The day-to-day variability of $\dot{Q}$, with a coefficient of variation of 7–8%, was found to be higher than when the CO_2 method has been applied in adults. This greater variability was related, in part, to a larger biological variation in children as depicted in such relatively simple measures as submaximal exercise heart rate. The larger variability was also related to inaccuracies in the methods of P_{aCO_2} estimation in children. Estimation from end-tidal CO_2 concentrations requires further research to establish a correction for the alveolar-arterial gradient during exercise in children. Estimation of the child's dead space in exercise, with subsequent derivation of P_{aCO_2} from the Bohr equation, also could be improved. Nevertheless, $\dot{Q}$ estimates in children exercising above $\dot{V}_{O_2}$ 1.0 l · min^{-1} showed a day-to-day and long term stability acceptable for use in research and clinical studies.

Key words: Cardiac output – Children – Intra-individual variability – Arterial P_{CO_2}

Introduction

The indirect CO_2 Fick method for the measurement of cardiac output ($\dot{Q}$) during exercise has been used in studies with adults (Jones et al. 1967; Ferguson et al. 1968; Clausen et al. 1970; Zeidifard et al. 1972; Knowlton and Adams 1974) and

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children (Gadhoke and Jones 1969; Bar-Or et al. 1971; Godfrey et al. 1971; Paterson and Cunningham 1976). In adults the variability is comparable to dye dilution or direct Fick method (Ferguson et al. 1968; Godfrey et al. 1972; Zeidifard et al. 1972; van Herwaarden et al. 1980), however the variability has not been determined for children.

The use of invasive techniques for measurement of $\dot{Q}$ is unjustifiable in healthy children. The CO_2 rebreathing method appears to give acceptable values in children (Paterson and Cunningham 1976); nevertheless its applicability has been criticized. The estimation of the CO_2 content of mixed venous blood ($P_{\bar{v}CO_2}$) may be influenced by shorter recirculation times in exercising children compared with adults (Cumming 1978). The estimate of arterial CO_2 tension (P_{aCO_2}) from end-tidal gas is subject to error in those children who have erratic breathing patterns. Alternatively, P_{aCO_2} may be derived from knowledge of the dead space; its estimation requires a suitable equation for exercising children. These problems may reduce the consistency of the measurement in children. The purposes of this study were: to describe the day-to-day and long-term (4 months) variability of $\dot{Q}$ during exercise, and to compare the $\dot{Q}$ using the end-tidal and dead space methods to determine P_{aCO_2} in children.

Material and Methods

Twelve 10–14 year old boys (mean age 11.6 ± 1.7 year; height 150.9 ± 11.6 cm; weight 40.7 ± 6.9 kg) were recruited. Each boy completed five cycle ergometer tests within a 2–3 week period, with an interval between tests of 48–72 h. The boys did not eat 2 h prior to the test, each was performed at the same time of day (after school). Each boy performed at the same three work rates at each of the five tests. Steady state was defined by a minute-to-minute heart rate fluctuation of less than 5 beats; usually this was achieved after 3.5 min of work, data were collected between the fourth and sixth minutes. Successive exercise levels were separated by 2–3 min of loadless pedalling. During two of the tests (3 and 5), subjects continued to pedal, after the normal third work rate, at progressively increased work rates (16.3 watts $\cdot$ min^{-1}) to exhaustion. $\dot{V}_{O_2}$ max, taken as the highest oxygen uptake found on either of these tests, averaged 57.9 ± 1.2 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} (2.38 ± 0.52 l $\cdot$ min^{-1}).

In addition, 47 9–11 year old boys (age 10.6 ± 0.3 year; height 141.8 ± 5.6 cm; weight 35.0 ± 5.4 kg) performed two $\dot{V}_{O_2}$ max tests, 4–5 months apart. The $\dot{V}_{O_2}$ max was 48.8 ± 0.8 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} (1.72 ± 0.38 l $\cdot$ min^{-1}).

All tests were performed in a laboratory with a dry bulb temperature of 20–23° C, and humidity 37–59%. Subjects breathed through a valve with a dead space of 76.6 ml (Koegel E 1974). Inspired volume was measured with a dry gas meter, expired gas was stored in a 350 l Tissot spirometer for analysis of CO_2 using a rapid response infrared analyzer and O_2 by a paramagnetic analyzer. Analyzers were calibrated with known gas mixtures as established by the micro-Scholander method. Heart rate (f_h) was continuously monitored from a bipolar chest lead. In addition expired gas was sampled continuously at the mouth and end-expiratory CO_2 was calculated from the mean concentration of all breaths (range 14–58) during the final minute of each steady state exercise. Immediately following this, subjects performed a 10–12 s CO_2 rebreathe manoeuvre as described by Jones et al. (1975).

P_{aCO_2} was estimated from corrected end-tidal concentration [P_{aCO_2} (mm Hg) = P_{ETCO_2} (mm Hg) + 4.43 + 0.034 f_b − 0.00226 VT (ml) − 0.085 P_{ECO_2} (mm Hg), Jones et al. 1975], or from a prediction formula for respiratory dead space in children [VD (ml) = −21.8 + 0.77 height (cm) + 0.11 VT (ml), Paterson and Cunningham 1976] with derivation of P_{aCO_2} from the Bohr equation. $P_{\bar{v}CO_2}$ was estimated according to the method described by Jones et al. (1967, 1975), with the downstream correction [$P_{\bar{v}CO_2}$ (mm Hg) = rebreathe P_{CO_2} (mm Hg) − 0.24 rebreathe P_{CO_2} (mm Hg)

– 11.0]. The veno-arterial content difference was calculated from the oxygenated CO_2 dissociation curve assuming an arterial saturation of 97%, and making appropriate corrections for individual haemoglobin (Paterson and Cunningham 1976).

In the study of five repeat tests on 12 subjects, steady state cardiovascular data were expressed at oxygen uptakes of 1,000, 1,250, and 1,500 ml · min^{-1}, by interpolation of the data.

Repeated measures analyses of variance were used to assess differences in the means of the five trials and to compare $\dot{Q}$ calculated by the end-tidal ($\dot{Q}_{ET}$) and dead space ($\dot{Q}_{VD}$) methods for the estimation of P_{aCO_2}.

Regression equations for $\dot{Q}$(ET)–$\dot{V}_{O_2}$ and $\dot{Q}$(VD)–$\dot{V}_{O_2}$ were calculated using data at the measured $\dot{V}_{O_2}$ (three exercise levels) for each of five tests in 12 subjects (180 data points). Thus, these regression lines include both the inter- and intra-individual variation.

Regression of $\dot{Q}$–$\dot{V}_{O_2}$ were also calculated for each individual (15 data points). The per cent differences between observed values and regression values were then calculated (SE_d) to represent intra-individual variation (McDonough and Danielson 1974).

In the duplicate study (4–5 month interval), values of $\dot{Q}_{ET}$ and f_h at $\dot{V}_{O_2}$ 1,100 and 1,500 ml · min^{-1} were used. Student's *t*-tests for paired observations were used to assess differences between trials. Intra-individual variation was assessed using the $SE_d = \sqrt{d^2/2k}$, where d equals difference in k pairs.

Results

Reproducibility of Group Means

Cardio-respiratory variables at each of the three $\dot{V}_{O_2}$ levels were reproducible from trial to trial ($p > 0.05$). A significant overall trial effect (F ratio) was observed only for $\dot{Q}_{VD}$ at $\dot{V}_{O_2}$ 1,500 ml · min^{-1}; however post-hoc analysis showed there were no significant differences between trials (Scheffé 1959). Also, there was no systematic trend across trials in the inter-individual coefficient of variation of $\dot{Q}$ (Fig. 1).

For the tests separated by the 4 month interval no significant difference was found for the $\dot{Q}$ at either of the power outputs. At 1,100 ml · min^{-1} the $\dot{Q}$ and f_h values were: 9.65 and 9.84 l · min^{-1}, and 150 and 153 beats · min^{-1} respectively, and at 1,500 ml · min^{-1} they were 11.56 and 11.46 l · min^{-1}, and 181 and 181 beats · min^{-1}, respectively.

Intra-Individual (Day-to-Day) Variability

The coefficients of variation of $\dot{Q}$ for repeated trials are shown in Table 1 and for f_h in Table 2. The variability in f_h did not appear to contribute to variability of $\dot{Q}$, as the calculated SV showed a coefficient of variation similar to that for $\dot{Q}$.

Among the variables in the CO_2 Fick equation for calculation of $\dot{Q}$, the coefficients of variation were in the range of 3–6% (Table 3). Nevertheless, while both $P_{\bar{V}CO_2}$ and P_{aCO_2} (both end-tidal and dead space methods) showed 3 and 5% coefficients of variation, respectively, the $P_{\bar{V}\text{-}aCO_2}$ difference showed an 8–9% coefficient of variation (Table 3).

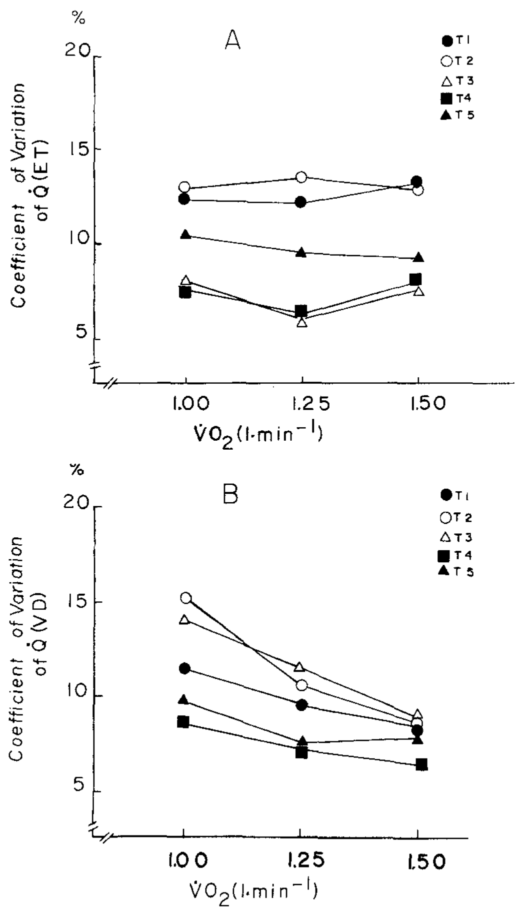

Fig. 1. Inter-individual coefficient of variation of $\dot{Q}$ at a given $\dot{V}_{O2}$ on each of the five repeat tests. **A** $\dot{Q}_{ET}$ vs $\dot{V}_{O2}$, **B** $\dot{Q}_{VD}$ vs $\dot{V}_{O2}$

Table 1. Mean cardiac output using end-tidal $\dot{Q}$(ET) or dead space methods $\dot{Q}$(VD) for P_{aCO2} determinations and cofficient of variation (CV) (CV = SD/mean · 100%)

	$\dot{V}_{O2}$ level (ml · min^{-1})[a]		
	1,000	1,250	1,500
$\dot{Q}$(ET) l · min^{-1}	9.1	10.7	11.1
CV (%)	8.2	6.6	6.9
$\dot{Q}$(VD) l · min^{-1}	8.7	10.2	11.6
CV (%)	8.5	7.2	7.0

[a] $\dot{V}_{O2}$ levels of 1,000, 1,250, 1,500 ml · min^{-1} represented relative intensities of 44 ± 9, 55 ± 11, and 65 ± 13 percent of $\dot{V}_{O2}$ respectively

Intra-Individual (4 Month) Variability

Variability of $\dot{Q}$ and f_h over the long-term was only slightly higher than the day-to-day variability: the coefficients of variation of the $\dot{V}_{O2}$ at 1,100 ml · min^{-1} and 1,500 ml · min^{-1}, were 9.7 and 9.2%, respectively and of f_h was 6%.

Table 2. Means and cofficient of variation (CV) for heart rate (f_h) and stroke volume (SV)

	$\dot{V}_{O2}$ level ($ml \cdot min^{-1}$)		
	1,000	1,250	1,500
f_h (min^{-1})	132	148	162
CV (%)	6.0	4.6	4.3
SV (ET) (ml)	69	69	69
CV (%)	8.5	7.2	8.0
SV (VD) (ml)	67	69	72
CV (%)	10.8	9.5	8.8

Table 3. Mean values and cofficient of variation (CV) of the variables used in the calculation of cardiac output

	$\dot{V}_{O2}$ level ($ml \cdot min^{-1}$)		
	1,000	1,250	1,500
A) Variables used in calculation of $\dot{Q}$(ET) and $\dot{Q}$(VD)			
$\dot{V}_{CO2}$ ($ml \cdot min^{-1}$)	876	1,123	1,377
CV (%)	5.6	5.4	5.6
$P_{\bar{V}CO2}$ (mm Hg)	60.9	63.3	65.9
CV (%)	3.3	3.2	3.3
B) Variables used in calculation of $\dot{Q}$ by end-tidal and by dead space methods			
$\dot{Q}$(ET)			
P_{ETCO2} (mm Hg)	35.9	35.4	34.4
CV (%)	5.6	5.1	5.2
P_{aCO2} (mm Hg)	36.7	35.8	35.5
CV (%)	4.6	4.8	5.3
$P_{\bar{V}\text{-}aCO2}$ (mm Hg)	23.9	27.8	31.4
CV (%)	9.0	8.3	8.6
$\dot{Q}$(VD)			
VD (ml)	207	219	231
CV (%)	4.5	3.8	3.8
P_{aCO2} (mm Hg)	35.7	35.7	35.8
CV (%)	5.4	5.1	5.2
$P_{\bar{V}\text{-}aCO2}$ (mm Hg)	24.3	27.6	30.5
CV (%)	9.0	8.2	7.6

Method of P_{aCO2} Estimation

$\dot{Q}$(ET) and $\dot{Q}$(VD) were not significantly different at the same $\dot{V}_{O2}$ levels. Further, the coefficients of variation were similar for the two methods of $\dot{Q}$ determination (Table 1). Regression equations for the prediction of $\dot{Q}$ for the two methods were:

$$\dot{Q}_{ET}\ (l \cdot min^{-1}) = 4.23\ \dot{V}_{O2}\ (l \cdot min^{-1}) + 4.71\ (SEE\ 1.17,\ r = 0.82)$$

and

$$\dot{Q}_{VD}\ (l \cdot min^{-1}) = 5.48\ \dot{V}_{O2}\ (l \cdot min^{-1}) + 3.25\ (SEE\ 1.12,\ r = 0.89).$$

P_{aCO_2} showed a slight decline with increasing $\dot{V}_{O_2}$ when the end-tidal estimate was used, while the dead space estimate resulted in a constant P_{aCO_2} with increasing $\dot{V}_{O_2}$ (Table 3).

Discussion

The $\dot{Q}$ values of the present study were in close agreement with dye dilution results in boys aged 12 years (Eriksson and Koch 1973). At $\dot{V}_{O_2}$ 1.5 $l \cdot min^{-1}$ the dye $\dot{Q}$ was 11.5 $l \cdot min^{-1}$; regressions of the present study yielded a $\dot{Q}$(ET) of 11.1 $l \cdot min^{-1}$ (and 11.6 $l \cdot min^{-1}$ for the 47 boys) and $\dot{Q}$(VD) of 11.5 $l \cdot min^{-1}$.

Variability statistics of $\dot{Q}$ measurement in exercise reported by others include per cent error of a single estimate (with measures at repeated steady state work rates), or the day-to-day variation from SE_d (for duplicates) and coefficient of variation (for repeated trials). These statistics have yielded similar variability data. The variability of direct methods has been reported to be as low as 4% (McDonough and Danielson 1974), but most investigators find values of 5–8% in adults and children (Clausen et al. 1970; Eriksson and Koch 1973; see Godfrey 1974). For CO_2 rebreathing methods, variability is at best 4–5% (Ferguson et al. 1968; Godfrey and Wolf 1972; Knowlton and Adams 1974), but usually between 5–7% (Clausen et al. 1970; Zeidifard et al. 1972). It appeared to be similar in children (5.7%) (Zeidifard et al. 1972) though the number (3) of subjects studied was inadequate and the age range different from the present study. The 7–8% coefficient of variation for exercise $\dot{Q}$ measures in young boys of the present study is greater than that found in adults.

An alternate method, for the study of intra-individual variability, is based on the difference between the observed and estimated regression values. The standard errors of these differences were 5.6% for $\dot{Q}$(ET) and 5.9% for $\dot{Q}$(VD). For adults a value of 4.1% was reported using the direct Fick method (McDonough and Danielson 1974). The variability of $\dot{Q}$ estimates in children in exercise above 1.0 $l \cdot min^{-1}$ $\dot{V}_{O_2}$, is acceptable for use in research and clinical studies. Further, the measurements are stable over a period of time and thus valuable in longitudinal intervention studies to observe changes in $\dot{Q}$ (SV and f_h).

The larger variability of $\dot{Q}$ in children compared with adults was accounted for in part by greater biological changes in the submaximal exercise response (a variability of 4–6% in f_h and 7% in $\dot{V}_E$ compared to 2–3% in f_h and 4% in $\dot{V}_E$, McDonough and Danielson 1974; Jones et al. 1975); the present study also has indicated where future research might improve the consistency of $\dot{Q}$ measurements in children.

Variability in P_{aCO_2} and $P_{\bar{v}CO_2}$ was no larger than for technically easier determinations of $\dot{V}_{CO_2}$ (5–6%) or f_h (4–6%). However, variation of P_{aCO_2} and $P_{\bar{v}CO_2}$ within a subject were not necessarily in the same direction (both higher or both lower on a given day); hence, $P_{\bar{v}\text{-}aCO_2}$ showed an 8–9% coefficient of variation.

The variability in $P_{\bar{v}CO_2}$ was small (3%) and similar to that found in adults (Godfrey and Wolf 1972; van Herwaarden et al. 1980). The value of using the downstream correction in deriving valid absolute values of $\dot{Q}$ is apparent in the present study as well as our previous data (Paterson and Cunningham 1976). Further, research in this area is often designed to make comparisons with older subjects, hence a constant protocol across ages seems appropriate.

End-tidal estimates of P_{aCO_2} had a coefficient of variation of only 4–5%. Thus the erratic breathing patterns of some children, and resultant difficulty in deriving a mean end-tidal gas concentration, was not a major problem in the age group studied. However, correction of P_{ETCO_2} to better estimate P_{aCO_2} did indicate a physiologically incorrect alveolar-arterial gradient. The end-tidal correction has been investigated in adults (Jones et al. 1966, 1975), but may not apply to children (Godfrey and Davies 1970). In this study, with the higher breathing frequency and lower tidal volumes of children compared with adults, use of the correction formula slightly increased the end-tidal concentrations. Further research is needed to indicate the $P_{ETCO_2} - P_{aCO_2}$ relationships in children during exercise.

Dead space estimates of P_{aCO_2} also had a coefficient of variation of only 5%, as in adults (van Herwaarden et al. 1980). Equations to estimate dead space in exercise for adults indicate an increase of 7 or 8 ml of dead space per 100 ml increase of VT from rest through exercise (from Asmussen-Nielson or Jones, as cited in Jones et al. 1966). The equation used to estimate the child's dead space in exercise indicated an increase of VD averaging 13 ml $\cdot$ 100 ml^{-1} increase of tidal volume. Godfrey (1974), on the other hand, estimated that dead space in children increased by 5 ml $\cdot$ 100 ml^{-1} VT increase. Thus the dead space at $\dot{V}_{O_2}$ 1.5 l $\cdot$ min^{-1} would be approximately 130 ml according to Godfrey (1974), but 230 ml according to the estimate used in this study. Use of the Godfrey VD estimate in the present study would yield lower P_{aCO_2} estimates (by 2–3 mm Hg) and lower $\dot{Q}$. The P_{aCO_2} values derived from the dead space equation used in the present study did correspond with previous literature. P_{aCO_2} of children exercising at $\dot{V}_{O_2}$ 1.5 l $\cdot$ min^{-1} was 36 mm Hg using arterial sampling (Eriksson et al. 1971). Using arterialized blood determinations Beaudry et al. (1967) reported a value of 35 mm Hg in light exercise and Godfrey et al. (1971) found 35 mm Hg at $^2/_3$ maximum exercise. Although Eriksson et al. (1971) showed a drop in P_{aCO_2} from moderate to maximum exercise (35–29 mm Hg) it is unlikely that this fall in P_{aCO_2} (indicating alveolar hyperventilation) occurs until exercise progresses beyond moderate intensity (> 70% $\dot{V}_{O_2}$ max), (Godfrey 1974; Jones et al. 1975). The greater variability of $\dot{Q}$ in children thus appeared to be associated with inaccuracies of the estimates of P_{aCO_2}.

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