Effective pulmonary blood flow in normal children at rest

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ABSTRACT Effective pulmonary blood flow was measured with a soluble inert gas uptake method (10% argon, 3.5% freon-22, 35% oxygen, balance nitrogen) in 98 apparently healthy children aged 5-14 years. None had any evidence of cardiorespiratory disease and all had normal values for absolute and dynamic lung volumes and transfer factor for carbon monoxide. Values of blood flow measured by a rebreathing method correlated reasonably closely with height, weight, body surface area, and lung volumes, and to a lesser extent with hand and foot size. The mean (SD) effective pulmonary blood flow index was $2.7 (0.31) \text{ l min}^{-1} \text{ m}^{-2}$. Small children found a single breath method of measuring flow more difficult to perform and the results were more variable.

Introduction

Respiratory methods for the determination of pulmonary blood flow estimate that part of the flow through lung capillaries which is effective in gas exchange. The principle of using soluble gas uptake to calculate this fraction was invented by Humphrey Davy in 1840 and developed by several people, notably Grollman,¹ Cander and Forster,² Teichman *et al.*,³ and Sackner.⁴ Soluble inert gas is removed from alveolar air at an exponential rate that is proportional to blood flow and the solubility of the gas in blood. Initially this process is complicated by gas mixing. Later it is disturbed by the recirculation of contaminated blood. When the logarithmic concentration of test gas in alveolar air is plotted against time the artefact free period between mixing and recirculation is recognised as a log-linear fall, from which the flow of blood effecting gas removal can be calculated. It is called effective pulmonary blood flow. The particular effective pulmonary blood flow variants of the principle used here are the rebreathing method and the single breath uptake of an argon-freon-22 mixture described by Denison *et al.*^{5,6} Both techniques are non-invasive and are suitable for use in children.

Since heart catheterisation became feasible the Direct Fick method of estimating cardiac output has become the most acceptable invasive way of assessing children with heart disease,⁷ but data in normal

children are understandably limited. The findings of Brotmacher and Felming⁸ are commonly used. Several workers have obtained non-invasive estimates of pulmonary blood flow in children, using respired soluble inert gas or carbon dioxide techniques. Godfrey *et al.*⁹ and Zeidifard¹⁰ measured pulmonary blood flow at rest and during exercise and found that the relation of blood flow to oxygen consumption was the same in children and adults. Chu *et al.*¹¹ and Cotton¹² have applied the method in neonates to study blood flow in the respiratory distress syndrome. None of these investigations, however, has provided sufficient data to establish normal values for children at rest. The present study describes rebreathing and single breath measurements of effective pulmonary blood flow ($\dot{Q}_{P_{\text{eff}}}$) in a total of 98 healthy schoolchildren from London.

Methods

SUBJECTS

The subjects, 53 girls and 45 boys aged 5-14 years, came from private schools in London, and are part of a larger study of respiratory function in healthy children (in preparation). Informed consent was obtained from the parents, who were also asked to complete a detailed questionnaire on past medical history, family history, and prevalence of smoking in the household. Each child was examined on the day of the tests for current disease of the respiratory tract and the presence of cardiac murmurs. Any child with a significant history of cardiorespiratory illness, particularly asthma, or with coryza or wheezing on the day, was excluded from the study.

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*Effective pulmonary blood flow in normal children at rest***ANTHROPOMETRY**

Each child was weighed and measured by the anthropometric techniques of Tanner and Whitehouse.¹³ Standing height was determined with a Harpenden stadiometer, and hand length (from the distal end of the radius to the tip of the middle finger) with a Harpenden anthropometer. Pubertal stage was noted. Body surface area was calculated from height and weight by means of the nomogram of Dubois.¹⁴

LUNG FUNCTION TESTS

Total lung capacity (TLC) and residual volume (RV) were determined by constant volume whole body plethysmography¹⁵ (Pulmstar SMB, Fenyves and Gut). A dead space adapter (40 ml) was used for children who had a tidal volume of 300 ml or less. No correction was made for abdominal gas. The transfer factor for carbon monoxide (TLCO) was measured (transfer test machine PK Morgan, series B) by the 10 second single breath procedure of Ogilvie *et al.*¹⁶ In seven children with a vital capacity of 700 ml or less the rebreathing procedure of Lewis¹⁷ was used. Combined inspiratory and expiratory maximal flow-volume loops were recorded, an Ohio 810 rolling seal spirometer being used.

EFFECTIVE PULMONARY BLOOD FLOW

Effective pulmonary blood flow was measured on the morning the other tests were done, when the subjects had sat and rested for at least 10 minutes, one hour or more after their normal breakfast. Most children did both the rebreathing and the single breath tests, in random order, with an interval of 10 minutes between the two tests. For both methods a mixture of 10% argon, 3.5% difluoromonochloromethane (freon-22) and 35% oxygen in nitrogen was breathed. The changing fractional concentrations of these gases with time were recorded continuously by respiratory mass spectrometry (Centronics MGA 200 analyser). The machine had a sample flow of 60 ml/min and a 95% response time of 0.2 second.

For the rebreathing estimate a rebreathing bag fitted with a half Haldane tap was filled with a measured volume of gas mixture, corresponding to about 80% of the subject's vital capacity. Subjects were asked to exhale to residual volume and then rebreathe deeply from the bag about 15 times over the ensuing 20–30 seconds. For the single breath procedure the bag was filled in the same way and subjects were asked to exhale to RV, inhale to TLC, hold their breath for two or three seconds, and then exhale at about 90 ml/s to reach RV some 20 seconds later. To help the children achieve a steady rate of expiration a volume trace and target ramp were presented to their field of view. The pen records of gas concentrations from both procedures were analysed as

described previously.^{5,6}

PRELIMINARY STUDIES

The final study design was influenced by the findings in several preliminary experiments. Some of these were done with adult subjects, who could more reasonably be asked to do repeated tests than children. The main findings in the preliminary studies were:

1 Studies in adults showed that if the measurement of pulmonary blood flow was repeated at 3.5 minute intervals estimates of blood flow were stable after the first two measurements.

2 So that we could examine the effects of varying inspired volume, four adults repeated the rebreathing and single breath procedures using an inspired volume corresponding to 75% and 100% of vital capacity. This made no significant difference to the calculated blood flow, the mean difference being only 0.1 l min⁻¹ for rebreathing and 0.2 l min⁻¹ for the single breath test.

3 The effect of varying the rate of expiration from 0.05 to 0.1 and 0.15 l s⁻¹ was investigated in six adults. A difference in the calculated flow was found in all subjects, with a mean value of 5.4 l min⁻¹ at the slower rate, 6.3 l min⁻¹ at the medium rate, and 6.7 l min⁻¹ at the fastest rate of exhalation. As children were not able to control their rate of expiration very precisely, we accepted that this might be a cause of variability in their single breath results.

4 To examine the effects of recirculation during rebreathing, we analysed 59 traces in 22 children from the start of the linear record to the 15th, 20th, and 25th second of the manoeuvre. There were no significant differences between the calculated results to the 15th and 20th second but there was a fall of 4.5% by the 25th second. The time limit to trace analysis was therefore set at 20 seconds.

5 The day to day variability in the estimates of pulmonary blood flow was studied in seven children who repeated the tests at the same time on three consecutive days. For the rebreathing test the coefficient of variation within each set of measurements was 6.7% and the day to day coefficient of variation of the mean value was 4.8%. For the single breath test the coefficient of variation within each set was 8.8% and the coefficient of variation between days 6.0%.

As a result of the pilot studies 98 children in the formal study were asked to perform at least five timed rebreathing and single breath tests. The third, fourth, and fifth traces were used to calculate effective pulmonary blood flow. Where one of these was clearly unsatisfactory, a sixth and occasionally a seventh test was carried out. The inspired volume chosen for the rebreathing test was between 75% and 100% of vital capacity.

CALCULATION OF RESULTS

A Numonics digitising tablet and a Prime 300 computer were used to analyse the data, employing the following steps:

1 The argon and freon traces were delineated, scaled, and aligned. The accessible lung volume was calculated from the dilution of the inspired argon.

2 The concentration of freon was expressed as a fraction of the simultaneous argon concentration for each end tidal point, and this fraction was plotted on a semilogarithmic scale against time. The computer program provided a visual display at this step, so that the linear portion of the log plot of freon uptake could be selected and measured.

3 The accessible lung water (Vw) and effective pulmonary blood flow Qp were then calculated from the following equations:

$$Vw = (VA/Sw) * ((100/I) - 1) * (760/(PB - 47))$$

$$Qp = \text{"slope"} * (((VA * 760)/(PB - 47) + Sw * Vw)/Sb),$$

where Sw and Sb are the Ostwald solubility coefficients of freon in water and blood respectively, I is the intercept of the linear part of the log plot with the time zero ordinate, and VA is the accessible gas volume of the lung. For the single breath trace the program includes a correction for diminishing lung volume.⁶

ANALYSIS

The study provided the following measurements on each child: (a) age, height, weight, hand and foot length, surface area estimate, and gender; (b) total lung capacity, residual volume, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), TLC, alveolar volume (VA), and transfer coefficient (KCO); (c) effective blood flow index determined by single breath or rebreathing procedures or both. This is the effective blood flow of the whole lung, divided by the body surface area, and is analogous to cardiac index.

Dynamic and static lung volumes and transfer factor for carbon monoxide were compared with the published values of Polgar and Promodhat.¹⁸ Results were surveyed initially by regression analysis and then inspected by multiple stepwise linear regression.

Results

The ages of the children varied from 5 to 14 years, with a mean of 7.2 years for the 45 boys and 9.3 years for the 53 girls. Most of the 98 subjects were white, but seven came from the Middle East, one from India, one from Pakistan, one from Japan, and two from Africa. All but five boys were prepubertal; 14 of the 53 girls were in pubertal stages 2-4 and three were fully mature (stage 5). In general, the children were easy subjects who appeared to enjoy doing the tests. A full size

Table 1 Absolute and dynamic lung volumes and transfer factor for carbon monoxide (TLCO) in 98 apparently healthy children aged 5-14 years

Variable	Mean (SD) (% pred ¹⁸)
FEV ₁	94.6 (11.7)
Forced vital capacity	91.9 (12.0)
Total lung capacity	101.1 (11.5)
Residual volume	147.3 (46.2)
TLCO	101.2 (12.2)

mouthpiece and nose clip presented no problem, even to the smallest, providing that they were allowed to put them on themselves.

Three children were not able or willing to complete the lung volume measurements in the body plethysmograph and have been excluded from the whole study. Four of the smallest children were unable to do the breath holding or steady exhalation required for the single breath tests but are included in the rebreathing analyses. Small children were sometimes unable to signal that they had reached residual volume during exhalation, and the observer then had to judge when this had occurred. In four children the traces for the single breath test were considered to be unsuitable for analysis, usually because expiration was too fast or the argon trace indicated poor and variable gas mixing. Estimates of effective pulmonary blood flow were therefore available for the rebreathing technique for 89 children and for the single breath tests for 81.

Values for FEV₁, FVC, TLC, and TLCO were close to those predicted by Polgar and Promodhat¹⁸ (table 1). The RV values are higher than predicted, but this was also true of a much larger group of children studied by the same methods in our laboratory. The data reviewed by Polgar and Promodhat were based on gas dilution estimates rather than plethysmography, and would be expected to be slightly smaller.

Table 2 Relation between rebreathing estimates of effective pulmonary blood flow (l min⁻¹) and anthropometric data, FEV₁, and total lung capacity in healthy children aged 5-14 years: slope and intercept of the regression line and the regression correlation coefficient

n	Variable	Slope	Intercept	r	SE of estimate
89	Height (cm)	0.040	-2.536	0.76	0.369
89	Weight (kg)	0.057	+1.178	0.79	0.347
89	Body surface area (m ²)	2.651	+0.091	0.80	0.336
89	Total lung capacity (l)	0.687	+1.031	0.71	0.402
89	FEV ₁ (l)	0.995	+1.181	0.73	0.386
86	Hand length (cm)	0.273	-1.142	0.66	0.399
86	Foot length (cm)	0.204	-1.349	0.67	0.394

Fig 1 Relation between rebreathing estimates of effective pulmonary blood flow ($\dot{Q}_{PR}$) at rest and body surface area in 89 apparently healthy children. The regression line, 95% confidence limits, and regression equation for flow on body surface are shown.

RELATION OF EFFECTIVE PULMONARY BLOOD FLOW TO ANTHROPOMETRIC INDICES AND PULMONARY FUNCTION

The correlations between blood flow measured by the rebreathing method and anthropometric variables, FEV₁, and TLC are given in table 2. The rebreathing estimates of effective pulmonary blood flow showed a reasonably close relation to height, weight, FEV₁, TLC, and surface area, but less so to hand and foot size. The relation of the rebreathing estimate of blood

flow to body surface area ($r = 0.8$) and to TLC ($r = 0.71$) is shown in figures 1 and 2. The mean (SD) effective pulmonary blood flow index obtained from the rebreathing method was $2.74 (0.31) \text{ l min}^{-1} \text{ m}^{-2}$, and was independent of height and age.

The relations of the anthropometric variables and TLC, FEV₁, and FVC with pulmonary blood flow determined by the rebreathing method were also analysed by multiple stepwise regression. The closest correlation was provided by surface area, and no further variable improved the correlation. As surface area is calculated from two measurements, height and weight, it may be subject to greater error; so the analysis was repeated excluding it. Weight then provided the closest correlation ($r = 0.75$) and the final model was improved by the addition of FEV₁ ($r = 0.77$).

The relation between the single breath estimates of blood flow and body surface area was poor ($r = 0.4$) and similar to that for height and weight ($r = 0.42$ and 0.36 respectively). The mean (SD) effective pulmonary blood flow index derived from single breath estimates was higher and more variable ($3.94 (0.74) \text{ l min}^{-1} \text{ m}^{-2}$) but fell substantially with age, suggesting that the high values in young subjects were unreliable. The coefficients of variation for effective pulmonary blood flow index for sets of three acceptable measurements on each child were 6.3% for rebreathing manoeuvres and 8.0% for single breath procedures.

The expiratory rate calculated from the volume trace in the single breath tests varied between 0.07 and 0.31 l s^{-1} . Multiple regression analysis of effective pulmonary blood flow against height and expiratory rate gave the regression equation

$$\dot{Q}_{PR} = -0.32 + 0.03 \cdot \text{Ht (cm)} + 3.0 \cdot \text{exp flow (l s}^{-1}\text{)}.$$

Variation in expiratory rate accounted for half of the variability in results.

Discussion

The purpose of this study was to determine normal values for effective pulmonary blood flow in children at rest, and relate them to body size. For the rebreathing method normal values may be predicted with reasonable confidence from height, weight, or calculated surface area. The mean value of $2.74 \text{ l min}^{-1} \text{ m}^{-2}$ is similar to other estimates using soluble gas methods, which range from 2.2^1 to 3.31^2 . Our mean, however, is consistently lower than Direct Fick estimates of the cardiac index—for example, 3.5 , 3.6 , and $4.3 \text{ l min}^{-1} \text{ m}^{-2}$ cited by Barratt Boyes,¹⁹ Brandfonbrenner *et al*,²⁰ and Brotmacher and Felmig⁸ respectively. In part this is due to body position, as moving from the supine to the sitting posture reduces cardiac output by 5–20%.²¹ Some 5% of blood flow apparently passes to unventilated alveoli and is

Fig 2 Relation between rebreathing estimate of effective pulmonary blood flow ($\dot{Q}_{PR}$) at rest and total lung capacity in 89 apparently healthy children. The regression line, 95% confidence limits, and regression equation for flow on total lung capacity are shown.

excluded from respiratory estimates of pulmonary perfusion.²² Thus the differences in rebreathing and Direct Fick estimates can be accounted for.

For practical reasons this study was performed in children from private schools. We accept that their stature may differ slightly from the norms in Britain, but the relations between the measured anthropometric variables, lung volumes, and effective pulmonary blood flow are likely to be representative of all children.

The soluble inert gas methods assume that the mixed venous content of indicator gas is zero, and pulmonary end capillary blood and alveolar gas are in equilibrium. Dissolved gas in recirculating blood will disturb the log-linear relation of gas uptake in the lung with time. With our methods this was detected only after 20 seconds as the absorbed gas is taken up by peripheral tissues before it reappears in the lung.²³ During successive manoeuvres at 3.5 minute intervals the end tidal concentration of freon-22 measured at the start of each manoeuvre rose slightly but did not exceed 1.3% of the inspired concentration. A quasi-steady state was usually established by the end of the third manoeuvre.

In some patients with cardiorespiratory disease early recirculation may occur through abnormal channels. One attraction of the single breath test is that it begins to provide useful information within four seconds of the onset of the manoeuvre. Unfortunately the results are substantially affected by the rate of expiration and it is difficult to fix this for some of the younger children.

Rebreathing creates a more homogeneous gas composition in the lung and minimises the effects of ventilation-perfusion inequality. In children with severe respiratory disease, with substantial areas of underventilation or ventilation-perfusion mismatch, the effective pulmonary blood flow is much lower than the total blood flow.²⁴ Nevertheless, serial measurements may be valuable in showing a change in the potential for gas exchange. Hypoxia is avoided by using an oxygen rich initial gas mixture. Fairly deep breaths are used to achieve good gas mixing, although this is bound to cause some increase in pulmonary blood flow.

The effective pulmonary blood flow measured by these soluble gas methods is a reflection of the blood flow that is useful for respiratory gas exchange. The values obtained by the rebreathing method are reproducible in children and the ranges predicted from this study are closely related to body size. We hope that this information will be of use in assessing patients with cardiopulmonary disorders when heart catheterisation is inappropriate. The method is particularly suited to serial measurements of pulmonary blood flow—for example, in assessing the value of vaso-

dilator treatment or the progression of kyphoscoliosis. Although the correlations with hand and foot sizes are not as close as those for weight and height, they may be useful in children with severe disorders of growth, such as osteogenesis imperfecta, and in children with spina bifida whose height cannot be measured.

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