Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts

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WHYTE, MOIRA K. B., J. M. B. HUGHES, J. E. JACKSON, A. M. PETERS, S. C. HEMPLEMAN, D. P. MOORE, AND HAZEL A. JONES. *Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts.* J. Appl. Physiol. 75(1): 321–328, 1993.—The majority of patients with intrapulmonary right-to-left shunting due to pulmonary arteriovenous malformations exhibit good maximum exercise capacity (>70% predicted) despite profound arterial oxygen desaturation. We studied seven such patients to assess tissue oxygen delivery during steady-state exercise. From rest to exercise [50 ± 7 (SE) W] arterial saturation fell from 80 ± 3 to 74 ± 3%, and mean right-to-left shunt increased slightly from 31 ± 4 to 34 ± 5% (P = NS). Minute ventilation was high for oxygen uptake, and the ventilatory equivalent was raised (174 ± 19% predicted) and was correlated with shunt size (r = 0.93). The majority of the patients maintained pulmonary alveolar blood flow within the predicted range for their power output, but total cardiac output was increased to 142 ± 11% predicted due to flow through the shunt. Consequently, on exercise, oxygen delivery per unit oxygen consumption [2.3–3.3 (normal range 1.6–2.4)] and calculated mixed venous oxygen tension (27.0 ± 0.8 Torr) were preserved. Arterial P_{CO_2} rose on exercise by 2.8 ± 1.2 Torr, in proportion to the ratio of flow through the shunt to total cardiac output (r = 0.73), but remained low (33.1 ± 1.4 Torr) in absolute terms. The high cardiac output on exercise may be facilitated by a low pulmonary vascular resistance (0.33 ± 0.08 mmHg · l^{-1} · min, measured at rest), which may explain why exercise performance is better in these patients than in patients with equivalent hypoxemia from other causes.

right-to-left shunt; pulmonary arteriovenous malformations; exercise hypoxemia

PULMONARY ARTERIOVENOUS (av) malformations arise from telangiectasiae of the pulmonary microvasculature, and the majority of cases are associated with hereditary hemorrhagic telangiectasia (3, 7, 10). Physiologically, patients with pulmonary av malformations have a reduced resting arterial oxygen saturation (Sa_{O_2}) (<95%) when measured in the supine position and desaturate further in the erect posture (orthostatic hypoxemia; Ref. 20) and on exercise (6). In our previous study (6) exercise capacity was remarkably well preserved, with 11 of 15 subjects achieving a work load >70% of predicted maximum exercise capacity despite profound arterial oxygen desaturation, from a mean value of 81% at rest to 73% on exercise. Moreover, dyspnea on exercise was a presenting symptom in only 8 of 15 patients. This finding contrasts with the results from studies on patients with equivalent hypoxemia due to congenital heart disease (23) or interstitial pulmonary fibrosis (1, 11) whose exercise capacity was less and in whom dyspnea was a more prominent symptom.

It is very likely that patients with intrapulmonary shunts have a normal or low pulmonary vascular resistance (PVR) at rest and on exercise. We postulated that the low right ventricular afterload might permit the patients to achieve a supranormal cardiac output on exercise to compensate, in terms of oxygen delivery, for the arterial hypoxemia associated with the shunts. This would set them apart from patients with hypoxemia who also have pulmonary hypertension.

We set out to investigate the cardiovascular and ventilatory adaptations that enable these patients to exercise well in the presence of profound hypoxemia. We measured ventilation, pulmonary gas exchange, pulmonary blood flow ($\dot{Q}_P$), and the size of the right-to-left shunt at rest and on exercise. From these measurements, we derived values for total cardiac output ($\dot{Q}_T$) and for mixed venous oxygen and carbon dioxide contents ($C\bar{v}_{O_2}$ and $C\bar{v}_{CO_2}$, respectively). At the time of pulmonary artery catheterization, we measured pulmonary hemodynamics at rest and calculated PVR.

METHODS

Subjects

Seven patients [3 female and 4 male, age 13–51 yr (mean 32 yr)], all with pulmonary av malformations demonstrated on pulmonary angiography, were studied. A total of 11 studies were performed, since *patients 1–3* were studied during subsequent admissions for further embolizations. Clinical details are given in Table 1. Six of the seven patients were diagnosed as having the Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia).

Approval fron the local Ethics Committee was ob-

TABLE 1. *Clinical details of patients at presentation*

Patient No.	Age, yr	Sex	HHT	Presentation	Hb, g/dl	R-L Shunt (Baseline)	Sa_{O_2}		Work at Max Ex		HR at Max Ex	
							%Rest	%Max Ex	W	%Pred	min^{-1}	%Pred
1	27	F	+	Dyspnea, cyanosis	18.4	47	77	48	75	50	141	78
2	13	F	+	Epistaxis, cyanosis	18.1	46	65	53	75	62	182	96
3	40	M	+	Dyspnea, epistaxis	17.6	43	74	66	150	79	159	91
4	26	M	−	Abnormal CXR	19.5	26	86	74	165	97	172	95
5	25	M	+	Abnormal CXR	19.1	30	88	83	180	75	171	92
6	45	M	+	Dyspnea, polycythemia	18.9	21	91	83	180	110	175	105
7	51	F	+	Dyspnea, epistaxis	13.7	20	84	74	112	87	147	87

Clinical details, including presence of hereditary hemorrhagic telangiectasia (HHT) and symptoms, together with results of baseline right-to-left (R-L) shunt measurements and exercise study at presentation. Arterial oxygen saturation (Sa_{O_2}) was determined at rest (erect posture) and at maximum exercise (Max Ex). Hb, hemoglobin; HR, heart rate; %Pred, percentage predicted; F, female; M, male; CXR, chest X ray; + and −, presence and absence of HHT, respectively.

tained in all cases, and the patients gave fully informed consent.

Exercise Studies

Patients were studied on sequential days immediately before embolization of the pulmonary av malformations. On the first day, measurements were made only at rest. On the second day, subjects performed steady-state exercise with a cycle ergometer at a work load equal to 50% of their predetermined maximum power output. Resting studies were performed with the patient sitting on the cycle ergometer but not pedaling to reproduce the same posture as during exercise. Sa_{O_2} (Biox 3700 Ohmeda pulse oximeter) was monitored via an ear probe, and heart rate (HR) was monitored via an electrocardiogram; oxygen consumption ($\dot{V}O_2$) and carbon dioxide production were measured, and pulmonary gas exchange and right-to-left shunt were measured, as described below, in the 5th min of exercise.

Measurement of pulmonary gas exchange. Pulmonary gas exchange at rest and on exercise was assessed as previously described (12). Ventilation, tidal volume (V_T), and frequency were measured. Mixed expired gas was sampled and analyzed for oxygen, carbon dioxide, and nitrogen by a mass spectrometer (Centronic 200 MGA, Croydon, UK), and $\dot{V}O_2$, carbon dioxide production, and respiratory exchange ratio (R) were calculated. End-tidal P_{CO_2} ($P_{ET_{CO_2}}$) was measured with an infrared analyzer (Capnograph IV, Gould, Ilford, UK).

Measurement of $\dot{Q}P$. For measurement of total $\dot{Q}P$ patients were switched into a closed circuit consisting of a 1-liter anesthetic bag filled with ~10% each of helium, sulfur hexafluoride, and freon-22 and with 30% oxygen and 40% argon. The rebreathing maneuver consisted of 10 breaths of ~1 liter each at a rate of 1 Hz, starting at end-tidal expiration. During rebreathing, freon-22 concentrations were monitored by mass spectrometry, and flow was monitored by a pneumotachograph and spirometer. $\dot{Q}P$ was thus calculated from the rate of alveolar uptake of the inert soluble gas freon-22 (12).

Measurement of right-to-left shunt. The right-to-left shunt through the pulmonary av malformations was measured by intravenous injection of ^{99m}Tc-labeled albumin microspheres followed by gamma camera imaging, as previously described (5). Briefly, the method employs microspheres of 23–45 μm diameter (CIS, Gif sur Yvette, France), which are too large to traverse normal pulmonary capillaries. However, a proportion of microspheres bypasses the normal pulmonary vasculature via the abnormally large shunt vessels and thus reaches the systemic circulation in proportion to the right-to-left shunt (as a fraction of cardiac output). Conversely, the number of microspheres, as a fraction of the injected dose, remaining trapped in the lungs reflects the nonshunted blood. We have validated the microsphere method of shunt measurement against the "gold standard" 100% oxygen rebreathing method at rest and have previously described the use of the method on exercise (28). In the present studies, 110 MBq of ^{99m}Tc-microspheres were injected 15 s before the end of the 5-min period of rest or steady-state exercise on the ergometer, and the patient was taken to the gamma camera room immediately after the end of the rebreathing study. Images were obtained of the upper abdomen, in posterior and lateral views, and of the lungs. Thus, total counts were obtained from regions of interest over the right kidney and both lungs. The total injected microsphere radioactivity was measured by counting the syringe that contained the dose, before and after injection, on the gamma camera. On the basis of previous radionuclide studies (17), the right kidney was assumed to receive 10% of the systemic cardiac output.

Thus, at rest

$$\text{R-L shunt} = (\text{R kidney counts} \times 10)/[(\text{R kidney counts} \times 10) + \text{total lung counts}]$$

where R is right and L is left.

Alternatively

$$\text{R-L shunt} = (\text{R kidney counts} \times 10 \times \text{attenuation constant})/\text{microsphere counts injected}$$

On exercise the kidney counts, as a fraction of cardiac output, fall by a variable amount. Because this fall in counts may be all or in part due to a fall in renal blood flow (by an unpredictable amount) on exercise rather than to a change in shunt flow ($\dot{Q}s$), an alternative method must be used for shunt calculation. The change in $\dot{Q}s$ is also related to the change in lung counts, since lung counts reflect the proportion of cardiac output that

is not shunted. The geometry of the lung and chest wall is complex, which makes the calculation of the lung counts of uncertain accuracy, particularly when the R-L shunt is small. However, if the lung counts (per megabecquerel of injected microspheres) on exercise are related to those at rest, then geometric factors are common to both. This ratio is expressed as a fraction (f).

Thus

$$f = \text{lung counts (exercise)/lung counts (rest)} \quad (1)$$

Because lung counts are proportional to the nonshunted $\dot{Q}P$ ($\dot{Q}P/\dot{Q}T$)

$$f = [1 - \dot{Q}s/\dot{Q}T(\text{exercise})]/[1 - \dot{Q}s/\dot{Q}T(\text{rest})] \quad (2)$$

Calculation of $\dot{Q}T$. $\dot{Q}T$ is the sum of $\dot{Q}P$ and $\dot{Q}s$. $\dot{Q}s$ was calculated from gamma camera measurements at rest and on exercise with (2)

$$\dot{Q}s/\dot{Q}T(\text{exercise}) = 1 - f[1 - \dot{Q}s/\dot{Q}T(\text{rest})] \quad (3)$$

where f equals [lung counts (exercise/rest)/injected counts (exercise/rest)].

Thus

$$\dot{Q}T = \dot{Q}P/(1 - \dot{Q}s/\dot{Q}T) \quad (4)$$

where $\dot{Q}P$ is the rate of alveolar uptake of freon-22 during rebreathing.

Derived measurements. The steady-state exercise measurements, apart from intravenous injection of ^{99m}Tc-microspheres, were noninvasive, and arterial blood was not sampled. Oxygen and carbon dioxide contents and pressures in arterial and mixed venous blood were derived from the Fick equation, using Kelman's routines (15) and the measurements of $P_{ET_{CO_2}}$, Sa_{O_2}, hemoglobin (Hb), $\dot{V}O_2$, R, $\dot{Q}s/\dot{Q}T$, and $\dot{Q}T$ as described below. We calculated alveolar P_{CO_2} (Pa_{CO_2}) from the formula of Jones et al. (14)

$$Pa_{CO_2}(\text{Torr}) = 5.5 + 0.9\, P_{ET_{CO_2}}(\text{Torr}) - 2.1\, V_T\,(\text{liters}) \quad (5)$$

assuming arterial P_{CO_2} (Pa_{CO_2}) equals Pa_{CO_2} (ignoring the small R-L anatomic shunt in the subjects from the study of Jones et al.). In a two-compartment model in which nonshunted blood equilibrates with Pa_{CO_2} and shunted blood has the same composition as mixed venous blood

$$Ca_{CO_2} = CA_{CO_2}(1 - \dot{Q}s/\dot{Q}T) + C\bar{v}_{CO_2} \cdot \dot{Q}s/\dot{Q}T \quad (6)$$

where Ca_{CO_2} and CA_{CO_2} are the arterial and alveolar contents of CO_2, respectively. Because $(C\bar{v} - Ca)CO_2 = R(Ca_{O_2} - C\bar{v}_{O_2})$ where Ca_{O_2} is the arterial content of O_2, we can substitute for $C\bar{v}_{CO_2}$

$$Ca_{CO_2} = CA_{CO_2}(1 - \dot{Q}s/\dot{Q}T) + R(Ca_{O_2} - C\bar{v}_{O_2})\dot{Q}s/\dot{Q}T + Ca_{CO_2} \cdot \dot{Q}s/\dot{Q}T \quad (7)$$

Rearranging, we have

$$Ca_{CO_2} = \frac{[CA_{CO_2}(1 - \dot{Q}s/\dot{Q}T) + R(Ca_{O_2} - C\bar{v}_{O_2})\dot{Q}s/\dot{Q}T]}{(1 - \dot{Q}s/\dot{Q}T)} \quad (8)$$

We calculated $(Ca - C\bar{v})O_2$ from $\dot{V}O_2$ and $\dot{Q}T$ (Fick) and Ca_{O_2} (ml/100 ml) as $\{(Sa_{O_2}/100) \cdot 1.34 \cdot [Hb]\}$. Pa_{CO_2}, arterial P_{O_2} (Pa_{O_2}), and mixed venous P_{O_2} ($P\bar{v}_{O_2}$) were derived from the calculated content measurements by using Kelman's algorithms (15).

Measurement of Pulmonary Hemodynamics

Measurements of pulmonary pressures and pulmonary arterial and aortic oxygen contents were performed at pulmonary angiography and embolization before the injection of contrast medium. These studies were performed at rest because exercise studies were not feasible with groin catheters in situ. Furthermore, geographical separation of respiratory and embolization equipment prevented simultaneous measurements of expired gases at rest and catheter measurements.

Mean pulmonary arterial and pulmonary capillary wedge pressures (Ppa and Ppcw, respectively) were measured via an end-hole catheter (7-Fr headhunter catheter, Cordis Europs NV). Free main Ppa was recorded, and the catheter was advanced and wedged in a peripheral vessel until a wedge trace was obtained on the pressure tracing. Arterial and mixed venous oxygen saturations were obtained. PVR was calculated using the Fick principle, assuming a resting $\dot{V}O_2$ derived from standard tables (19) corrected for age, sex, and calculated body surface area.

Statistical Methods

All parameters measured are given as means ± SE. Rest and exercise values were compared using paired t tests.

RESULTS

In the rest studies, performed on *day 1*, minute ventilation ($\dot{V}E$) was 14.0 ± 0.8 l/min, V_T was 0.97 ± 0.09 liters, $\dot{V}O_2$ was 0.29 ± 0.03 l/min, and R was 0.85 ± 0.03. At rest Sa_{O_2} was 80 ± 3%, and the R-L shunt was 31 ± 4%. On *day 2*, patients exercised at a mean power output of 54 W (33% of their predicted maximum). HR increased from 89 ± 5 min^{-1} at rest to 128 ± 6 min^{-1} ($P < 0.001$) during steady-state exercise. Sa_{O_2} fell significantly, from 80 ± 3 to 74 ± 3% ($P < 0.001$). Mean R-L shunt increased only slightly, from 31 ± 4 to 34 ± 5%, a change that was not significant ($P = 0.16$). However, calculated $\dot{Q}s$ increased in all patients, from 3.1 ± 0.6 l/min at rest to 5.0 ± 1.0 l/min on exercise ($P < 0.03$, $n = 8$).

The ventilatory responses to exercise are shown in Table 2. $\dot{V}E$ was high for the $\dot{V}O_2$. Calculated ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) was high [46 ± 5 (or 175 ± 19% predicted)] compared with the normal range of 23–28 (13). There was a close positive correlation on exercise between $\dot{V}E/\dot{V}O_2$ and the R-L shunt (Fig. 1*A*) and a negative correlation between $\dot{V}E/\dot{V}O_2$ and Sa_{O_2} (Fig. 1*B*). Data from *patient 6* were not included in the calculations of correlation values because of gross hyperventilation (see DISCUSSION).

$\dot{Q}P$ and R-L shunt fraction were measured on exercise and, by using *Eq. 4*, $\dot{Q}s$ and $\dot{Q}T$ were calculated (Table 3). The majority of the $\dot{Q}P$ values lay within the predicted normal range (Fig. 2*A*), but seven of the nine measure-

TABLE 2. *Ventilatory response to exercise*

Patient No.	Work Load W	Work Load %Pred	$\dot{V}_E$, l/min	$\dot{V}_{O_2}$, l/min	$\dot{V}_E/\dot{V}_{O_2}$	$\dot{V}_E/\dot{V}_{O_2}$ %Pred	V_T, liters	R	Sa_{O_2}, %Ex	R-L Shunt, %	Δ Shunt
1											
Study 1	45	36	51.0	0.88	58	227	1.46	1.12	70	53	+9
Study 2	45	36	45.2	0.74	61	239	1.37	1.16	65	57	+15
2											
*Study 1**	30	25	29.5	0.57	52	189	1.18	1.07	61	51	+4
Study 2	30	25	30.9	0.68	45	164	1.34	0.91	67	39	−7
3											
Study 1†*	75	40							70	52	+17
Study 2	75	40	37.9	1.16	33	127	1.89	0.91	75	28	+4
4	90	53	34.1	1.25	27	108	2.13	1.04	87	16	−10
5	75	30	44.1	1.40	32	131	2.76	0.88	83	28	+11
6	45	28	51.8	0.76	68	261	1.73	1.25	74	25	+3
7	50	30	34.0	0.95	36	124	1.40	1.12	83	11	+5
Mean	54	33	39.8	0.93	46	175	1.70	1.05	74	34	4
±SD	21	9	8.5	0.28	15	57	0.50	0.13	9	17	8
±SE	7	3	2.8	0.09	5	19	0.17	0.04	3	5	3

Measurements of minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), derived ventilatory equivalent ($\dot{V}_E/\dot{V}_{O_2}$; as ratio and as percentage predicted), and tidal volume (V_T) immediately before end of 5 min of steady-state exercise. Sa_{O_2} and R-L shunt were measured simultaneously. R, respiratory exchange ratio; Δshunt, change in R-L shunt from measurement at rest. * Embolization performed subsequent to these measurements and before 2nd study in this patient. † This study was not included in statistical analysis.

ments of $\dot{Q}_T$ (Fig. 2*B*) were well above the normal range obtained from Cerretelli and Di Prampero (4). Oxygen delivery to the tissues on exercise was closely related to $\dot{V}_{O_2}$ (r = 0.89) and was normal or slightly increased in relation to the normal range (Fig. 3). When corrected for individual values of $\dot{V}_{O_2}$, the mean oxygen delivery ratio was 2.85 ± 0.13 [normal range 1.6–2.4 (4)].

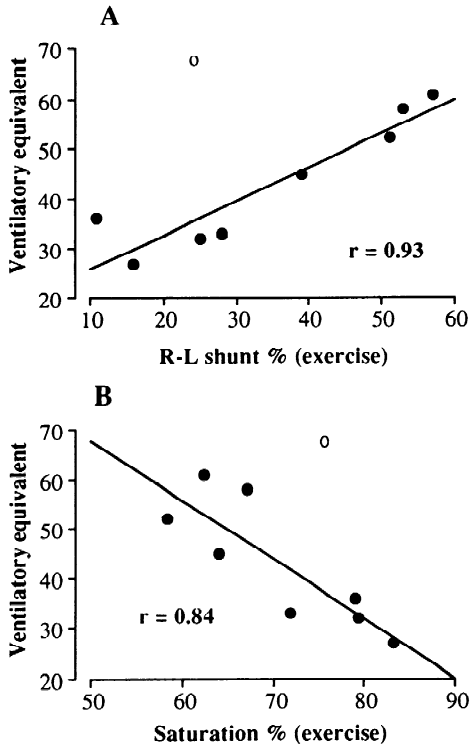

FIG. 1. *A*: ventilatory equivalent [ratio of minute ventilation to oxygen consumption ($\dot{V}_E/\dot{V}_{O_2}$)] plotted against right-to-left (R-L) shunt on exercise (as percentage of cardiac output) measured with radiolabeled microspheres (r = +0.93). *B*: $\dot{V}_E/\dot{V}_{O_2}$ plotted against arterial oxygen saturation measured by oximetry. An inverse correlation was observed (r = −0.84). For both graphs, *patient 6* (○) was not included in calculation of correlation coefficients (see text).

The product of $\dot{Q}_S$ and $C\bar{v}_{CO_2}$ in liters per minute, which can be considered to reflect the carbon dioxide shunt, shows a direct relationship with ventilation (Fig. 4). In addition, the increase in Pa_{CO_2} on exercise (Table 4) was related both to $\dot{Q}_S \cdot C\bar{v}_{CO_2}$ (r = +0.695) and to the R-L shunt (r = +0.73).

Finally, measurements of pulmonary hemodynamics were obtained at rest immediately before embolization (Table 5). $\dot{Q}_T$ was derived from Ca_{O_2} and $C\bar{v}_{O_2}$; the value of 8.0 ± 0.8 l/min was higher, but not significantly higher, than the value of 6.6 ± 0.6 l/min obtained by the rebreathing method two days previously. The slightly higher value may reflect the more stressful situation in which the catheter measurements were obtained. PVR was calculated and was found to be reduced in all cases compared with the normal range (18), and PVR was lower in those individuals with the larger R-L shunts (Fig. 5). PVR in the "normal" lung [(mean Ppa − Ppcw)/$\dot{Q}_P$] was 0.49 ± 0.11 mmHg · min · l^{-1} (n = 10), significantly higher than the overall PVR [(mean Ppa − Ppcw)/$\dot{Q}_T$] of 0.33 ± 0.08 mmHg · min · l^{-1} (P = 0.003) but less than the comparable normal range of 0.80 ± 0.04 mmHg · min · l^{-1} (18).

DISCUSSION

The combination of profound arterial oxygen desaturation on exercise and normal or low PVR makes pulmonary av malformations a human physiological model of great interest. In terms of ventilatory control, the combination of hypoxemia and hypocapnia is analogous to residence at high altitude, and the pattern of chemoreceptor stimulation is probably similar. However, the analogy is imperfect since the cardiovascular system is operating without the constraint of the pulmonary hypertension that develops at altitude. The well-preserved exercise capacity appears to be related to an ability to increase $\dot{Q}_T$ on exercise by an amount approximately equal to the flow through the pulmonary av malformations (Fig. 2),

TABLE 3. *Circulatory response to exercise*

Patient No.	Work load, W	$\dot{Q}_P$, l/min	$\dot{Q}_S$, l/min	$\dot{Q}_T$ l/min	$\dot{Q}_T$ %Pred	HR min^{-1}	HR %Pred	SV, ml
1								
Study 1	45	8.1	8.3	16.4	160	148	123	111
Study 2	45	5.8	7.7	13.5	132	129	108	105
2								
*Study 1**	30	6.4	6.4	12.8	142	136	113	94
Study 2	30	10.1	6.4	16.5	183	109	91	80
3	75	13.1	5.1	18.2	152	122	111	149
4	90	11.0	2.1	13.1	101	118	103	111
5	75	16.2	5.4	21.6	180	159	138	136
6	45	6.6	1.9	8.5	85	99	109	86
7	50	12.6	1.6	14.2	139	135	115	105
Mean	54	10.0	5.0	15.0	142	128	112	109
±SD	21	3.6	2.5	3.7	33	19	13	22
±SE	7	1.2	0.8	1.2	11	6	4	7

Measurements of pulmonary capillary flow ($\dot{Q}_P$), calculated shunt flow ($\dot{Q}_S$), and total cardiac output ($\dot{Q}_T$) immediately before end of steady-state exercise. SV, stroke volume. * Embolization performed subsequent to these measurements and before 2nd study in this patient.

ensuring normal oxygen delivery (Fig. 4) and preserving $P\bar{v}_{O_2}$ (Table 4).

Critique of Methods

Arterial blood gases were not sampled (the central purpose of the investigation was the noninvasive measurement of $\dot{Q}_P$ and $\dot{Q}_S$ on exercise), and we recognize the uncertainty of the estimation of Pa_{O_2} from transcutaneous Sa_{O_2} with the use of a standard oxygen dissociation curve. Pulse oximetry is unreliable at very low values of Sa_{O_2}, but we were largely operating on a part of the oxygen dissociation curve favorable for our purpose (Sa_{O_2} = 83–61%). The accuracy of pulse oximetry itself is only ±2% (16), and, although precise measurements of $P\bar{v}_{O_2}$, Pa_{O_2}, and Pa_{CO_2} are not crucial to the message of this paper, a deviation of ±2% of Sa_{O_2} from the nominal, introduced into the calculations (*Eq. 6*), did not make a significant difference, i.e., there was a change of 1 Torr in $P\bar{v}_{O_2}$ per 2% change in Sa_{O_2}. Unfortunately, invasive measurements with pulmonary arterial and aortic catheters were available only at the time of embolization and not during the studies with the cycle ergometer at rest and on exercise.

The validity of the measurement of $\dot{Q}_S/\dot{Q}_T$ with ^{99m}Tc-microspheres has been tested at rest against simultaneous measurements with the 100% oxygen breathing method (28). Over a wide range of shunt values, the mean difference between the two methods was 1.0 ± 0.8% (n = 36). The precision of radioisotopic $\dot{Q}_S/\dot{Q}_T$ measurements has not been independently assessed on exercise. Nevertheless, the crucial parameter f correlates well (r = +0.80) with the fall in Sa_{O_2} from rest to exercise (28). Finally, the measurement of total $\dot{Q}_P$ with freon-22 and inert gas normalization (with helium and sulfur hexafluoride) to mol wt 86 has been compared with simultaneous measurements of cardiac output with indocyanin green (12). In 51 measurements with dogs, the mean difference was 0.052 ± 0.22 (SD) l/min (12 points where gas mixing was extremely slow have been excluded).

The exclusion of *patient 6* from the correlation coefficients shown in Figs. 1 and 4 was on grounds of gross hyperventilation, as judged by a higher $\dot{V}_E/\dot{V}_{O_2}$ (1.94

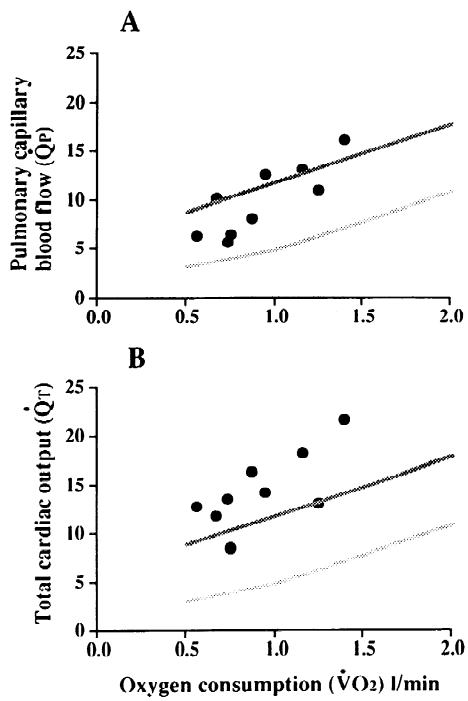

FIG. 2. *A*: pulmonary capillary blood flow ($\dot{Q}_P$; l/min) plotted against $\dot{V}_{O_2}$. *B*: total cardiac output ($\dot{Q}_T$; l/min) plotted against $\dot{V}_{O_2}$. Lines, normal range with 95% confidence intervals (from Refs. 4 and 13).

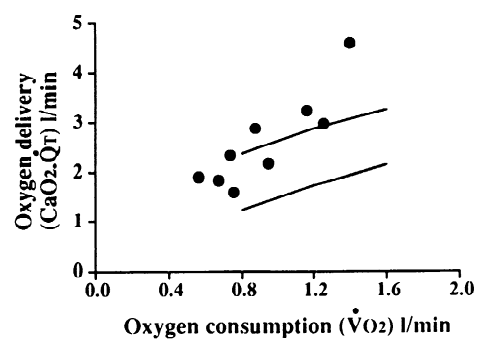

FIG. 3. Oxygen delivery [product of arterial oxygen content (Ca_{O_2}) and $\dot{Q}_T$] plotted against $\dot{V}_{O_2}$ on exercise. Lines, normal range with 95% confidence intervals.

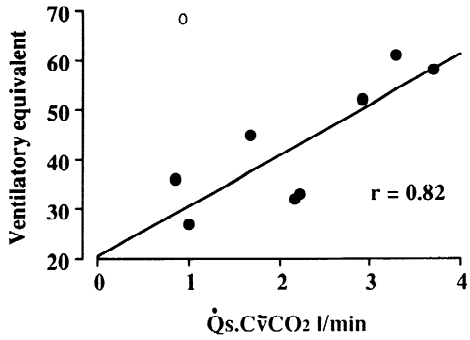

FIG. 4. $\dot{V}E/\dot{V}O_2$ plotted against "carbon dioxide shunt" on exercise [product of shunt flow and mixed venous carbon dioxide content ($\dot{Q}s \cdot C\bar{v}_{CO_2}$)]. *Patient 6* (O) was not included in correlation coefficient (r).

SD above mean of the others) and a higher R (Table 2) and lower derived Pa_{CO_2} (Table 4) than in the remaining subjects.

Ventilatory Control

$\dot{V}E$ during steady-state exercise was high in relation to the power output, and $\dot{V}E/\dot{V}O_2$ was increased, averaging 174% predicted. The excess ventilation on exercise shown by our patients is similar to that reported for children (21), adolescents (22), and adults (23) with intracardiac right-to-left shunts. For example, the mean $\dot{V}E/\dot{V}O_2$ in patients from the study of Streider et al. (26) was almost identical to our value of 46 (Table 2). This hyperventilation contrasts with the reduced hypoxic ventilatory responses at rest measured by transient (8) and steady-state techniques (24). Nevertheless, the metabolic demands during exercise bring about important changes. In the presence of anatomic R-L shunting, reductions in Pa_{O_2} and increases in Pa_{CO_2} are likely to occur, and this combination is a very powerful ventilatory stimulus. A metabolic acidosis may also stimulate ventilation. We did not measure pH, so we cannot comment on this, except that oxygen delivery and $P\bar{v}_{O_2}$ were well maintained, so severe tissue acidosis is unlikely.

Despite reduced hypoxic ventilatory sensitivity at rest (8, 24), resting Pa_{CO_2} in patients with right-to-left shunts is low (23). During steady-state exercise a small but significant increase in Pa_{CO_2} (1.0–1.4 Torr) is generally found (23, 27), but without a change in pH (23). Sietsema et al. (23) postulated that exercise-induced alveolar and pulmonary capillary hypocapnia compensated appropriately for the venous-to-arterial carbon dioxide shunt. Our derived measurements of exercise Pa_{CO_2} are in the same range as those measured by Sietsema et al., but we did not find the compensation [at higher work loads than the patients of Sietsema et al. (30–90 vs. 7–20 W)] so good; ΔPa_{CO_2} (exercise-rest) ranged from −1.8 to +8.9 (Table 4). Although a correlation existed between the excess ventilation on exercise and the carbon dioxide shunt (Fig. 4), there was an even better relationship with the oxygen shunt (Fig. 1). This suggests a role for hypoxemia as well as hypercapnia (the one potentiating the other) in maintaining high levels of ventilation. When 100% oxygen was breathed during a progressive exercise test (unsteady state) by patients with pulmonary av malformations (n = 10), Sa_{O_2} at maximum exercise was raised from 78 to 88% and $\dot{V}E$ was reduced by 19% (2).

Cardiovascular Control

All the patients studied had a normal or low PVR at rest (Fig. 5). Although there are reports in the literature (22) of pulmonary hypertension associated with pulmonary av malformations, it is probable that pulmonary hypertension occurs only when the av malformations are combined with another pathology, e.g., airflow obstruction or thromboembolic disease. Calculation of the PVR in the normal lung showed this PVR to be higher than the total PVR, as would be predicted, but lower than that in normal subjects. These findings may suggest more diffuse vascular disease than is visible on pulmonary angiography.

In all patients there was an increase in $\dot{Q}s$ on exercise, from 3.1 ± 0.6 to 5.0 ± 1.0 l/min ($P < 0.03$). However, in some patients (e.g., *patient 4*) $\dot{Q}s$ as a proportion of total

TABLE 4. *Derived values for CO_2 and O_2 contents and partial pressures on exercise*

Patient No.	PET_{CO_2}, Torr	CA_{CO_2}, ml/100 ml	$C\bar{v}_{CO_2}$, ml/100 ml	Ca_{CO_2}, ml/100 ml	Pa_{CO_2}, Torr	ΔPa_{CO_2}, Torr (Ex-Rest)	$C\bar{v}_{O_2}$, ml/100 ml	Ca_{O_2}, ml/100 ml	Pa_{O_2}, Torr	$P\bar{v}_{O_2}$, Torr
1										
Study 1	24.10	31.5	44.2	38.0	35.6	5.7	11.9	17.3	37.1	28.4
Study 2	19.87	28.4	42.6	36.5	33.7	4.5	11.6	17.1	33.8	26.2
2										
*Study 1**	30.01	35.2	44.9	40.1	39.2	8.9	10.3	14.8	32.9	25.8
Study 2	21.59	27.8	36.5	31.2	27.4	2.5	9.9	15.7	34.2	24.8
3	29.43	35.4	43.4	37.6	33.2	2.8	11.3	17.7	39.1	27.2
4	32.53	36.5	48.3	38.4	36.0	4.5	13.2	22.7	49.2	29.9
5	26.70	32.9	40.5	34.8	29.8	0.1	14.7	21.2	43.6	31.0
6	22.21	30.1	44.4	33.2	26.9	−1.8	9.8	18.7	36.6	24.1
7	35.60	45.3	53.7	46.3	36.4	−1.6	8.5	15.2	43.2	25.7
Mean	28	33.7	44.3	37.3	33.1	2.8	11.2	17.8	38.9	27.0
±SD	5	5.3	4.8	4.4	4.3	3.5	1.9	2.7	5.5	2.3
±SE	2	1.8	1.6	1.5	1.4	1.2	0.6	0.9	1.8	0.8

Calculations of CO_2 contents in blood equilibrated with alveolar gas (CA_{CO_2}), mixed venous blood ($C\bar{v}_{CO_2}$), and arterial blood (Ca_{CO_2}) were derived from end-tidal PCO_2 (PET_{CO_2}), the Fick equation for cardiac outputs, and Kelman's subroutines. See text for details. Pa_{CO_2} and Pa_{O_2}, arterial PCO_2 and PO_2, respectively; $C\bar{v}_{O_2}$ and $P\bar{v}_{O_2}$, mixed venous oxygen content and pressure, respectively; Ca_{O_2}, arterial oxygen content.
* Embolization performed subsequent to these measurements and before 2nd study in this patient.

TABLE 5. *Measurements of resting pulmonary hemodynamics*

Patient No.	Ca_{O_2}, ml/100 ml	$C\bar{v}_{O_2}$, ml/100 ml	$\dot{Q}_T$, l/min	Mean Ppa, mmHg	Ppcw, mmHg	PVR, mmHg·min·l^{-1}
1						
Study 1	21.7	17.3	6.7	11	10	0.15
*Study 2**	23.6	21.5	9.5	14	12	0.21
Study 3	21.2	18.1	6.6	14	12	0.30
2						
*Study 1**	22.2	20.5	10.1	16	13	0.27
Study 2	21.6	20.2	12.3	16	15	0.08
3						
*Study 1**	20.0	17.0	7.1	14	9	0.7
Study 2	22.2	19.6	8.4	13	12	0.12
4	24.0	21.7	9.5	17	15	0.21
6	22.8	21.5	3.7	16	14	0.6
7	16.7	15.1	5.6	14	10	0.7
Mean	21.6	19.3	8.0	14	12	0.33
±SD	2.1	2.3	2.5	1.8	2.1	0.24
±SE	0.7	0.7	0.8	0.6	0.7	0.08

Pulmonary hemodynamics measured at rest before angiography and embolization. Ca_{O_2} and $C\bar{v}_{O_2}$ were derived from measured saturations on arterial and mixed venous blood. Mean pulmonary arterial pressure (Ppa) and pulmonary capillary wedge pressure (Ppcw) were measured with end-hole catheter, and pulmonary vascular resistance (PVR) was calculated. * Embolization performed subsequent to these measurements.

flow (i.e., %shunt) fell on exercise, and, in our previous study (28), we were able to relate this fall to the presence of large isolated pulmonary av malformations that may put anatomical constraints to increases of flow.

These patients displayed a remarkable ability to maintain a normal $\dot{Q}_P$ on exercise in the face of R-L shunts varying from 11 to 57%. This required $\dot{Q}_T$ to rise to 120–220% predicted with a corresponding reduction in the arterial-mixed venous oxygen difference [6.6 ml/100 ml, normal range 9–10 ml/100 ml (Table 4; Ref. 13)]. Supply was tailored to demand (Fig. 4), and derived $P\bar{v}_{O_2}$ (assuming a normal half-maximal oxygen saturation for the oxygen dissociation curve) was preserved (Table 4). What mechanisms were responsible?

First, the low $(Ca - C\bar{v})O_2$ for their level of $\dot{V}O_2$ is linked via the Fick equation to the high cardiac output, averaging 142% predicted (Table 3). Second, six of the seven subjects were polycythemic, with [Hb] > 17 g/dl (Table 1), and, despite a low Sa_{O_2} on exercise (mean 74%; Table 2), the Ca_{O_2} at 17.8 ml/100 ml (Table 4) was ~90% predicted. This combination of high cardiac output and near-normal Ca_{O_2} was the reason for preservation of $C\bar{v}_{O_2}$ and partial pressure (Table 4). In fact, the oxygen delivery was slightly higher than predicted (Fig. 3).

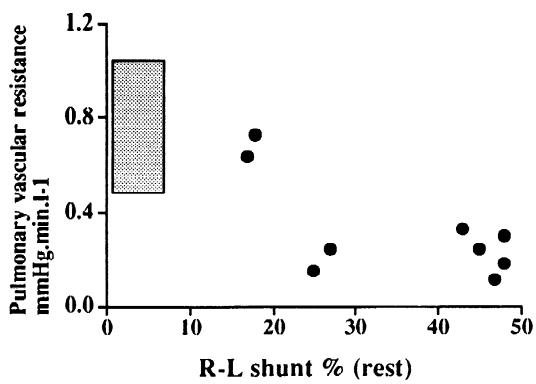

FIG. 5. Pulmonary vascular resistance plotted against R-L shunt on exercise. Stippled box, normal range.

At a simulated altitude of 4,000 m (Sa_{O_2} = 72%) and a $\dot{V}O_2$ of 1.5 l/min, cardiac output in normal subjects was 20% higher and HR was 31% higher than in subjects exposed to normoxemia (25). Stroke volume, mean arterial pressure, and av oxygen content difference were all somewhat less. Because they increased their cardiac output somewhat less than our patients with pulmonary av malformations (mean increase 42%), these subjects developed a larger av oxygen content difference and their $P\bar{v}_{O_2}$ values on exercise were <20 Torr. The difference between the patients at simulated altitude and our patients with pulmonary av malformation is the right ventricular afterload. In the presence of generalized alveolar hypoxia, vasoconstriction leads to pulmonary hypertension, which constrains the rise in right ventricular stroke volume. In patients with pulmonary av malformations, there is no alveolar hypoxia and the pulmonary pressures are low due to the anatomic shunts. There is thus nothing to prevent the right ventricle from increasing its output to maintain oxygen delivery at the level appropriate for the metabolic demand. Hypoxemia during exercise raises plasma norepinephrine and epinephrine more than normoxemia does (9), and the increased HR (compared with predicted HR, Table 3) in our patients probably reflects this difference. Indeed, in patients with pulmonary av malformations, HR at an equal power output (mean 95 W) was significantly less (142 vs. 151 min^{-1}) when subjects breathed 100% oxygen (Sa_{O_2} = 88%) than when they breathed air (Sa_{O_2} = 78%) (2). Isolated working muscle vasodilates greatly when exposed to hypoxemia, so much so that maximum cardiac output would be exceeded if the body as a whole were working. The increased norepinephrine concentration in hypoxemic exercise probably originates from working muscle, stemming from local arterial baroreflexes that keep muscle vasodilatation in check (21). Nevertheless, the high oxygen delivery (Fig. 3) and $P\bar{v}_{O_2}$ (Table 4) on exercise implies a higher than normal blood flow-to-work rate ratio in exercising muscle in these subjects. This in turn suggests a low systemic PVR on exercise (unfortunately

not measured), either due to hypoxemic vasodilatation or to increased muscle vascularity in response to chronic hypoxemia.

Conclusions

These studies, at rest and on exercise, on patients with pulmonary av malformations have revealed both ventilatory and cardiovascular adaptations to exercise. $\dot{V}E/\dot{V}O_2$ was increased and was correlated with the magnitude of right-to-left shunt. Remarkable cardiovascular adaptation was achieved: normal $\dot{Q}P$ was generally achieved at the expense of large increases in $\dot{Q}T$. We suggest that increases in cardiac output are achieved because of pulmonary vascular pressures considerably lower than those found in other causes of profound hypoxemia.

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