

Haemodynamics in children during rest and exercise: methods and normal values

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ABSTRACT: Measuring haemodynamic performance in children is either invasive, and thus unacceptable, or noninvasive when the measured variable is often remote from the true variable. Measuring only maximum performance variables relies too heavily on motivation, especially in disease groups. We describe a method for the measurement of haemodynamic performance using respiratory mass spectrometry during rest, exercise and recovery therefrom.

One hundred and six healthy children (55 male, 51 female) aged 8–16.9 yrs underwent an identical exercise protocol. Following studies at rest, they initially bicycled at $25 \text{ W}\cdot\text{m}^{-2}$, increasing every 3 min by $15 \text{ W}\cdot\text{m}^{-2}$ until exhaustion, after which measurements were made during recovery. Effective pulmonary blood flow, stroke volume, oxygen consumption, arteriovenous oxygen difference and functional residual capacity (FRC) together with estimates of pulmonary capillary blood volume and transit time were assessed at every exercise stage using inert gas rebreathing techniques.

Haemodynamic performance is highly dependent on surface area, age, gender and pubertal stage. Many parameters, for example transfer factor, demonstrate pubertal stage-dependent differences at identical workloads even after correction for size. Females have a lower capillary blood volume at rest compared to age and size-matched males, but it is equalized during exercise. FRC unexpectedly rose with exercise, and peak exercise was associated with a falling stroke volume in 91% (95% CI 84–96%) of children, a possible demonstration of Starling's law of the heart. Oxygen pulse (oxygen consumption/cardiac frequency) is a very poor marker for pulmonary blood flow.

Normal values are provided for all haemodynamic parameters for rest and every exercise stage for all subgroups of children. This should allow accurate comparison of normal and disease groups in future.

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Innumerable papers describe values for cardiopulmonary variables in children during rest and exercise using a wide variety of protocols and these have been summarized by JAMES *et al.* [1]. The majority measure cardiac frequency (f_C), oxygen consumption ($V'O_2$), carbon dioxide production ($V'CO_2$), and respiratory frequency (f_R) with standards quoted for peak $V'O_2$, f_C , anaerobic threshold and ventilatory threshold. From these surrogate markers, inferences are often made about cardiac performance. There are few direct catheter measurements of cardiac output (\bar{Q}) in healthy children [2–4]. Catheterization is nowadays unacceptable in healthy children and the data collected under such a stress bear little resemblance to normal life. Noninvasive measures of effective pulmonary blood (Q^{eff}) flow are only available in resting children [5], but during exercise a $Q^{\text{eff}}/V'O_2$ linear equation is frequently used [6, 7]. Such a linear relationship is unlikely [8]. There are few paediatric data on stroke volume, and none concerning gas transfer during exercise. There is little data on how children recover from exercise.

It is doubtful whether normal values of variables at "maximum" exercise are useful as the concept of a maxi-

mum will depend on the motivation of the child and the exercise protocol rather than some physiological plateau. It is, therefore, desirable to know haemodynamic performance at defined submaximal levels of exercise so that comparison between normals and disease groups is possible, regardless of motivation.

We therefore present a method for the simultaneous assessment of cardiopulmonary haemodynamics using noninvasive respiratory mass spectrometry during rest, exercise and recovery.

Methods

The study received approval from the Royal Brompton Hospital ethics committee and informed, written consent was obtained from all parents and children.

The study population

One hundred and six healthy children (55 male, 51 female) were recruited from the three London state schools closest to the study venue. Two hundred and thirty nine

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Table 1. – Growth variables for each subgroup of children together with numbers of children completing a particular workload, their group median maximum workload and group lower limit of normality

Growth variables	Age group yrs							
	δ10.50		10.51–12.50		12.51–14.50		>14.50	
	M	F	M	F	M	F	M	F
Subjects n	11	12	13	11	18	19	13	9
Height cm	137	139	150	152	160	157	173	162
	(129–151)	(129–147)	(144–164)	(142–163)	(144–174)	(145–170)	(167–183)	(148–167)
Height z-score	0.23	1.22	0.79	0.53	0.07	-0.1	0.27	-0.1
	(-1.0–3.0)	(-1.2–2.3)	(-0.4–2.5)	(-0.2–1.6)	(-1.7–1.9)	(-1.6–1.8)	(-0.6–1.9)	(-0.2–0.9)
Weight kg	36 (23–57)	32 (23–46)	41 (37–68)	44 (33–61)	52 (36–61)	48 (31–65)	62 (51–75)	52 (44–66)
Surface area m ²	1.16	1.12	1.33	1.37	1.54	1.49	1.71	1.53
	(0.9–1.5)	(0.9–1.4)	(1.2–1.8)	(1.1–1.7)	(1.2–1.7)	(1.1–1.7)	(1.5–1.9)	(1.4–1.7)
Triceps skinfold z-score	1.16	1.21	1.25	1.06	0.69	0.82	0.72	0.83
	(0.5–2.8)	(-0.9–2.8)	(-0.4–2.3)	(0.1–2.3)	(-1.0–2.4)	(-1.3–2.1)	(-0.9–1.9)	(-1.2–2.4)
Subscapular skinfold z-score	0.59	0.77	0.24	0.80	0.55	0.56	0.13	0.52
	(-0.2–2.7)	(-0.5–2.4)	(-0.6–2.0)	(-0.7–1.7)	(-0.5–1.8)	(-1.1–2.0)	(-0.1–1.3)	(-0.5–1.8)
Children completing each exercise stage n								
Rest	11	12	13	11	18	19	13	9
25 W·m ⁻²	11	12	13	11	18	19	13	9
40 W·m ⁻²	11	12	13	11	18	19	13	9
55 W·m ⁻²	11	7	12	10	18	19	13	9
70 W·m ⁻²	4	3	9	2	18	15	11	9
85 W·m ⁻²	1		4	1	11	2	11	2
100 W·m ⁻²					1		7	
115 W·m ⁻²							3	
Median maximum workload W·m ⁻²	55	55	70	55	85	70	87.5	70
Maximum workload defined as below normal W·m ⁻²	<55	<40	<55	<55	<70	55	70	<70

Values are presented as absolute number of subjects (n) or as medians, with ranges in parentheses. M: male; F: female.

out of 312 invited parents gave consent and 106 out of 239 were chosen at random to ensure even representation across the age range for each sex once entry criteria were satisfied. These were: 1) >7.5 yrs old, the minimum age which, based on a pilot study, ensured co-operation; 2) >125 cm tall, the minimum height for using the exercise bicycle; and 3) no history of recent (3 weeks) acute or significant chronic respiratory or other conditions and not receiving medications.

Twenty three subjects were aged 8.00–10.50 yrs, 24 were aged 10.51–12.50 yrs, 37 were aged 12.51–14.50 yrs and 22 were aged 14.51–16.9 yrs (table 1).

Children were studied in pairs and walked from school to hospital. All children had been starved for at least 1 h prior to study. On arrival, their date of birth, race, height (Harpenden height stadiometer; Holtain Ltd, Crymmych, UK), weight (SECA, Birmingham, UK) and two site skinfold measurements (triceps and subscapular; Holtain Ltd, Crymmych, UK) to estimate fat mass [9] were recorded. They then underwent a physical examination to exclude unexpected disease and to assess pubertal status [10]. This was possible in 104 out of 106 subjects, with two boys refusing; 30 were pre-pubertal, 36 in early and 38 in late puberty. Spirometry was used to exclude unexpected airways obstruction (forced expired volume in one second (FEV₁) <80% of predicted).

Measurements

The methods for obtaining the physiological measurements were not novel and used inert gas rebreathing. Briefly, rebreathing from a bag containing non-native gases

allows equilibrium with the resident lung gas. From this closed system, the rate of uptake of a soluble gas into the pulmonary blood stream is used to calculate the Q'_{eff} in contact with ventilated alveoli [5, 11–14]; and with knowledge of f_c the effective stroke volume is found. The uptake of oxygen from the same closed system allows measurement of $V'O_2$. Using the Fick equation allows the arteriovenous oxygen content difference (AVO) to be calculated from the ratio of $V'O_2$ to Q'_{eff} . The mixing and dilution of a test insoluble gas with the native lung gas permits calculation of functional residual capacity (FRC), thus being the end of an unforced expiration at the start of a test. The transfer factor of the lung for carbon monoxide ($T_{L,CO}$) can be used as an estimate of pulmonary capillary blood volume [15–20] from the formula:

$$1/T_{L,CO} = 1/Dm + 1/(\theta \cdot V_c)$$

where Dm represents the "resistance" due to the alveolar capillary membrane, θ is the reaction rate of carbon monoxide with haemoglobin and V_c is the pulmonary capillary blood volume [15–17]. As time = volume/flow then, from the above, the transit time of blood across the respiratory vasculature may be qualitatively estimated from the ratio of $T_{L,CO}$ to Q'_{eff} [20].

The mass spectrometer and gas mixtures

The study used an Innovision 2000 mass spectrometer (Innovision, Odense, Denmark) of a very similar specification to that used for the European Space Agency physiological experiments performed aboard the US space

shuttle in March 1993. It separates gases by their mass: charge ratio and their concentration is proportional to their amplified electrical signal. Comparing the signal with a calibration gas allows concentrations to be calculated. Errors due to changes in gas viscosity, the addition of exhaled water vapour or electrical drift were avoided by ensuring that the total electrical signal represented 100% of the gas, with the known components correctly apportioned, *i.e.* automatic total pressure correction.

The calibration gases (tolerance $\pm 2\%$, BOC, UK) had a typical make-up of acetylene 0.3%, argon 1%, helium 1%, sulphur hexafluoride 3%, carbon dioxide 5%, oxygen 25% and balance nitrogen. This tolerance for high concentration gases was further refined by the spectrometer, using the known concentration of oxygen in room air, 20.93%.

The rebreathing test gas had typical contents of 0.3% carbon monoxide (of stable isotope oxygen-18), 0.3% acetylene (the soluble gas), 35% oxygen, 5% sulphur hexafluoride (the insoluble, inert gas) and balance nitrogen. These cylinders were of absolute grade (zero error; BOC, UK) and all gases were certified of medicinal quality. The ideal rebreathing bag gas volume was found, from a pilot study, to be 40% of the subject's predicted forced vital capacity. This allowed complete emptying with minimal effort at rest, but was sufficiently large for all stages of exercise.

The pneumatic valve

A rebreathing manoeuvre requires the accurate detection of the change from expiration to inspiration, in this study at FRC, so that the rebreathing bag can be activated to allow the subject to subsequently breathe by mouth (wearing a nose clip) from a closed system. To avoid the use of inaccurate manually controlled "half-Haldane" valves, the mass spectrometer has a pneumatic valve activated *via* a calibrated pneumotachograph at the inflection point between expiration and inspiration to close off room air ventilation to the subject and open ventilation to the rebreathing bag. The delay time is 75 ms and the deadspace is 106 mL. The primary advantage is complete independence from subject co-operation.

Calibration

The accuracy of the rebreathing bag volume was calibrated daily. Over the entire study, no two consecutive calibrations varied by $>5\%$. The mass spectrometer was activated at least 12 h prior to any study to ensure maximum stability. A two-point calibration (zero and calibration gas) was performed three times for each subject and a one point calibration (calibration gas only) >10 times. The pneumotachograph zero flow "offset" voltage was calibrated >3 times per study.

The exercise protocol

An electromagnetically braked bicycle (SECA 100, Birmingham, UK) was used for the study as it is less intimidating than a treadmill for young children and workload on such a bicycle is independent of pedal speed over a wide

range (4–150 revolutions per minute (rpm)). The protocol consisted of the following steps:

- 1) The subject arrived, was examined, measured and underwent spirometry.
- 2) The equipment was explained and the subject underwent two practice rebreathing manoeuvres.
- 3) The bicycle was adjusted for each subject such that the angle at the knee on full depression of the pedal was approximately 160° degrees.
- 4) The child rested silently for 10 min.
- 5) Whilst the fourth step was in progress, the mass spectrometer underwent a two point calibration. A calibrated pulse oximeter (Nellcor, Hatwood, CA, USA) recording f_c and oxygen saturation was placed over the right supraorbital artery fixed with a bandanna, this site being the least prone to exercise artifact.
- 6) After resting, the subject performed, whilst seated, five 20 s rebreathing manoeuvres every 3 min over a 15 min period. Between manoeuvres the subject removed the noseclip and mouthpiece and remained seated. The mass spectrometer had a one point calibration after the third manoeuvre. The pneumotachograph zero offset voltage was checked and adjusted at least twice during this 15 min period.
- 7) After the five resting manoeuvres, the subject immediately moved from the chair to the bicycle and was now continuously attached to the mass spectrometer, breathing orally and wearing a noseclip. The subject rested in this position for 4 min. All rebreathing manoeuvres after this point were of 12 s duration to prevent excess accumulation of carbon dioxide during exercise.
- 8) The subject, still fully attached to the mass spectrometer, pedalled backwards at "zero" load at "walking pace" speed, to loosen up and get used to the novel feelings engendered by exercising in this manner. During the last 30 s of this 3 min stage a further 12 s rebreathing manoeuvre was performed.
- 9) The subject then pedalled forwards and was encouraged to maintain a speed of 50–70 rpm signalled by a display. The initial load was $25 \text{ W}\cdot\text{m}^{-2}$. During the last 30 s of this stage, a 12 s rebreathing manoeuvre was again performed. Before any rebreathing manoeuvre, a one point (calibration gas) calibration was performed.
- 10) Following this 3 min stage, the load was increased every 3 min by $15 \text{ W}\cdot\text{m}^{-2}$. Again, during the last 30 s of each stage a rebreathing manoeuvre was performed. These processes were repeated seamlessly without the subject changing their cycling pattern or disconnecting themselves from the noseclip or mouthpiece until exhaustion was reached.
- 11) Exhaustion was heralded by: 1) the subject whilst pedalling, beginning to labour and rock from side to side; 2) the pulse rate was almost always >190 beats per minute (bpm); and 3) the pedalling speed would involuntarily speed up then progressively slow. If, on these occurring, the subject had just completed an exercise stage, a question of the form: "Do you think you can carry on for another three minutes" was invariably met with a shake of the head and exercising therefore ceased. If these features suddenly presented early on in an exercise stage, the individual was exhorted to finish that stage, including the rebreathing test, and then stop. Thus, the objective was for all children to stop exercising at the end of a completed 3 min exercise stage.

12) Upon cessation of exercise, the subject remained seated on the bicycle attached to the mass spectrometer for 9 min undergoing three further 12 s rebreathing manoeuvres.

13) Nine minutes after completion of exercise, the study terminated. The study lasted, on average 75 min and was performed only once per child.

Data analysis

The mass spectrometer software uses algorithms to calculate the core data (Q'_{eff} , f_c , $V'O_2$, $T_{L,CO}$). However, to minimize error, all 6,921 traces were scrutinized for confounding factors: 1) Was the point of "complete" gaseous mixing between the test gas and resident lung air correctly identified? 2) Was there evidence of pulmonary blood recirculation of the test gas? 3) Was there evidence of any leak, *i.e.* had the subject inhaled room air around the mouthpiece during rebreathing? 4) Were there other artifacts (*e.g.* coughing) distorting the validity of the result? All such problems were easily identifiable and corrected. Only six of the 6,921 traces could not be used.

The data was analysed using the Statistical Package for the Social Sciences (SPSS) for Windows V6-0 (SPSS, Chicago, USA). Medians and ranges are used for growth variables. Mean (SD) are quoted in the tables and mean and 95% confidence intervals in the figures for the cardiopulmonary variables. Extreme values greater than three times the interquartile range were excluded. Forward, step-wise, multiple linear regression was used to determine the significant factors in a variable and was tested both at rest and after completing the 40 $W \cdot m^{-2}$ exercise stage. The factors used were gender, surface area ($(\text{weight} \cdot \text{height} / 3,600)^{0.5}$), height, weight, age and pubertal stage. Significance was defined as $p < 0.05$.

Results

Every child performed all the resting manoeuvres, exercised for at least 9 min and completed the 40 $W \cdot m^{-2}$ exercise stage. The number of children completing each stage is shown in table 1. One male refused to complete the recovery part of the study. The growth variables for each sex and age group are shown in table 1. Table 1 also shows the median maximum exercise staged achieved for each subgroup and a completed workload which would be deemed abnormally low.

Physical factors influencing the cardiopulmonary variables during rest and exercise

Surface area, sex and age were the significant ($p < 0.05$) factors influencing Q'_{eff} and in particular $V'O_2$ where weight was excluded from the regression in preference to surface area. Surface area and gender only were significant in explaining variability in effective stroke volume and $T_{L,CO}$ per unit lung volume, but age was not. Transit time and AVO were affected by age and sex but not surface area. FRC and $T_{L,CO}$ were significantly influenced by surface area, gender and pubertal stage but not age.

The variability of resting values

The median coefficient of variation (standard deviation/100/mean; CV) of the last three resting values for each child (the first two being discarded [5]), was $< 12\%$ for all parameters. The median CV was 7.8% for Q'_{eff} and 4.9% for $T_{L,CO}$. There was no gender effect. The CV was generally less in children > 12.5 yrs; for example the $T_{L,CO}$ median CV was 5.4% when < 12.5 yrs and 3.6% when > 12.5 yrs (Mann Whitney, $p = 0.003$). For FRC, the median CV was 10.9% when < 12.5 yrs and 6.7% when > 12.5 yrs ($p = 0.002$).

The mean (SD) for each haemodynamic variable at rest and during exercise are shown in tables 2–11.

Resting values

At rest, there were age-dependent effects even after gender and surface area correction, particularly for $V'O_2$ (table 2), AVO (table 3) and "transit time" (table 4) where the eldest group of male children had a transit time 60% longer, despite surface area correction, than the youngest children (< 10.50 yrs). Transfer factor (table 5) and FRC (table 6) at rest both showed a sharp rise in late pubertal boys even after surface area correction, which was less evident in girls.

Children undergoing exercise

Effective pulmonary blood flow at a given surface area-corrected workload showed a weak nonsignificant negative trend with age (table 7). In the latter stages of exercise ($\geq 55 W \cdot m^{-2}$) only, there was a marked negative trend in f_c with increasing age with a 27 and 19 bpm difference for boys and girls, respectively, between the oldest and youngest age groups (table 8) although the expected effect on stroke volume was not manifested, perhaps because this value is a ratio and, thus, prone to greater error. During exercise, age effects are also manifested in several variables including $V'O_2$ and particularly AVO (table 3) where in both sexes 31% of the variance is explained by age ($p < 0.001$).

To determine whether a single linear equation related $V'O_2$ to effective pulmonary blood flow, the Fick equation was rewritten as:

$$Q'_{\text{eff}} = (1/AVO) \cdot V'O_2$$

i.e., that $1/AVO$ represents the slope of the equation. Figure 1 shows a declining $1/AVO$ with increasing workload signifying a nonlinear relationship.

At a given surface area-corrected workload, the surface area-corrected $T_{L,CO}$ was consistently greater in late puberty compared to prepubertal children in both sexes (table 5). However, the transfer constant ($T_{L,CO}$ corrected for lung volume, table 9) did not show such differences. The transit time showed marked age dependence with the oldest children of both sexes showing a longer transit time (table 4). FRC was higher in late- compared to pre-pubertal children after correcting for surface area and did not fall (table 6) with exercise as might be expected (see Discussion).

Table 2. – Mean and standard deviation (SD) for oxygen consumption for each age group and sex for rest and each stage of exercise

Exercise stage	Oxygen consumption mL·min ⁻¹ ·m ⁻²							
	≤10.50 yrs		10.51–12.50 yrs		12.51–14.50 yrs		>14.50 yrs	
	M	F	M	F	M	F	M	F
Rest	234±46	188±26	171±34	165±35	182±54	141±28	167±27	165±40
25 W·m ⁻²	612±108	556±100	523±102	532±93	491±95	458±115	592±209	449±152
40 W·m ⁻²	822±196	710±165	666±153	691±81	670±154	598±132	715±211	607±90
55 W·m ⁻²	948±165	887±172	809±177	803±210	779±147	784±126	829±182	787±102
70 W·m ⁻²		845±312	952±155		952±155	856±157	952±155	937±135
85 W·m ⁻²			1075±161		1066±161		1075±161	
100 W·m ⁻²					1220±120		1220±120	
115 W·m ⁻²							1510±140	

For numbers of observations, see table 1. M: male; F: female.

Table 3. – Mean and standard deviation (SD) for arteriovenous oxygen difference for each age group and sex for rest and each stage of exercise

Exercise stage	Arteriovenous oxygen difference mL							
	≤10.50 yrs		10.51–12.50 yrs		12.51–14.50 yrs		>14.50 yrs	
	M	F	M	F	M	F	M	F
Rest	62±7	61±11	56±11	54±14	51±14*	46±8†	52±10*	51±11‡
25 W·m ⁻²	93±22	106±15	92±22	97±16	93±22	83±14	93±22	78±18
40 W·m ⁻²	113±22	119±19	103±17	110±15	99±20	92±11	100±20	91±14
55 W·m ⁻²	123±14	118±30	107±14	115±21	106±16	109±17	113±21	106±17
70 W·m ⁻²	115±23	113±29	124±14		120±17	119±13	124±21	115±18
85 W·m ⁻²			123±13		123±13		123±13	
100 W·m ⁻²							135±13	
115 W·m ⁻²							148±12	

For numbers of observations, see table 1. *: p<0.05 compared to males <10.5 yrs; †: p<0.05 compared to males <10.5 yrs; ‡: p<0.05 compared to female <10.5 yrs; §: p<0.05 compared to females <10.5 yrs; M: male; F: female.

Table 4. – Mean and standard deviation (SD) for transit time (transfer factor/effective pulmonary blood flow) for each age group and sex for rest and each stage of exercise

Exercise stage	Transit time mmol·kPa ⁻¹ ·L ⁻¹							
	≤10.50 yrs		10.51–12.50 yrs		12.51–14.50 yrs		>14.50 yrs	
	M	F	M	F	M	F	M	F
Rest	1.01±0.11	1.04±0.13	1.22±0.17*	1.18±0.17	1.25±0.17+	1.20±0.16‡	1.56±0.32++†	1.33±0.28‡
25 W·m ⁻²	0.74±0.10	0.74±0.10	0.77±0.15	0.78±0.10	0.86±0.20	0.81±0.11	1.00±0.15	0.96±0.26
40 W·m ⁻²	0.65±0.09	0.74±0.10	0.78±0.09	0.73±0.10	0.75±0.13	0.71±0.08	0.88±0.16	0.81±0.15
55 W·m ⁻²	0.68±0.12	0.69±0.13	0.67±0.08	0.69±0.13	0.70±0.09	0.69±0.13	0.84±0.12	0.69±0.13
70 W·m ⁻²	0.61±0.13	0.71±0.13	0.64±0.0		0.68±0.10	0.71±0.13	0.82±0.13	0.71±0.13
85 W·m ⁻²			0.72±0.09		0.72±0.09		0.72±0.09	
100 W·m ⁻²							0.73±0.10	
115 W·m ⁻²							0.99±0.22	

For numbers of observations, see table 1. *: p<0.05 compared to males <10.5 yrs; †: p<0.05 compared to males <10.5 yrs; ++: p<0.05 compared to males <10.5 yrs; ‡: p<0.05 compared to male 12.51–14.50 yrs; §: p<0.05 compared to females <10.5 yrs; ¶: p<0.05 compared to females <10.5 yrs; M: male; F: female.

Table 5. – Mean and standard deviation (SD) for transfer factor for each pubertal stage and sex for rest and each stage of exercise

Exercise stage	Transfer factor mmol·min ⁻¹ ·kPa·m ⁻²					
	Prepuberty		Early puberty (T2–T3)		Late puberty (T4–T5)	
	M	F	M	F	M	F
Rest	3.73±0.38	3.37±0.47	4.14±0.69	3.53±0.55	4.93±0.67*	3.89±0.52
25 W·m ⁻²	4.82±0.62	3.92±0.68	4.74±0.91	4.32±0.69	5.43±1.19	4.75±0.84
40 W·m ⁻²	4.75±0.88	4.47±0.83	5.03±1.08	4.54±0.57	5.98±1.18	4.85±0.84
55 W·m ⁻²	5.22±1.02	5.66±1.88	5.08±1.28	4.43±0.92	5.76±0.91	5.22±0.84
70 W·m ⁻²	5.28±1.11	5.27±2.45	5.21±1.19	5.40±1.12	6.07±1.32	5.37±1.05
85 W·m ⁻²	5.95±1.49		5.90±1.47		6.71±1.00	6.23±0.53
100 W·m ⁻²					6.59±1.21	
115 W·m ⁻²					10.0±2.2	

For numbers of observations, see table 1. *: p<0.05 compared to males in pre- or early puberty. M: male; F: female.

Table 6. – Mean and standard deviation (SD) for functional residual capacity for each pubertal stage and sex for rest and each stage of exercise

Exercise stage	Functional residual capacity L·m ⁻²					
	Prepuberty		Early puberty (T2–T3)		Late puberty (T4–T5)	
	M	F	M	F	M	F
Rest	1.23±0.08	1.25±0.30	1.37±0.26	1.36±0.19	1.75±0.21*	1.52±0.36
25 W·m ⁻²	1.20±0.30	1.42±0.42	1.47±0.38	1.40±0.25	1.83±0.32	1.62±0.33
40 W·m ⁻²	1.55±0.59	1.53±1.03	1.36±0.31	1.52±0.18	1.90±0.33	1.75±0.43
55 W·m ⁻²	1.50±0.35	1.63±0.55	1.39±0.41	1.56±0.44	1.93±0.45	1.80±0.42
70 W·m ⁻²	1.46±0.33		1.5±0.27	1.63±0.55	1.82±0.41	1.63±0.55
85 W·m ⁻²			1.66±0.39		1.98±0.42	
100 W·m ⁻²					1.97±0.45	
115 W·m ⁻²					2.76±0.25	

*: p<0.05 compared to males in pre- or early puberty. M: male; F: female.

Table 7. – Mean and standard deviation (SD) for effective pulmonary blood flow for each age group and sex for rest and each stage of exercise

Exercise stage	Effective pulmonary blood flow L·min ⁻¹ ·m ⁻²							
	≤10.50 yrs		10.51–12.50 yrs		12.51–14.50 yrs		>14.50 yrs	
	M	F	M	F	M	F	M	F
Rest	3.80±0.52	3.16±0.57	3.08±0.44*+	3.10±0.40	3.57±0.48	3.07±0.40	3.30±0.63++	3.24±0.54
25 W·m ⁻²	6.71±0.55	5.31±0.88	5.78±0.98	5.53±0.78	5.58±0.98	5.54±0.95	5.87±1.24	5.61±1.33
40 W·m ⁻²	7.26±1.16	6.17±1.44	6.40±1.16	6.34±0.65	6.85±1.11	6.44±1.06	7.12±1.16	6.72±1.00
55 W·m ⁻²	7.62±1.32	8.25±3.45	7.56±1.51	6.95±0.97	7.42±1.35	7.26±1.26	7.31±0.85	7.48±1.03
70 W·m ⁻²	8.23±1.36	9.08±4.47	8.03±1.47		8.16±1.56	7.26±1.50	7.44±1.57	8.25±1.31
85 W·m ⁻²			8.53±1.87		8.92±1.61		8.72±0.93	
100 W·m ⁻²							9.06±0.85	
115 W·m ⁻²							10.20±0.2	

For numbers of observations, see table 1. *: p<0.05 compared to males <10.5 yrs; +: p<0.05 compared to males 12.51–14.50 yrs; ++: p<0.05 compared to males <10.5 yrs. M: male; F: female.

Table 8. – Mean and standard deviation (SD) for cardiac frequency for each age group and sex for rest and each stage of exercise

Exercise stage	Cardiac frequency beats·min ⁻¹							
	≤10.50 yrs		10.51–12.50 yrs		12.51–14.50 yrs		>14.50 yrs	
	M	F	M	F	M	F	M	F
Rest	87±7	88±10	88±15	88±11	85±15	83±12	81±10	86±9
25 W·m ⁻²	131±16	131±9	117±16	122±9	114±15	121±14	110±15	119±9
40 W·m ⁻²	149±18	156±13	141±20	148±13	131±16	140±16	136±24	137±12
55 W·m ⁻²	174±20	180±10	163±19	172±13	150±18	164±14	146±16	160±4
70 W·m ⁻²	170±23	192±10	179±14	185±3	173±19	181±13	161±15	179±13
85 W·m ⁻²			190±11	179±13	188±11	189±12	175±12	189±12
100 W·m ⁻²					184±10		184±10	
115 W·m ⁻²							188±4	

For numbers of observations, see table 1. M: male; F: female.

Table 9. – Mean and standard deviation (SD) for transfer constant for each sex for rest and each stage of exercise

Exercise stage	FRC mmol·min ⁻¹ ·kPa ⁻¹ ·min ⁻¹	
	M	F
Rest	2.86±0.42	2.65±0.42
25 W·m ⁻²	3.35±1.00	3.07±0.53
40 W·m ⁻²	3.30±0.70	3.13±1.10
55 W·m ⁻²	3.30±0.70	3.13±1.10
70 W·m ⁻²	3.45±0.72	3.25±0.65
85 W·m ⁻²	3.40±0.39	
100 W·m ⁻²	3.32±0.39	
115 W·m ⁻²	3.61±0.53	

Note that age was not a significant factor in this variable. For numbers of observations, see table 1. FRC: functional residual capacity; M: male; F: female.

Table 10. – Mean and standard deviation (SD) for effective stroke volume for each sex for rest and each stage of exercise

Exercise stage	Effective stroke volume mL·beat ⁻¹ ·m ⁻²	
	M	F
Rest	41±9	37±8
25 W·m ⁻²	51±8	45±9
40 W·m ⁻²	51±9	46±11
55 W·m ⁻²	48±10	45±10
70 W·m ⁻²	47±11	43±10
85 W·m ⁻²	49±10	48±6
100 W·m ⁻²	49±9	
115 W·m ⁻²	51±2	

Note that age was not a significant factor in this variable. For numbers of observations, see table 1. M: male; F: female.

Table 11. — Values for haemodynamic variables at maximum exercise and after 9 min rest for each sex alone and for each gender and age group

	δ10.50 yrs						10.51–12.50 yrs						12.51–14.50 yrs						>14.50 yrs						Variance explained by age against variable when p<0.01*		All ages combined	
	M		F		M		F		M		F		M		F		M		F		M		F		M	F		
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F				
<i>Q</i> _{eff}																												
Maximum exercise	128±44	151±99	160±57	129±28	141±43	155±37	163±45	183±39	142 (127–156)	143 (127–164)																		
After 9 min rest	15±25	17±22	3±17	11±35	2±21	12±27	3±26	12±28	5 (-1–11)	12 (5–20)																		
<i>fc</i>																												
Maximum exercise	85±17	113±21	100±40	80±15	112±37	112±24	120±24	106±18	105 (96–117)	103 (96–112)																		
After 9 min rest	8±13	24±16	22±16	21±10	28±16	30±15	32±11	30±14	24 (19–29)	26 (23–32)																		
Stroke volume																												
Maximum exercise	10±19	25±45	27±37	18±25	11±29	15±26	15±27	23±27	15 (8–24)	19 (11–28)																		
After 9 min rest	-1±17	-7±18	-14±17	-7±23	-22±18	-16±23	-25±22	-18±20	-16 (-11–21)	-13 (-7–18)																		
<i>V</i> _{O₂}																												
Maximum exercise	331±157	358±120	440±116	380±116	518±201	551±227	607±189	512±163	28	15	462 (382–522)	447 (408–515)																
After 9 min rest	26±51	25±57	55±74	35±82	29±55	43±66	9±71	2±54	27 (10–42)	28 (13–47)																		
AVO																												
Maximum exercise	93±43	99±60	110±59	127±84	160±71	162±82	171±61	132±50	132 (105–153)	128 (113–155)																		
After 9 min rest	-2±40	-2±31	32±37	18±39	21±55	15±46	7±78	-7±54	19 (2–34)	14 (1–32)																		
<i>T</i> _{L,CO} /FRC																												
Maximum exercise	12±35	25±76	21±26	18±33	22±18	29±25	23±24	19±17	19 (13–27)	21 (12–36)																		
After 9 min rest	-13±23	-8±19	-12±21	-18±15	-9±27	-5±12	-7±11	-7±16	-11 (-4–16)	-9 (-5–13)																		
"Transit time"																												
Maximum exercise	-34±12	-35±19	-43±10	-42±7	-45±7	-45±6	-45±15	-40±18	-43 (-38–45)	-43 (-37–45)																		
After 9 min rest	-13±11	-15±14	-4±18	-12±16	-7±21	-6±25	-3±25	-5±23	-8 (-1–12)	-10 (-14–2)																		

Values are expressed as percentage change from baseline (value-resting value)/(value-resting value×100). Values are presented as mean±SD or as mean and 95% confidence interval in parenthesis. *: given where p<0.01 to avoid the effects of multiple contrasts. M: male; F: female; *Q*_{eff}: effective pulmonary blood flow; *fc*: cardiac frequency; *V*_{O₂}: oxygen consumption; AVO: arteriovenous oxygen difference; *T*_{L,CO}: transfer factor of the lung for carbon monoxide; FRC: functional residual capacity.

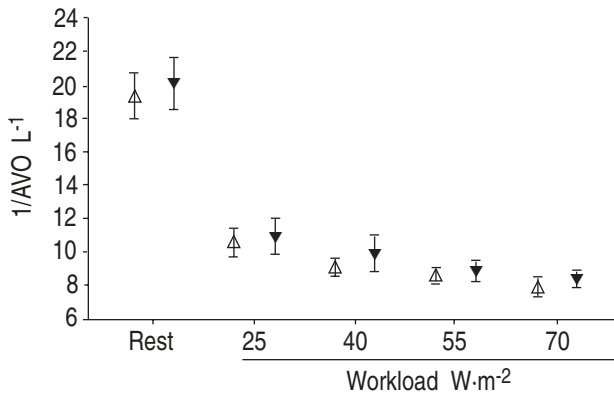


Fig. 1. – The nonlinearity of the gradient (1/AVO) of the Fick equation (effective pulmonary blood flow = (1/AVO)·oxygen consumption) as a function of increasing workload for each gender. Δ: male; ▼: female. Values are presented as mean±95% confidence interval.

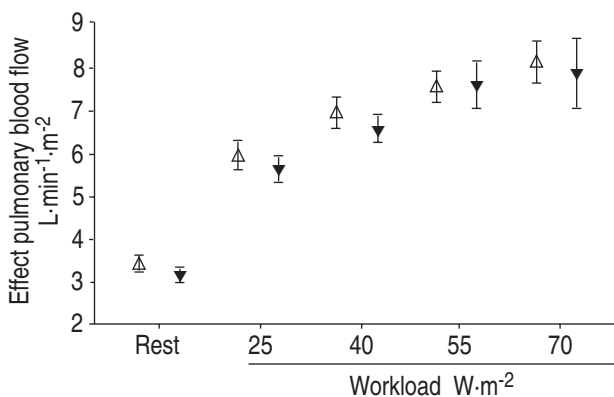


Fig. 2. – Effective pulmonary blood flow (mean±95% confidence interval) for males (Δ) and females (▼) as a function of workload. Note the gender difference at rest which is lost with increasing exercise.

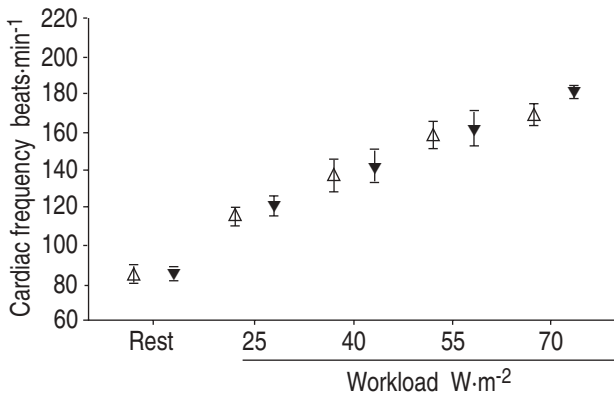


Fig. 3. – Cardiac frequency (mean±95% confidence interval) for males (Δ) and females (▼) as a function of workload. Note the increased female values compared to males with exercise.

Differences between sexes during rest and exercise

Q'_{eff} at rest was significantly lower in girls by some 0.34 L·min⁻¹·m⁻² at rest (fig. 2) but during exercise, this difference gradually disappeared so that from 55 W·m⁻² onwards, the sexes were similar. This convergence appears largely to be due to the greater increase in f_c with exercise in females compared to males (fig. 3). At rest, f_c

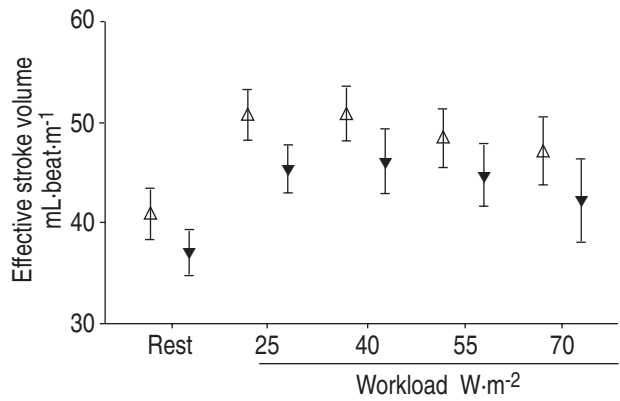


Fig. 4. – Effective stroke volume (mean±95% confidence interval) for males (Δ) and females (▼) against workload. Note the lower female stroke volume despite surface area correction at all workloads and the decline in stroke volume at high exercise levels.

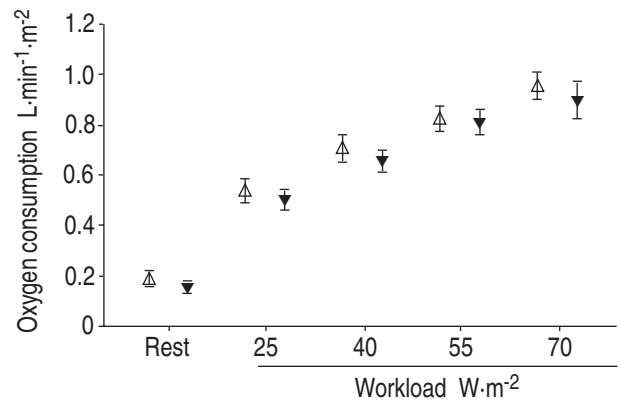


Fig. 5. – Oxygen consumption (mean±95% confidence interval) for males (Δ) and females (▼) as a function of workload. Note the gender difference at rest, which is lost with increasing exercise.

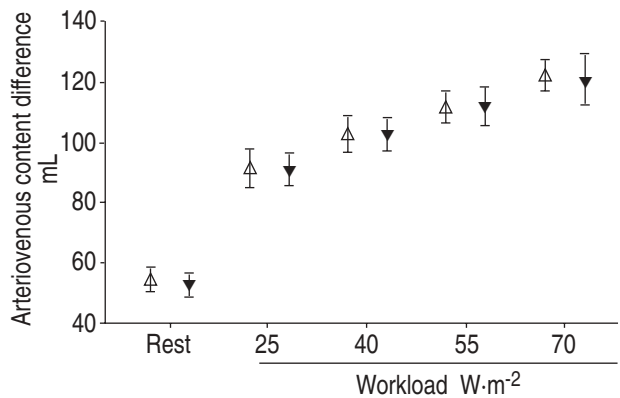


Fig. 6. – Arteriovenous content difference (mean±95% confidence interval) for males (Δ) and females (▼) as a function of workload.

was the same in both sexes, but by the exercise stages of 55 W·m⁻² and 70 W·m⁻² the f_c values were 9 and 14 bpm greater, respectively, in females ($p < 0.05$). This increase in f_c appeared to compensate for the significantly lower effective stroke volume present in girls compared to boys during both rest and exercise (fig. 4, table 10). Effective stroke volume was 3.8 mL·beat⁻¹·min⁻² (8–10%) less in females at rest and this discrepancy remained throughout exercise (fig. 4).

$V'O_2$ (fig. 5) was 22 mL·min⁻¹·m⁻² lower in females compared to males at rest, but was very similar in the later

stages of exercise. As this pattern was similar to the Q'_{eff} (fig. 2), from the Fick equation, there were no gender differences in the AVO during rest or exercise (fig. 6).

At rest, $T_{L,CO}$ (fig. 7) was $0.71 \text{ mmol}\cdot\text{min}^{-1}\cdot\text{kPa}\cdot\text{m}^{-2}$ lower in females than males ($p < 0.01$). It then approached, but consistently remained significantly below, the value in their male counterparts (*e.g.*, $0.49 \text{ mmol}\cdot\text{min}^{-1}\cdot\text{kPa}\cdot\text{m}^{-2}$ less at $55 \text{ W}\cdot\text{m}^{-2}$) during exercise. This pattern was also seen with FRC (fig. 8) and the transfer constant (fig. 9) tended to mirror this effect. The "transit time" showed a small but significant trend to be shorter in females than males (fig. 10).

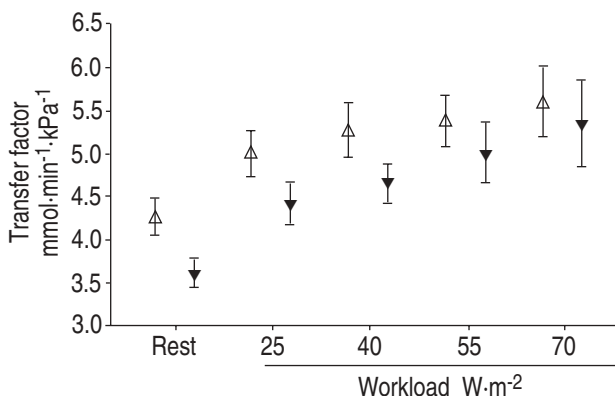


Fig. 7. – Transfer factor (mean \pm 95% confidence interval) for males (Δ) and females (\blacktriangledown) as a function of workload. Note the gender difference at rest which is partly lost with increasing exercise.

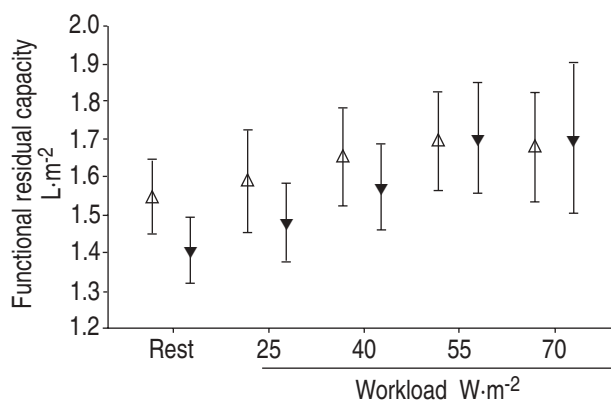


Fig. 8. – Functional residual capacity (mean \pm 95% confidence interval) for males (Δ) and females (\blacktriangledown) as a function of workload. Note the gender difference at rest which is lost with increasing exercise.

Maximum exercise and recovery

Using the arbitrary definition of "sufficient exercise" to be an $f_c > 170$ bpm at "exhaustion" and a respiratory quotient (data not shown) > 1.1 , 3 min after maximal exercise [21], 16 out of 23 (70%) children < 10.5 yrs fulfilled these criteria compared, with 21 out of 23 children aged > 14.5 yrs, a nonsignificant difference.

To facilitate understanding and to avoid spurious comparisons between age groups and sex, each subject's result at the end of exercise was expressed as a percentage change from their own resting value. All children could,

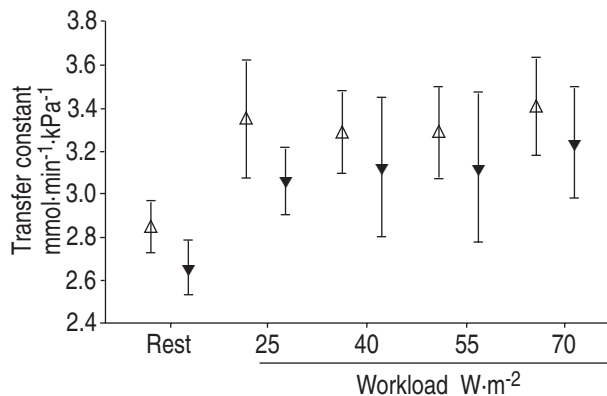


Fig. 9. – Transfer constant (mean \pm 95% confidence interval) for males (Δ) and females (\blacktriangledown) as a function of workload. Note the gender difference at rest which is lost with increasing exercise.

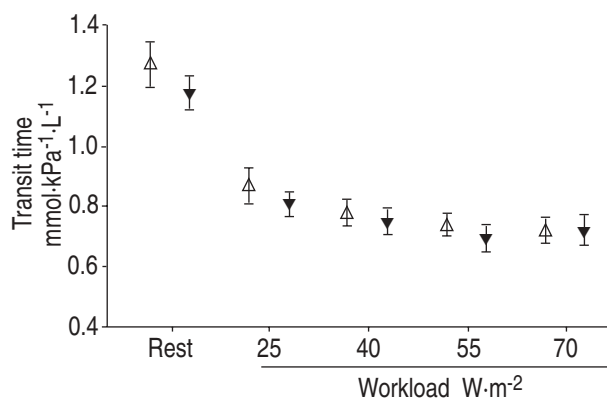


Fig. 10. – Transit time (mean \pm 95% confidence interval) for males (Δ) and females (\blacktriangledown) as a function of workload.

Table 12. – Values for haemodynamic variables at maximum exercise and after 9 min rest for each sex alone and for each sex and age group

	Change from initial resting values %							
	Prepuberty		Early puberty		Late puberty		All stages	
	M	F	M	F	M	F	M	F
$T_{L,CO}$								
Maximum exercise	45 \pm 31	46 \pm 51	30 \pm 31	36 \pm 24	38 \pm 32	40 \pm 20	38 (29–48)	38 (32–50)
After 9 min rest	-2 \pm 17	0 \pm 17	-7 \pm 10	-7 \pm 14	-6 \pm 12	6 \pm 14	-5 (-1–8)	0 (-4–5)
FRC								
Maximum exercise	29 \pm 39	27 \pm 46	10 \pm 35	26 \pm 35	16 \pm 30	11 \pm 24	18 (9–29)	19 (10–30)
After 9 min rest	17 \pm 26	13 \pm 26	3 \pm 20	5 \pm 7	5 \pm 17	12 \pm 19	8 (2–17)	9 (5–17)

Values are expressed as percentage change from baseline ($(\text{value} - \text{resting value}) / \text{resting value} \times 100$). Values are presented as mean \pm SD or as mean and 95% confidence interval in parenthesis. For definitions of abbreviations, see legend to table 11.

thus, be compared at different peak workloads to determine their relative capabilities. The mean (SD) for each variable, subdivided by gender and either age or pubertal stage, is shown in tables 11 and 12 together with a mean and 95% confidence interval for each gender, but with all age groups/pubertal stages combined.

At maximal exercise, the percentage change in Q'_{eff} above resting was remarkably similar in males (143%) and females (142%). There were no differences in effective stroke volume across the age groups in either sex at maximal exercise. The percent rise in $V'O_2$ was higher in the older two age groups at maximal exercise than the younger age groups, in both sexes. Mean maximal $V'O_2$ ranged 30–33 mL·kg⁻¹·min⁻¹ in males across the age groups, which was significantly higher ($p < 0.001$) than females, in whom it ranged 23–28 mL·kg⁻¹·min⁻¹ across the age groups.

After 9 min rest, Q'_{eff} was just above resting, but f_c remained some 25% above baseline in both sexes, such that effective stroke volume was significantly (12–16%) below resting ($p < 0.05$). $V'O_2$ after 9 min rest was 25% above resting; the AVO (as an estimate of oxygen debt) was, thus, still 14–19% ($p < 0.05$) above resting.

The percentage reduction in transit time was equal across the age groups in females at maximal exercise, but was shorter in the older two male age groups compared to the younger two. After 9 min rest, transit time remained 10% less than baseline. TL_{CO} increased equally (38%) in males and females with no differences across the pubertal stages and returned to baseline by 9 min. FRC rose during exercise to some 18% above resting and remained significantly raised (8–9%) after 9 minutes rest. This unexpected excess of FRC above resting is considered in the discussion.

Comparing the results for each subject's last (peak) exercise stage and their penultimate one, demonstrated that at peak exercise, f_c and $V'O_2$ were at that child's maximum recorded value in 95% of cases, but in contrast, stroke volume was falling in 91% (95% confidence interval 84–96%) of cases and the diffusion constant (K_{CO}) was falling in 77% (68–85%) of cases. Q'_{eff} was falling in 30% (20–38%) of cases and transit time was increasing in 42% (32–52%) of cases.

Discussion

This study provides comprehensive, noninvasive haemodynamic values for healthy children of both sexes over the age range 8–17 yrs using a simple, enjoyable exercise protocol. Values are available at all relevant workloads rather than only their maximum, thus eliminating the quandary of whether an individual's maximum performance was limited by physiological or motivational reasons [22]. This communication establishes SD scores, taking into account the child's sex, age or pubertal status for all stages of exercise. The study principally found that children at different stages of life adapt to exercise differently, even after allowing for size differences.

Nevertheless some of the measurements still remain surrogate markers for the desired variables, namely \bar{Q}' , pulmonary capillary number and volume, and pulmonary capillary recruitment during exercise. Instead, due to the requirements for noninvasiveness, the study actually measured, for example, Q'_{eff} rather than \bar{Q}' . This has the ad-

vantage of being a functional measure of useful blood flow, but ignores shunts. In healthy children, right to left shunting of blood represents 5% of the total \bar{Q}' , decreasing on exercise. Similarly, TL_{CO} represents a surrogate marker for pulmonary capillary blood volume. Nevertheless this marker is only a composite value representing functioning rather than total pulmonary capillaries. Its derivation also assumes that this volume is a single "well" of haemoglobin, that the flow through it is constant, non-pulsatile and is ventilated by a single alveolus. These ideas are clearly simplistic [19, 20, 23]. FEDERSPIEL [24] addressed the idea of uneven flow, whilst newer concepts of fractal geometry render the idea of a single "well" even less tenable [25–27].

The literature contains suggestions for the correction of TL_{CO} according to the amounts of carboxyhaemoglobin present, the alveolar oxygen tension [28–30] and the varying diffusion rates of the gases [31]. One correction, for example results in a 7% change in TL_{CO} for a 2.7 kPa (20 mmHg) change in alveolar oxygen tension from 16.0 kPa (120 mmHg). Such corrections lend a sense of spurious accuracy to the result and we believe it is more important that comparisons between groups are made under identical conditions so that qualitative differences may be highlighted.

A further ideal of studies such as ours is that the act of measurement ought not to affect the variable in question. A child obliged to breathe orally through a pneumatic valve with a small, but measurable, deadspace is clearly different from the same child riding a bicycle in the street. In this study, f_c and FRC may demonstrate the effects of testing. Although resting f_c showed only minimal age and gender differences, the resting level of 85 bpm measured in this study is some 10–15 bpm higher than would be expected and demonstrates not only anxiety/excitement but the exertion involved in performing a rebreathing manoeuvre to total lung capacity at 40 breaths per minute. The f_c and the Q'_{eff} may also change due to the increased vigour of breathing [32]; indeed, maximum voluntary ventilation at rest increases Q'_{eff} by 4.3 L·min⁻¹ in adults [33] reflecting increased respiratory muscle blood flow. The perturbation in blood flow is less in our study than in others [11], as rebreathing commenced at FRC rather than residual volume.

FRC in this study rose during exercise, when, with the increasing depth of respiration on exertion, it might be expected to fall. One possible explanation for this is the increased airflow resistance that occurs with breathing across a pneumotachograph with an increased amount of saliva on it, despite a drain being present. The pneumotachograph grill cannot be cleaned and recalibrated during exercise as this would involve disconnecting the child from the mouth piece, interrupting the exercise test at a crucial time. Evidence for this explanation may be found when examining FRC 9 min after recovery, where as a group, it remained significantly above resting in both sexes. An alternative explanation is that, unlike adults, airway resistance rises during exercise in the narrower children's airways, increasing FRC.

A strength of this study has been the consistency of the resting measurements, particularly Q'_{eff} and TL_{CO} . Resting Q'_{eff} measurements in this study accord with those in the literature [5]. There are few data on haemodynamics in children during exercise. Nevertheless, using the same

flawed [34] statistical methodology as GODFREY [6] on the current data to construct a $Q'_{\text{eff}}/V'O_2$ relationship, we obtained similar results. The equation of GODFREY [6] was:

$$Q'_{\text{eff}} (\text{L}\cdot\text{min}^{-1}) = 3.3 + 6.3 O_2$$

and that of the present study was:

$$Q'_{\text{eff}} = 3.8 + 5.7 O_2$$

Thus, at $1 \text{ L}\cdot\text{min}^{-1} V'O_2$, the children in the study of GODFREY [6] had a Q'_{eff} of $9.6 \text{ L}\cdot\text{min}^{-1}$ and those in the present study had $9.5 \text{ L}\cdot\text{min}^{-1}$.

Gender clearly influences the physiology of exercise, with females having a lower Q'_{eff} at rest but a similar output during exercise, due to their greater increase in fC . One might speculate, therefore, that females with complete heart block may be more compromised when exercising than males, though exercise studies have not addressed this issue [35]. The study by BAR-OR [36] on 10–13 yr old children found that for a given level of $V'O_2$, girls had a higher Q' and fC , but a lower AVO. Boys had a lower stroke volume at low level exercise, but not at higher level exercise. The current study showed an equal AVO between the sexes, *i.e.* a similar Q'_{eff} for similar $V'O_2$, which accords with the data of GODFREY [37]. However, girls in the current study have a lower $V'O_2$ per unit work and, thus, have a lower Q'_{eff} . This may be due to their greater percentage body fat, which has a lower metabolic rate. If TL_{CO} is indeed a measure of pulmonary capillary blood volume then, at rest, males have a greater volume of functioning pulmonary capillaries than females, but during exercise, as females recruit proportionately more capillaries, their values converge towards their male counterparts (fig. 9).

The present study, together with others [8, 11] in adults, though unrecognized at the time, confirms the observation that the relationship of Q'_{eff} and $V'O_2$ is not linear, as had previously been thought [6]. This is manifested by the nonlinear slope of $1/\text{AVO}$ from the Fick equation (fig. 1). This is not surprising, as an increase in peripheral oxygen extraction/utilization is a predictable part of exercise adaptation.

As this study demonstrates that fC does not bear a constant relationship to Q'_{eff} either between the sexes or during exercise, and that $V'O_2$ does not bear a constant relationship to Q'_{eff} , we question the widespread use of fC and $V'O_2$, and derivatives such as the oxygen pulse ($V'O_2/fC$), as surrogates for Q'_{eff} , at least in children. In particular, the oxygen pulse which, from the Fick equation, is assumed to equal the product of the stroke volume and AVO, is potentially highly misleading especially in disease groups where multiple interactions may occur. Even though a crude correlation of oxygen pulse with Q'_{eff} explained nearly 60% of the variance in our study in normal children, the range for an individual value was up to 250% (data not shown). Similarly, in the present study, at an fC of 160 bpm, Q'_{eff} ranged 4–9 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$.

During recovery, we were surprised to find a rapid resolution in resting values of Q'_{eff} , despite the expected finding of a persistently mildly raised fC . The net result was a significantly lower stroke volume than resting value. How long this situation may continue after 9 min recovery, is unknown. One explanation may be that this study exam-

ined Q'_{eff} rather than total \bar{Q} and, that the discrepancies found may be due to changes in the shunt fraction within the pulmonary circulation. This may explain the TL_{CO} and KCO being below resting values, particularly in males 9 min after maximal exercise, implying a lower pulmonary capillary blood volume taking part in gas exchange, than at rest. Given that FRC was slightly above resting at this stage, there may be a greater proportion of pulmonary alveolar/capillaries units not being perfused. This is not a likely explanation for the nonlinearity of the $Q'_{\text{eff}}/V'O_2$ relationship since the shunt fraction would need to increase from its assumed resting value of approximately 5% to 40% for such a discrepancy to occur, and it is widely believed that shunt fraction declines with exercise.

The present study has also shown that there may be a difference between a variable at peak exercise, and its maximum, after which physiological adaptation to exercise begins to falter. This is most manifest by the observation of a falling effective stroke volume and KCO at peak exercise. The stroke volume findings may be an *in vivo* demonstration of Starling's law of the heart; namely that there is a maximum end-diastolic volume/stroke volume relationship after which there is a decline in function. This phenomenon was observed but not commented on in an adult study [38].

In conclusion, reference standards cannot be extrapolated from adults to children and need to take account of size, age, sex and pubertal stage. Standardization of all the results for these factors is crucial if children with disease states are being compared. Without the requirement of relying on the subject's motivation or talent to achieve a true maximum exercise in this study, function can be assessed at submaximal exercise, which is a more realistic test of everyday activity, especially in diseased children.

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