

Exercise induced pulmonary vasoconstriction

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SUMMARY Pulmonary vascular resistance normally falls or remains unchanged during exercise. Seven children with pulmonary hypertension were exercised during cardiac catheterisation after operative correction of ventricular septal defect (6) and truncus arteriosus (1). Except for the presence of moderate pulmonary hypertension, resting haemodynamics in these seven children were similar to those of normal children of equal age, but during exercise the postoperative patients showed a rise rather than a fall (+2% vs -18%) in total pulmonary vascular resistance. Two of the seven children had a substantial increase in pulmonary arteriolar resistance during exercise (from 509 to 715 dyne s cm⁻⁵ in one patient and from 606 to 828 dyne s cm⁻⁵ in the other). These two patients did not differ from normal children in respect of arterial or mixed venous oxygen saturations or of pH with exercise, nor was left atrial pressure related to the rise in pulmonary resistance. These two patients, however, had only a small rise in cardiac output during exercise (6.8% and 43.1%) in spite of a substantial increase in oxygen consumption (121% and 373%). One of the patients with exercise-induced pulmonary vasoconstriction had an 82% increase in resting pulmonary vascular resistance over a five year period subsequent to her first exercise study. Analysis of these data, and those previously reported, suggests that exercise induced pulmonary vasoconstriction may occur in 10 to 25% of patients who survive correction of certain congenital cardiac defects. The vasoconstriction cannot be attributed to abnormal changes in blood gases or left atrial pressure, and may be an early sign of progressive pulmonary hypertension.

Studies on the effect of exercise in healthy human subjects have shown that the pulmonary vascular bed reacts to an exercise induced increase in blood flow in a consistent way. Though pulmonary artery pressure usually rises with exercise, total pulmonary vascular resistance and pulmonary arteriolar resistance change little or fall.¹⁻¹⁵ In contrast, patients catheterised after operation for lesions associated with a left to right shunt may have a large increase in either pulmonary artery pressure¹⁶ or total pulmonary vascular resistance with exercise,^{17,18} as may subjects with congestive heart failure⁸ or primary pulmonary arterial hypertension.^{19,20} Unfortunately, most studies of such patients lack sufficient data to characterise fully the response of the pulmonary vasculature to exercise.

We became interested in exercise induced pulmonary vasoconstriction when one of our patients, who had residual pulmonary artery hypertension after

closure of a ventricular septal defect, had a large rise in pulmonary arteriolar resistance with exercise. This patient had a progressive increase in her pulmonary arteriolar resistance over the next five years. We therefore reviewed our studies of patients exercised at cardiac catheterisation after repair of ventricular septal defect (6) and truncus arteriosus (1) in an attempt to address three issues: (1) how frequently does exercise induced pulmonary vasoconstriction occur? (2) what is its aetiology? and (3) what is its clinical significance?

Patients and methods

Paediatric patients at the University of Minnesota are not routinely catheterised after intracardiac repair; but those with preoperative rise in pulmonary vascular resistance are catheterised postoperatively. We reviewed all postoperative catheterisations in paediatric patients after repair of left to right shunting lesions associated with pulmonary hypertension from 1969 to 1980. All patients included in this study: (1) had no residual intracardiac shunt at postoperative catheterisation, (2) had normal resting pulmonary capillary wedge pressures (<12 mm/Hg), (3) had

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raised postoperative total pulmonary vascular resistance (>400 dyne s cm^{-5}), and (4) performed supine exercise as a part of the catheterisation, with measurement of oxygen consumption, cardiac output, and pulmonary and systemic vascular resistances at rest and during exercise. There were seven patients in this group 1 (one patient was studied twice at an interval of five years); six had repair of ventricular septal defect (including one patient with ventricular septal defect and coarctation of the aorta) and one had repair of truncus arteriosus. Four were female and three male patients, and ranged in age from 6 years to 18 years (mean 11.6 years). Preoperatively, all patients had raised pulmonary artery pressure and raised pulmonary to systemic resistance ratios (0.4 to 0.6), but there were insufficient data in most cases to calculate the preoperative total pulmonary vascular resistance. Postoperative catheterisations were performed from one year to 12 years (average of 6.1 years) after operation. All patients were asymptomatic except one (case 2) who had mild congestive heart failure. Light sedation, using phenobarbitone (3 mm/kg) and morphine sulphate (0.1 mm/kg), was used. Intravascular pressures were measured using fluid filled catheters. Cardiac output was determined by the Fick method in six

(and by indicator dilution curves in one patient). After measurement of resting cardiac output, the patients performed submaximal supine exercise using a bicycle ergometer. Exercise cardiac output and pressures were measured between three and six minutes after initiation of exercise.

These data are compared with those obtained from group 2, consisting of 23 essentially normal children of similar age (10 normal subjects and 13 with mild pulmonary stenosis) catheterised at this institution in an identical fashion and previously reported.¹⁵ Paired and unpaired Student's *t* tests were used as appropriate.

Results

Group 1 patients were similar to normal children with regard to age (see Table 1). Except for raised pulmonary arterial pressures and resistances, patients in both groups had similar resting haemodynamic data, including heart rates, systemic blood pressures, cardiac output, oxygen consumption, wedge pressures, and systemic vascular resistances. Unlike the control group, the pulmonary artery mean pressure (45.0 vs 14.3 mmHg) and total pulmonary vascular resistance (875 dyne s cm^{-5} vs 269 dyne s cm^{-5}) were consider-

Table 1 Rest and exercise haemodynamic data obtained at cardiac catheterisation in seven group 1 patients and in group 2 control children (see text)

Case No.	Age(y)	Exercise HR load (watts/ m^2)	Exercise HR (beats/min)	Pa O ₂ sat (%)	Sa O ₂ sat (%)	Pa pH	Sa pH	$\dot{V}O_2$ (ml/min per m^2)	CI (l/min per m^2)	PAP (mmHg)	SAP (mmHg)	RAP (mmHg)	PCWP (mmHg)	TPVR (dyne s cm^{-5})	PAR (dyne s cm^{-5})	SVR (dyne s cm^{-5})	SI (ml/beat per m^2)
Group 1																	
1	8	—	102	75.7	95.4	7.34	7.35	151	4.4	33	94	8	5	600	509	1710	43.1
		43	155	54.0	95.1	7.29	7.34	334	4.7	48	92	—	6	817	715	1560	30.3
2	10	—	90	73.7	95.3	—	7.38	149	4.3	30	97	7	8	558	409	1805	47.8
		43	180	40.8	93.7	—	7.34	682	7.4	50	100	—	—	541	—	1081	41.1
3	13	—	75	68.8	95.1	7.39	7.41	150	3.04	51	95	8	10	1342	1079	2500	40.5
		67	171	17.8	93.6	7.14	7.31	754	5.43	93	110	—	—	1370	—	1621	31.8
4	6	—	108	68.0	95.3	7.36	7.39	200	6.0	52	88	2	3	693	653	1173	55.6
		43	165	—	—	—	—	747	9.6	90	105	—	—	750	—	875	58.2
5	12	—	102	80.0	94.7	7.40	7.40	178	6.2	52	93	5	11	671	529	1200	60.8
		58	180	46.0	87.3	7.22	7.31	695	8.4	68	105	—	—	648	—	1000	46.7
6	13	—	82	76.7	98.7	7.48	7.53	208	5.1	28	88	—	8	439	314	1380	62.2
		36	115	46.8	97.2	7.33	7.40	562	5.8	70	104	—	—	966	—	1435	50.4
		71	145	26.7	93.1	7.23	7.30	888	6.7	90	118	—	—	1075	—	1409	46.2
6	18	—	62	77.3	94.8	7.43	7.45	131	3.3	33	80	4	8	800	606	1939	53.2
		41	108	44.1	95.2	7.32	7.40	620	5.8	73	108	10	13	1007	828	1490	53.7
7	14	—	96	63.0	91.4	7.46	7.47	193	3.5	64	92	8	10	1463	1234	2103	36.5
		51	162	33.4	94.2	7.31	7.38	696	5.8	80	115	14	8	1103	993	1586	35.8
Rest mean*	11.6	—	91	72.4	94.6	7.40	7.41	165	4.39	45	91	6.0	7.9	875	717	1776	48.2
SD	3.99	—	16.6	5.99	1.42	0.044	0.041	25.9	1.27	13.0	5.7	2.38	2.91	370	313	476	8.76
Exercise mean*	49	160	39.4	93.2	7.26	7.35	647	6.73	71.1†	105	—	—	—	891†	—	1316	42.5
SD	9.83	24.8	12.5	2.96	0.076	0.037	145	1.78	17.8	7.39	—	—	—	278	—	318	10.8
Group 2																	
Rest mean	11.1	—	86.1	76.3	96.7	7.40	7.41	159	4.41	14.3	90	4.1	—	269	—	1687	52.7
SD	2.88	—	18.2	3.84	4.32	0.033	0.034	22.5	0.72	3.36	7.67	1.92	—	91.1	—	379	9.59
Exercise mean	49	142	49.6	95.7	7.33	7.39	675	8.00	20.9	120	3.1	—	—	216	—	1046	57.3
SD	11.5	23.5	9.59	1.44	0.058	0.039	151	1.29	4.32	7.67	2.88	—	—	62.3	—	187	11.0

CI, cardiac index; HR, heart rate; Pa pH, pulmonary arterial pH; Pa O₂ sat, pulmonary arterial oxygen saturation; PAP, mean pulmonary arterial pressure; PAR, pulmonary arteriolar resistance; PCWP, mean pulmonary capillary wedge pressure; RAP, mean right atrial pressure; Sa O₂ sat, systemic artery oxygen saturation; SAP, mean systemic artery pressure; Sa pH, systemic arterial pH; SD, standard deviation; SI, stroke index; SVR, systemic vascular resistance; TPVR, total pulmonary vascular resistance.

*Calculated using data from the second postoperative catheterisation case 6; †Indicates a statistically significant difference between rest and exercise with *t* < 0.05 .

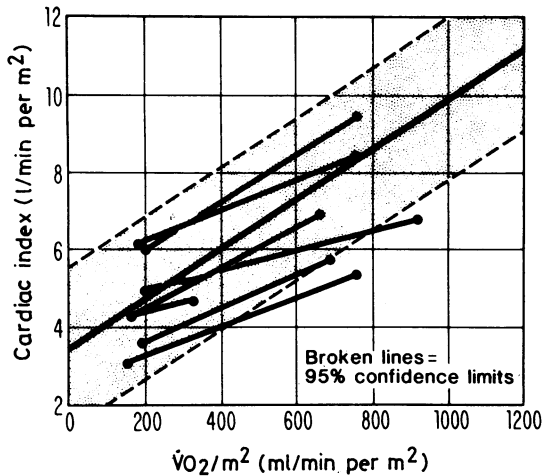


Fig. 1 The change in cardiac index when compared with oxygen consumption ($\dot{V}O_2$) (ml/min per m^2) for seven children in group 1. The shaded area represents 95% confidence limits for the normal children in group 2.

ably raised in the postoperative group.

Both groups performed similar work loads, and had similar oxygen consumption levels both at rest and on exercise. The rise in cardiac output was slightly, but not significantly lower in group 1 than in normal children (Fig. 1); the rise in heart rate, however, was greater in group 1 patients. As a result, though stroke index rose significantly ($p < 0.02$) in the normal children, there was a fall in stroke index with exercise in the postoperative patients (48 to 42 ml/beat per m^2), a change that was significantly different from that of normal children ($p < 0.01$).

The children with pulmonary hypertension also showed an abnormal response of the pulmonary circulation to exercise. Though total pulmonary vascular resistance fell 18% ($p < 0.001$) in normal children during exercise, it rose 2% in the postoperative group (Fig. 2). Though all seven patients had normal pulmonary capillary wedge pressure at rest, only three had exercise pulmonary capillary wedge pressure measurements. Thus, this rise in total pulmonary vascular resistance could conceivably be the result of a rise in left atrial pressure. Since, however, the two patients with the greatest rise in total pulmonary vascular resistance with exercise also had increases in pulmonary arteriolar resistance, it is clear that the rise in total pulmonary vascular resistance with exercise was not secondary to an increase in left atrial pressure.

In two group 1 patients, both the total pulmonary vascular resistance and pulmonary arteriolar resistance rose by more than 25% during exercise. Mechanical factors (such as exercised induced changes in left atrial pressures, or diminished cardiac

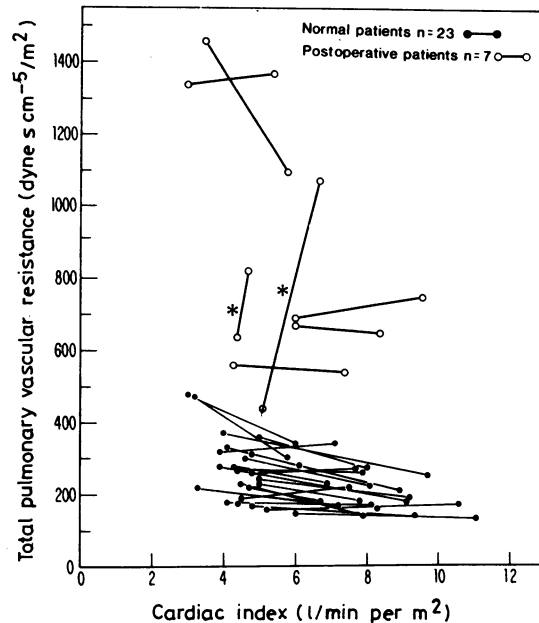


Fig. 2 The change in total pulmonary vascular resistance with exercise for 23 normal children (group 2, solid circles) and seven children with pulmonary hypertension (group 1, open circles) when compared with cardiac index. Asterisks (*) mark the lines for cases 1 and 6 (see text).

output) cannot be reasonably implicated as the cause of this rise in total pulmonary vascular resistance, indicating that the rise in resistance is almost certainly the result of active pulmonary vasoconstriction. Case 1, an 8 year old girl who presented at 7 years of age with a small ventricular septal defect and pulmonary hypertension, had no symptoms or history of cardiac failure. Though her pulmonary artery pressure fell after closure of the ventricular septal defect, pulmonary hypertension and a raised total pulmonary vascular resistance persisted. Case 6 presented at 2 months of age with signs of a ventricular septal defect, and at the age of 10 months had congestive heart failure, pulmonary hypertension, and a large left to right shunt. Her pulmonary to systemic resistance ratio was only mildly raised (0.4) when her ventricular septal defect was closed at the age of 5 years, but pulmonary hypertension persisted after closure. Though her pulmonary arteriolar resistance was only moderately raised at postoperative catheterisation (439 dyne s cm^{-5}), it rose conspicuously with exercise (to 1075 dyne s cm^{-5}). A large exercise induced rise in pulmonary vascular resistance was still present at repeat catheterisation five years later. Of particular concern, the resting pulmonary arteriolar resistance rose during the five year interim from 439 to 800 dyne s cm^{-5} .

In addition to these two patients, it is notable that

case 4 showed an 8% rise in total pulmonary vascular resistance during exercise at her initial postoperative catheterisation. A subsequent catheterisation 12 years later (at the age of 18 years) showed a dramatic increase in resting pulmonary arteriolar resistance (from 693 to 2544 dyne s cm⁻⁵) and suprasystemic pulmonary artery pressure (mean pulmonary arterial pressure 96 mmHg, mean systemic arterial pressure 89 mmHg); the cardiac index was 2.83 l/min per m².

No clinical or haemodynamic variables could be related to the presence of an exercise induced rise in pulmonary vascular resistance, including age at operation, the resting pulmonary artery pressure and resistance, and pulmonary artery pH and oxygen saturation with exercise. The response of the pulmonary circulation to oxygen was also tested in four patients (cases 1, 3, 4, and 6) and did not correlate with the presence or absence of exercise induced pulmonary vasoconstriction.

Discussion

In 1919 Dunn²¹ exercised a goat, measured its right ventricular pressure and cardiac output, and showed that with exercise cardiac output rose out of proportion to right ventricular systolic pressure. Numerous studies of human subjects have followed. Though these studies are heterogeneous regarding the intensity, duration, and type of exercise used they consistently show that, on average, in normal subjects total pulmonary vascular resistance (and pulmonary arteriolar resistance when available) changes little^{3 5 7 14} or falls^{1 2 6 8 9 12 15} with exercise.

There are, however, a few normal subjects in whom total pulmonary vascular resistance or pulmonary arteriolar resistance rises with exercise.^{3-5 7 13} Analysis of the haemodynamic data from these normal individuals shows the following: (1) the rise in resistance is nearly always small (10%); (2) the few individuals with a large increase in total pulmonary vascular resistance have a very low apparent resting pulmo-

nary vascular resistance, suggesting that the resting pulmonary vascular resistance may be inaccurate; and (3) the total pulmonary vascular resistance in normal subjects remains normal on exercise. Therefore, we use exercise induced pulmonary vasoconstriction to denote an increase in *both* total pulmonary vascular resistance and pulmonary arteriolar resistance of at least 25%, resulting in raised pulmonary arteriolar resistance (greater than 400 dyns s cm⁻⁵) on exercise. Total pulmonary vascular resistance should be considered as well as pulmonary arteriolar resistance since a fall in left atrial pressure with exercise might increase calculated pulmonary arteriolar resistance on a purely mechanical basis by decreasing the pressure distending pulmonary vessels.²² Though arbitrary, this definition will exclude all normal subjects.

INCIDENCE

Exercise induced pulmonary vasoconstriction is not rare in patients after repair of left to right shunt lesions, occurring in two of seven (29%) of our patients. From the previously reported postoperative studies of left to right shunt lesions,^{17 18 23-26} that included relatively complete haemodynamic data, it appears that exercise induced pulmonary vasoconstriction may have occurred in four of 33 such patients.

CAUSE

Although exercise induced pulmonary vasoconstriction has been described in other clinical settings (Table 2), its aetiology remains unknown. The most obvious known causes of pulmonary vasoconstriction are hypoxia, acidosis, and left atrial hypertension. Blood oxygen desaturation (either mixed venous or arterial) can cause pulmonary vasoconstriction.³¹ No previous studies documenting exercise induced pulmonary vasoconstriction, however, measured both arterial and mixed venous oxygen levels. In our study, the arterial and mixed venous oxygen saturations in

Table 2 Summary of previous studies which include patients who had exercise induced pulmonary vasoconstriction

Clinical setting	Reference	Comments
(1) Congestive heart failure, in adults, mostly secondary to valve lesions (excluding mitral stenosis) or systemic hypertension	8 27-29	Exercise induced pulmonary vasoconstriction seen with little change or fall in cardiac output
(2) Chronic pulmonary disease, in adults with emphysema or pulmonary fibrosis	28	Exercise induced pulmonary vasoconstriction is an infrequent finding in these patients; pulmonary vascular resistance generally decreases or does not change
(3) Primary pulmonary hypertension, in adults	19	Exercise induced pulmonary vasoconstriction was seen in one patient, and was associated with decrease in cardiac output with exercise
	20	Case report of single patient who showed a rise in pulmonary arteriolar resistance (456 dyne s cm ⁻⁵ to 1096 dyne s cm ⁻⁵) associated with a 13% fall in cardiac output; exercise induced pulmonary vasoconstriction abolished by phentolamine
	30	Three of nine patients exercised showed exercise induced pulmonary vasoconstriction

Exercise pulmonary vasoconstriction

patients in group 1 were not significantly different from those of subjects in group 2, nor did cases 1 and 6 have low oxygen saturations relative to other group 1 patients. Thus, the data available indicate that exercise induced pulmonary vasoconstriction is not a result of low blood oxygen saturation. Similarly, none of the cited studies measured pH during exercise. Our group 1 patients showed no significant difference in pH of either arterial or mixed venous blood compared with our normal subjects, nor did cases 1 and 6 have an especially low pH relative to other patients in this group.

Left atrial hypertension (secondary to mitral valve disease) has been implicated as a cause of active pulmonary vasoconstriction.³² Case 1 showed little change in pulmonary capillary wedge pressure with exercise and case 6 showed only a modest rise. The two patients of Maron *et al.*¹⁸ showed a nearly identical picture, and Beck *et al.*²³ had no patients with exercise induced pulmonary vasoconstriction in spite of a large mean increase in left atrial pressure. It seems unlikely that a rise in left atrial pressure causes exercise induced pulmonary vasoconstriction in these children.

One finding common to all studies is that exercise induced pulmonary vasoconstriction occurred with a small rise—or even a fall—in cardiac output with exercise. Cases 1 and 6 had exercise induced increases in cardiac output of only 6.8% and 43.1% (normal subjects showed an increase of 81.4%), in spite of rises in oxygen consumption of 121% and 373%. Most patients with exercise induced pulmonary vasoconstriction cited in Table 2 had an exercise induced increase in cardiac output of 25% or less and many had a cardiac output with exercise of less than 3 l/min per m².

Although a lower than normal increase in cardiac output during exercise may somehow contribute to the observed vasoconstriction, we cannot identify a cause for low exercise cardiac output in either our patients or in those reported previously. Specifically, it is unlikely that the low cardiac output with exercise is the result of acute right ventricular hypertension. We have reviewed a group of 28 children³³ with moderate pulmonary stenosis (pulmonary valve area 0.5–1.0 cm²/m²) who had right ventricular systolic pressures during exercise indistinguishable from those of our group 1 patients (106 and 99 mmHg, respectively), yet had a normal rise (81%) in cardiac output with exercise. These patients had no signs of exercise induced pulmonary vasoconstriction.

CLINICAL SIGNIFICANCE

The outlook for patients with exercise induced pulmonary vasoconstriction is unknown. None the less, case 6, who had exercise induced pulmonary vasocon-

striction at two postoperative heart catheterisations, had a substantial increase in resting pulmonary vascular resistance over a five year interval. Case 4, whose pulmonary vascular response to exercise was also abnormal (albeit total pulmonary vascular resistance rose less than 25%), had a progressive increase in pulmonary arteriolar resistance. These observations raise the question of whether an exercise induced increase in pulmonary vascular resistance in such patients may be a harbinger of progression of pulmonary vascular disease.

In summary, analysis of our data and those reported previously, suggests that exercise induced pulmonary vasoconstriction is a not uncommon finding in children who have survived cardiac correction of left to right shunting lesions. The vasoconstriction cannot be attributed to abnormalities in left atrial pressure, blood gas levels, or acute right ventricular hypertension. Finally, the presence of pulmonary vasoconstriction during exercise may be an early sign of progressive pulmonary hypertension.

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