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Pulmonary vascular resistance in children with congenital heart disease

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ABSTRACT Pulmonary and systemic blood flow and pulmonary vascular resistance were measured in 21 children with congenital heart disease. Blood flow was calculated by the direct Fick method, using measurements of metabolic gas exchange obtained by remote respiratory mass spectrometry. The observations showed that the administration of oxygen caused an appreciable fall in pulmonary vascular resistance in 16 of the 21 children studied and that this fall would not have been appreciated from a study of pulmonary arterial pressure alone as it was masked by a corresponding rise in blood flow. In 10 of 14 children, in whom superior vena caval blood was also sampled, the rise in flow was largely due to an increase in intracardiac left to right shunt. It was accompanied by widening of the alveolar-arterial oxygen gradient, perhaps due to imperfect gas equilibration within the lung.

Pulmonary vascular resistance is conventionally calculated as the mean pressure drop across the lungs' vascular bed divided by the flow (per square metre of body surface) passing through it.[1] Pulmonary vascular disease is inferred from the presence of an irreversibly raised resistance, reversibility being assessed by the response of the vascular bed to oxygen or to other vasodilator agents such as tolazoline.[2]

Use of the direct Fick principle to measure pulmonary blood flow, on which the assessment of reversibility depends, requires sampling of pulmonary arterial and pulmonary venous blood as well as measurements of metabolic gas exchange. Elegant techniques have been developed for the determination of oxygen consumption in air,[3] but simple, rapid, and accurate estimation of gas exchange while the patient breathes 100% oxygen has proved more difficult to achieve. Remote mass spectrometry simplifies this problem because it permits continuous monitoring of end tidal and mixed expired gas tensions, which in turn permits the easy recognition of respiratory steady states.

Methods

Measurements were made in 21 children referred for further study of suspected congenital heart disease. Table 1 gives anthropometric data and the final diagnoses made on these patients, who were between 5 months and 11 years old. They are listed in order of their pulmonary artery pressures, when breathing air, at the time of study. Intravascular pressures were measured via size 6 or 7 French NIH catheters filled with heparinised saline, connected to Bell and Howell pressure transducers (4-327-L223); they were displayed on a Patient Automated Monitor (S E Laboratories, amplifer type SEM 312) with an ultraviolet chart recorder. In 14 patients left atrial (pulmonary venous) pressure was measured directly, and in seven pulmonary arterial wedge pressure was measured with a Swan-Ganz inflatable balloon catheter.

The same protocol was followed on all occasions. Children were premedicated with trimeprazine, papaveretum, and either atropine or hyoscine. They were anaesthetised with alphaxolone-alphadolone acetate (Althesin) by continuous intravenous infusion. The depth of anaesthesia was followed using a Cerebral Function Monitor (Devices). Pancuronium bromide was used for muscle relaxation. After induction the children were intubated and ventilated with a Brompton-Manley ventilator. All breathed from the same circuit (fig 1). Compressed air or oxygen was delivered to the ventilator via graduated air or oxygen flowmeters (Rotameter), which were set to give a constant minute volume throughout a study on any one child. The outflow from the ventilator led to a low volume and low resistance valve box (Hans Rudolph) modified to fit directly on to an

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Table 1 *Anthropometric details, mean pulmonary artery pressure ($\overline{PAP}$), and final diagnosis in 21 children studied*

Case No	$\overline{PAP}$ (mm Hg)	Age (y)	Height (cm)	Weight (kg)	Diagnosis
1	13	3	103	15·0	ASD, PDA
2	13	4	109	16·5	ASD
3	15	13/12	70	9·4	VSD
4	15	5	120	21·5	ASD
5	15	3	98	14·7	ASD
6	17	3	91	10·5	ASD
7	18	2	100	14·0	ASD
8	18	3	100	14·5	HAPVD
9	19	10/12	71	9·4	VSD, coarctation
10	22	2	81	10·0	VSD, PAB
11	23	2	84	8·4	VSD, PAB
12	48	3	88	12·3	VSD
13	52	6	108	14·9	VSD, PDA
14	52	3	93	11·4	PDA
15	56	6	96	12·6	ASD, VSD
16	60	8	125	22·9	VSD
17	63	11	134	24·0	APW
18	85	8	122	20·0	VSD
19	120	8	122	17·7	VSD
20	32	5/12	61	5·5	PDA, coarctation
21	54	6	106	14·6	TGA, VSD

ASD and VSD—atrial and ventricular septal defects; HAPVD—hemianomalous pulmonary venous drainage; PDA—patent ductus arteriosus; TGA—arterial transposition; PAB—pulmonary artery band; APW—aortopulmonary window.

uncuffed endotracheal tube. These were carefully chosen to match the size of the child's trachea and to minimise gas leaks.

The return flow from the child to the ventilator passed through a mixing box (fig 1). A small and constant flow of an indicator gas, argon, was injected into the breathing circuit, immediately upstream of this box, and the composition of the mixed expirate so marked was determined continuously at the outflow of the box by remote mass spectrometry. Expired flows of individual gases (oxygen, carbon dioxide, and nitrogen) were measured from the dilution of the indicator, and oxygen consumption

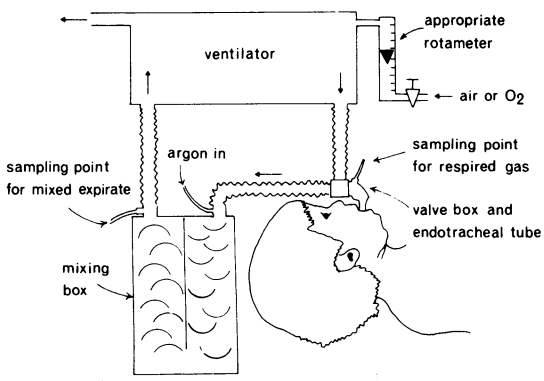

Fig 1 *Diagram of the breathing circuit.*

($\dot{V}O_2$), carbon dioxide production, ($\dot{V}CO_2$), respiratory exchange ratio (R), and expired minute volume ($\dot{V}E$), were calculated on an effectively continuous basis. The analyser was a quadrupole instrument (200 MGA, T C Centronic). This method of measuring respired volumes and metabolic gas exchange is known to be accurate to within ±5%.[4]

The partial pressures of nitrogen, oxygen, and carbon dioxide could also be followed continuously in gas flowing through the endotracheal tube which enabled us to determine easily whether ventilation was adequate, to decide when respiratory steady states has been achieved, and to know when alveolar nitrogen had been washed out sufficiently for measurements of the effects of oxygen to proceed. In a steady state the respiratory exchange ratio equals the respiratory quotient. Thus, if carbon dioxide production is known, oxygen consumption during a period of breathing pure oxygen can be calculated using the R value measured during the previous period breathing air, as the respiratory quotient depends solely on the nature of the fuel being burnt and this is independent of the gas inspired.

At the beginning and end of each study the air or oxygen passing through the rotameter to the ventilator was led directly into the mixing box, and the extent to which it diluted the incoming argon was noted. In this way the flow of gas escaping from the child, past the uncuffed endotracheal tube, could be calculated. This leak was found to be negligible on all occasions.

In the present study argon was delivered to the breathing circuit and gas samples were drawn from the circuit through lengths of fine polythene tubing 30 metres in length. This permitted all the analytical equipment apart from the tubing to be outside the laboratory and so allowed routine cardiac catheterisation to proceed without interruption. The systematic error of measurement of metabolic gas exchange by this method is equal to or less than 0·6% and the standard deviation of single estimates is ±3%.[5]

Once the catheters were in place and end tidal carbon dioxide tension was constant (within 2 mm Hg (0·27 kPa) over several minutes), volumes of at least 5 ml blood were withdrawn to clear the dead space. Blood samples were then withdrawn from both catheters simultaneously at the same steady rate, over one minute. During the sampling period repeated measurements of metabolic gas exchange were obtained from the composition of the marked expirate in the mixing box. After an interval of one to two minutes, to confirm that the child was still in a steady state, these blood and gas measurements were repeated. The inflow to the ventilator was then changed from air to oxygen. After an

interval of at least 10 minutes, during which end tidal gas tensions were monitored to ensure that alveolar nitrogen pressure (P_{N_2}) fell below 30 mm Hg (4 kPa) and alveolar carbon dioxide pressure (P_{CO_2}) remained constant, duplicate sets of measurements were repeated. In 14 of the 21 children blood was also sampled from a point high in the superior vena cava while the patient was breathing air at the beginning of the study, and again when breathing oxygen at the end of the study.

The blood samples were drawn into heparinised 1 ml plastic syringes. The syringes were checked for the absence of gas bubbles, capped, and stored in a vacuum flask filled with crushed ice until the samples were analysed on an automatic pH and blood gas electrode system (Corning 165) 1–20 minutes later. The apparatus was calibrated immediately before and after each set of measurements with moist gas mixtures of known composition and buffer solutions of known pH. Studies with blood tonometered with physiological concentrations of oxygen and carbon dioxide had previously shown that the system measured blood gas tensions to an accuracy of ±2 mm Hg (0·27 kPa). A separate sample of each child's blood was analysed spectrophotometrically to determine its haemoglobin concentration.

The extent to which diffusion of oxygen out of those syringes containing blood with a very high oxygen pressure (P_{O_2}) might introduce error was examined in a separate experiment. A pair of syringes was filled from the same blood sample after tonometry with 100% oxygen. One of the pair was analysed immediately, the other after storage on ice (as described above) for 20 minutes. The mean (SD) values of P_{O_2} in 15 such comparisons were 635 (22) mm Hg (84 (2·9) kPa) in the aliquot analysed immediately and 581 (21) mm Hg (77 (2·8) kPa) in the delayed sample. Tonometry with a mixture of 95% oxygen and 5% carbon dioxide had no effect on the magnitude of this drop in P_{O_2}. The importance of this fall on the calculation of blood flow is considered later.

The gas contents of systemic arterial, pulmonary arterial, and vena caval blood were calculated from their measured tensions, using the oxygen and carbon dioxide dissociaton curve data of Kelman.[6] The solubility of free oxygen in blood was assumed to be 0·003 ml/100 ml/mm Hg. Total pulmonary and systemic blood flows were determined by combining these data with the measurements of steady state gas exchange, using the Fick principle[7] and assuming that the respiratory quotient was unchanged. Pulmonary vascular resistance was calculated in the normal way—that is, by dividing the pressure gradient across the vascular bed by the total pulmonary flow (Qp).

Table 2 *Oxygen uptakes ($\dot{V}O_2$) and blood gas measurements breathing air and breathing oxygen*

Case No	*$\dot{V}O_2$ (ml STP/min)*		*PaO_2 (mm Hg)*		*PvO_2 (mm Hg)*		*$PaCO_2$ (mm Hg)*	
	obs	*pred*	*Air*	*Oxygen*	*Air*	*Oxygen*	*Air*	*Oxygen*
1	57	113	114	491	53	133	39	35
2	95	124	98	439	53	103	32	35
3	66	70	86	350	46	72	31	31
4	125*	150	123*	375	69*	196	35*	35
5	70	108	93	403	52	178	35	37
6	54	89	92	527	61	287	38	41
7	79	108	109	491	50	187	20	19
8	73	128	100	395	55	162	31	32
9	57	72	74	362	45	67	44	46
10	77	83	77	389	47	104	32	31
11	84	80	73	394	43	77	32	34
12	61	92	89	411	43	66	26	28
13	71	126	85	385	56	185	33	35
14	48	94	80	445	42	117	31	30
15	73	102	65	333	53	223	22	21
16	104	156	54	157	42	58	37	40
17	96	143	112	406	38	46	33	33
18	99	140	62	339	40	62	31	31
19	84	132	76	450	34	40	36	36
20	38	43	67	369	29	40	23	28
21	63	118	54	304	43	62	60	39

Conversion: traditional to SI units—PaO_2, PvO_2, and $PaCO_2$: 1 mm Hg ≈ 0·13 kPa.
STP—standard temperature and pressure;
obs—values obtained in this study;
pred—predicted values from Lee and Iliff[7];
PaO_2—systemic arterial oxygen tension;
PvO_2—pulmonary arterial oxygen tension;
$PaCO_2$—systemic arterial carbon dioxide tension.
*Measurements made breathing 41% oxygen rather than air.

Table 3 *Systemic and pulmonary arterial blood oxygen content differences ($C(a\text{-}v)O_2$), blood flow, and pressure gradient measurements*

Case No	$C(a\text{-}v)O_2$ (ml/100 ml)		$\dot{Q}p$ (l/min)		dp (mm Hg)	
	Air	Oxygen	Air	Oxygen	Air	Oxygen
1	2·8	1·4	2·0	4·4	7	6
2	2·0	1·4	4·8	6·6	8	6
3	2·8	1·8	2·4	3·7	8	8
4	0·91*	0·63	13·8*	21·3	9*	9
5	1·6	0·77	4·4	9·2	9	9
6	1·1	0·76	5·1	7·4	7	10
7	2·2	1·0	3·7	7·8	10	11
8	1·8	0·60	4·1	12·7	11	11
9	2·4	2·1	2·3	2·6	9	7
10	2·1	1·3	3·7	5·8	15	15
11	2·6	1·6	3·4	4·8	16	17
12	2·5	2·1	2·4	3·0	41	41
13	1·2	0·69	5·8	10·8	36	32
14	2·4	0·99	2·1	5·3	45	47
15	0·61	0·43	12·0	17·0	52	50
16	5·2	4·1	3·6	4·7	53	65
17	5·6	4·9	1·7	2·0	56	54
18	3·6	2·5	2·8	3·5	78	79
19	5·7	5·6	1·5	1·5	110	104
20	0·67	0·55	0·58	0·92	20	21
21	4·2	2·8	1·5	2·9	44	41

Conversion: SI to traditional units—dp: 1 mm Hg ≈ 0·13 kPa.
$\dot{Q}p$—total pulmonary flow;
dp—pressure gradient across the pulmonary vascular bed.
*Measurements made breathing 41% oxygen rather than air.

Results

In two of the 21 children the systemic arterial carbon dioxide tensions in air and oxygen differed by more than 4 mm Hg (0·5 kPa), although their end tidal P_{CO_2} while breathing the gases were much the same. Results from these children (cases 20 and 21) appear at the bottom of tables 1–3 and are shown by open circles in the figures that follow. In the other 19 children the arterial and end tidal carbon dioxide tensions agreed closely—that is, to within 4 mm Hg (0·5 kPa)—and the values obtained breathing oxygen were similar to those obtained breathing air so that mean metabolic carbon dioxide production in oxygen was 100·6% (SD 5·2%) of that in air.

Figure 2 shows graphs of the ratios of mean pulmonary arterial pressure, total pulmonary flow, and pulmonary vascular resistance in air and oxygen, plotted against the patients' mean pulmonary artery pressure breathing air. The graphs show that, in these children, pulmonary arterial pressure remained constant or rose on the administration of oxygen (fig 2*a*). Total blood flow, however, showed a considerable rise (fig 2*b*) and vascular resistance a clear and substantial fall (fig 2*c*) in almost all patients.

Details of the data presented in figure 2 are listed in tables 2–4 together with predictions of oxygen consumption, based on the data of Lee and Iliffe.[8] Inspection of the tables and figures permits the following conclusions: (1) the children appeared to be in the same metabolic state when breathing air and when breathing oxygen; (2) the agreement between predicted and measured oxygen uptake in these children was poor and the observed oxygen uptake varied widely between individuals; (3) administration of oxygen caused an appreciable fall in pulmonary vascular resistance in 16 of the 21 children studied; (4) this fall would not have been detected by measurement of pulmonary vascular pressures alone as it was masked by a corresponding rise in blood flow; and (5) one child with a normal pulmonary artery pressure and the four oldest children (aged 8–11 years) with very high pulmonary arterial pressures did not show a rise in blood flow or a fall in pulmonary vascular resistance.

Table 4 *Effect of breathing oxygen on indices of respiration and blood flow expressed as ratio of mean value while breathing oxygen to mean value while breathing air*

Index	Ratio $\frac{\text{mean value breathing } O_2}{\text{mean value breathing air}}$ (SD)	No of children
$\dot{V}CO_2$	1·011 (0·056)	19
$PaCO_2$	1·017 (0·054)	19
$C(a\text{-}v)O_2$	0·665 (0·167)	21
$\dot{Q}p$	1·658 (0·515)	21
$\dot{Q}p/\dot{Q}s$	1·578 (0·495)	14
dp	1·000 (0·143)	21
$dp/\dot{Q}p$	0·650 (0·191)	21

Abbreviations as in tables 2 and 3.

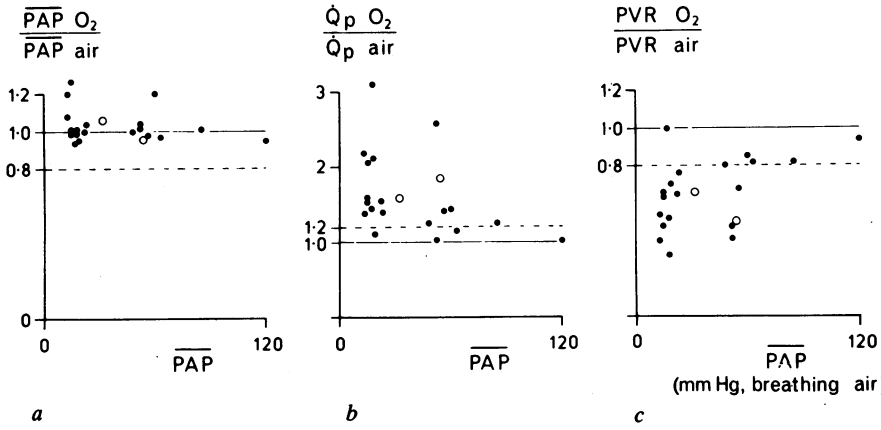

Fig 2 *Effects of breathing oxygen on: (a) mean pulmonary arterial pressure ($\overline{PAP}$); (b) total right to left blood flow ($\dot{Q}p$); (c) pulmonary vascular resistance (PVR) calculated from $\dot{Q}p$. All are expressed as ratios of values seen in oxygen and air, plotted against $\overline{PAP}$. Open circles represent patients 20 and 21 in whom systemic arterial carbon dioxide tensions breathing air and oxygen differed by more than 4 mm Hg (0·5 kPa). A 20% change in the ordinate is represented by a broken line.*

Discussion

The comparison of measured and predicted oxygen consumption (table 2) underlines the findings of others that it may be unwise to predict metabolic gas exchange from published data in children, particularly when they are sedated or anaesthetised.[3 9–11] It is much easier to maintain a steady respiratory state in patients who are mechanically ventilated under general anaesthesia, and it seems reasonable to assume that oxygen consumption remained constant during this time as carbon dioxide output and end tidal carbon dioxide were little altered. The maintenance of a fairly constant alveolar partial pressure of oxygen may be important in patients in whom an accurate comparison of haemodynamics is essential.

Classical methods for the direct measurement of respiratory gas exchange are cumbersome and therefore difficult to use during cardiac catheterisation. In the present study the use of long sampling probes and remote mass spectrometry allowed respired and mixed expired gas tensions to be monitored continuously with ease, and metabolic gas exchange to be determined at will, with little or no interference with normal catheterisation routines. If mass spectrometry is used during anaesthesia nitrous oxide should not be used as it has the same mass as carbon dioxide. Automatic methods for distinguishing the two gases are available but, at best, correct for the presence of a gas that can often be avoided. Similarly, it is quite practicable to measure oxygen consumption directly rather than from carbon dioxide production in atmospheres as rich as 90% oxygen providing 5% or more of inert gas is included in the inspirate. Although instruments exist for the direct measurement of blood gas contents, they are not particularly suitable for studies such as the one described in which many blood samples are taken over a short time. Instruments that measure blood gas tensions are quicker and simpler to use and reduce delays between sampling and analysis that can be an important source of error.

In the few arterial samples (taken while breathing 100% oxygen) that had to be kept as long as 20 minutes between drawing and analysis, some diffusion of oxygen through the syringe wall would have occurred. The mean fall in P_{O_2} over 20 minutes in the samples equilibrated in vitro with 100% oxygen was 54 mm Hg (7·2 kPa), representing a fall in oxygen content of 0·15 ml/100 ml. Such an error in every arterial sample would lead to an overestimate of the response of the pulmonary vasculature to oxygen. In most of our patients this would have been minor, and only two (case 19, the child with the most severe pulmonary hypertension, and case 20) would have shown no fall in pulmonary vascular resistance.

Our observations show that almost all patients showed a considerable rise in the oxygen tension of pulmonary arterial blood when oxygen was breathed, while carbon dioxide excretion (and by assumption oxygen uptake) was unaltered. This implies a large increase in total pulmonary blood flow, which could simply reflect a rise in systemic cardiac output or greater intracardiac left to right shunting, or both. In the 14 children in whom superior vena caval blood was sampled the relative contributions of these mechanisms were calculated

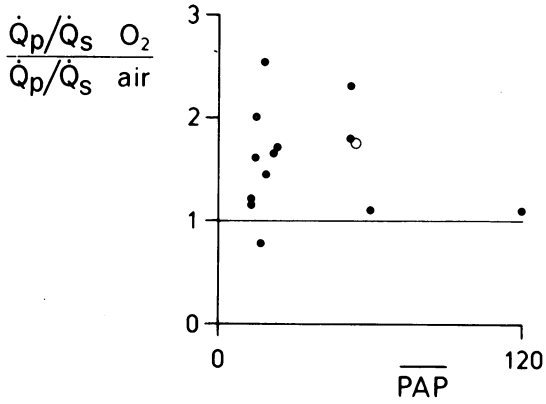

Fig 3 *Effects of breathing oxygen on the ratio of total pulmonary flow ($\dot{Q}p$) to systemic venous return ($\dot{Q}s$) calculated from the composition of superior vena caval blood in 14 of the 21 children studied. Results are expressed as in fig 2. Open circles represents (1) patient in whom systemic arterial carbon dioxide tensions breathing air and oxygen differed by more than 4 mm Hg (0·5 kPa). $\overline{PAP}$ represents mean pulmonary arterial pressure.*

with the caval P_{O_2} as an admittedly imperfect index of the oxygen tension in systemic venous blood.

Figure 3 shows the results, presented as the ratio of total pulmonary flow ($\dot{Q}p$) to systemic return ($\dot{Q}s$) under the two conditions (oxygen and air). It suggests that an increase in intracardiac left to right flow was an important contributor to the greater pulmonary blood flow while breathing oxygen in 10 of the 14 patients. This is a common finding in patients with congenital heart disease. An increase in pulmonary flow, however, has also been noted, in the absence of a shunt, in adults with primary pulmonary hypertension studied in the same manner in these laboratories.[12] In these subjects the vasodilatation was induced by the intravenous administration of diazoxide. We have also seen the same phenomenon in patients with pulmonary hypertension secondary to chronic obstructive airway disease, after they have been given pirbuterol.[13]

If the ideal alveolar air equation is applied to the data in table 2 it becomes apparent that oxygen administration was accompanied by an appreciable widening of the alveolar-arterial P_{O_2} gradient, often by much more than would have been predicted from the shape of the oxygen-haemoglobin dissociation curve alone. This could be due to a real increase in intracardiac right to left shunt or to less perfect equilibration in the lung. We think that the second is the more likely explanation and that the alveolar-arterial P_{O_2} gradient widens because the pulmonary vasodilatation is not uniform and in some zones very high pulmonary blood flow may not allow sufficient time for the transfer of oxygen to be completed. For this reason we have presented our results on the assumption that the total pulmonary flow passed through the lung capillaries. Our results show that blood flow must be measured as well as pressure if one wishes to determine the reversibility of a raised pulmonary vascular resistance as a fall in resistance may be manifest solely by a rise in blood flow.

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