Cardiopulmonary function in patients with pulmonary hypertension

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The effects of pulmonary hypertension on cardiopulmonary function were investigated by ventilatory, haemodynamic, and metabolic studies at rest and during exercise. The studies were carried out in 12 patients with primary, thromboembolic, or residual pulmonary hypertension after surgical closure of intracardiac defects, and in 11 patients with pulmonary hypertension secondary to obstructive lung disease. The findings have been compared with earlier published results of similar studies, performed in other situations associated with pulmonary hypertension.

The cardiac output is reduced in most forms of pulmonary hypertension. A relation was found between the reduction in exercise output and the level of pulmonary arterial pressure. Exceptions occur, indicating the contribution of additional factors to the circulatory response.

Lung function tests usually gave normal results in primary thromboembolic and residual pulmonary hypertension. The variability of findings in the different conditions associated with pulmonary hypertension suggests that increased pulmonary arterial pressure, per se, has no effect on lung function.

Some degree of exercise hyperventilation is present in most forms of pulmonary hypertension. This is usually pronounced in primary and thromboembolic pulmonary hypertension but it is less pronounced in obstructive lung disease.

The factors determining exercise ventilation in the various forms of pulmonary hypertension are discussed. Evidence is given that tissue hypoxia may be implicated in the genesis of the mild hyperventilation seen in lung disease. In primary and thromboembolic pulmonary hypertension the haemodynamic abnormalities, changes in arterial blood composition, or tissue hypoxia are apparently not responsible for the excessive ventilatory response. It is believed that hyperventilation in these conditions is a consequence of abnormal receptor impulses from the lungs.

The study of functional disturbances in patients with pulmonary hypertension has attracted the attention of many investigators and several reports have been published over the past few years. Particularly intriguing is the exercise hyperventilation seen in some of these patients.

In previous papers, we have described the respiratory, circulatory, and biochemical changes, at rest and on effort, in patients with pulmonary hypertension accompanying left heart disease (Gazetopoulos, Davies, and Deuchar, 1966a), left-to-

right shunts (Gazetopoulos and Davies, 1966), and Eisenmenger syndromes (Davies and Gazetopoulos, 1965, 1966a).

We now present the results of similar studies on patients with primary, thromboembolic, or residual postoperative pulmonary hypertension and in patients with pulmonary hypertension accompanying obstructive lung disease. No attempt has been made to separate primary from thromboembolic pulmonary hypertension since the pathophysiological features of both conditions are similar and their differentiation is difficult and often impossible (Evans, Short, and Bedford, 1957; Rosenberg, 1964; Fowler *et al.*, 1966; Storstein *et al.*, 1966; Walcott, Burchell, and Brown, 1970; Trell, 1972).

Particular attention is given to the interrelation of the various disturbances and their effects on exercise ventilation.

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TABLE 1 Clinical details of subjects studied

Case No.	Sex	Age (yr)	BSA (m ²)	Oxygen capacity (vol %)	Disability grade	Diagnosis
1	F	34	1.7	18.1	3B	Primary/thromboembolic hypertension
2a	M	55	2.1	21.4	2	" " "
2b	M	58	2.1	20.0	3A	" " "
3	M	50	1.7	19.9	3B	" " "
4	F	45	1.6	19.4	3B	" " "
5	M	61	1.7	21.7	3B	" " "
6	M	44	1.7	21.7	3A	" " "
7	F	41	1.4	21.2	2	" " "
8	F	62	1.6	19.4	3A	" " "
9	F	40	1.8	17.6	3B	" " "
10	F	37	1.8	18.4	3B	Postoperative, atrial septal defect
11	M	21	1.7	23.6	2	Postoperative, persistent ductus arteriosus
12	M	16	1.3	20.5	2	Postoperative, ventricular septal defect
13	M	38	1.7	19.6	3B	Chronic obstructive pulmonary disease
14	M	58	2.0	20.1	3A	" " " "
15	M	61	1.9	18.6	3A	" " " "
16	F	57	1.7	20.4	3B	" " " "
17	M	55	2.0	22.2	3A	" " " "
18	M	51	1.8	18.7	3A	" " " "
19	F	33	1.5	18.6	3A	" " " "
20	F	39	1.6	25.0	2	" " " "
21	F	54	1.6	19.2	3A	" " " "
22	M	62	1.8	19.8	2	" " " "
23	F	51	1.5	21.7	3A	" " " "

Note: Grade of disability according to New York Heart Association, Grade 3 being divided into 3A and 3B after Donald, Bishop, and Wade (1954).

Subjects and methods

Twenty-three patients were studied. Cases 1-9 had primary or thromboembolic pulmonary hypertension, Cases 10-12 had residual pulmonary hypertension after surgical closure of intracardiac defects, and Cases 13-23 had pulmonary hypertension in association with chronic obstructive lung disease. Patients with pulmonary venous hypertension or a shunt in either direction were thus excluded. One patient (Case 2) was studied twice. At the time of the second study, 3 years after the first, his clinical condition had deteriorated and congestive heart failure had appeared. Clinical data on patients studied are shown in Table 1.

All patients were investigated at Guy's Hospital, London or at Nosileutikon Idryma M.T.S., Athens. The techniques of study in both centres were similar, with only minor differences, and details of these have been given previously. Lung function was studied by techniques described by Davies and Gazetopoulos (1967), predicted values being taken from Bates, Macklem, and Christie (1971). Haemodynamic and ventilatory measurements at rest and on effort were made during cardiac catheterization by standard techniques (Gazetopoulos *et al.*, 1966b). Arterial blood oxygen saturation, pH, PCO₂, lactate, and pyruvate were estimated by methods described by Davies, Gazetopoulos, and Oliver (1965).

Exercise was performed in the supine position and lasted for 10 minutes. All measurements were made simultaneously after the 5th minute of constant exercise

when a steady state had been reached. The exercise load was low (100-400 kpm/min), being set according to the ability of each patient. If the patient were able to complete one exercise level without distress, the load was increased and the measurements were repeated during exercise of the same duration.

Results

Table 1 shows the clinical characteristics of the patients. Table 2 shows the results of the lung function tests. There is little abnormality of the measured respiratory parameters in patients with primary, thromboembolic, and residual pulmonary hypertension. Table 3 shows the ventilatory and haemodynamic findings and the arterial blood composition at rest and on effort.

The relation between exercise oxygen uptake and cardiac output is shown in Fig. 1. Cardiac output is reduced in patients with primary, thromboembolic, and residual pulmonary hypertension, though in the group with lung disease there is little or no reduction. Fig. 2 shows the relation between pulmonary arterial pressure and reduction in cardiac output, expressed in litres per minute, below the mean predicted value for the given exercise oxygen uptake. In general, an inverse relation is seen. The patient,

TABLE 2 Lung function data

Case No.	Vital capacity: % deviation from predicted	Functional residual capacity: % deviation from predicted	RV* TLC × 100	Maximal breathing capacity: % deviation from predicted	FEV _{1.0} † VC × 100	Compliance l./cm H ₂ O	Distribution N ₂ % 750–1250‡	Diffusing capacity (CO uptake %)
1	+17	+5	21	+10	76	—	2	42
2a	-26	-8	39	-17	70	—	1	46
2b	-35	-17	43	-27	67	—	3	40
3	-33	-20	34	-33	71	—	2	—
4	-24	—	—	+7	80	0.133	—	52
5	-13	+10	46	+1	75	0.083	—	60
6	-27	-15	36	-25	80	—	—	—
7	+5	-4	36	-8	78	0.205	2	46
8	-19	—	—	+4	84	0.108	1	57
9	-3	—	—	-2	75	0.250	—	55
10	+4	+13	30	-4	77	0.105	—	—
11	-10	-15	35	+8	80	—	1	—
13	-48	-27	51	-64	57	—	8	41
14	-41	-4	54	-78	40	—	—	—
15	-23	+49	58	-79	29	—	10	37
16	-38	+10	50	-62	48	—	8	—
17	-50	-18	48	-60	41	0.098	10	42
18	-41	—	—	-69	36	0.126	—	46
19	-62	-9	62	-74	54	—	—	35
20	-49	+13	58	-65	48	0.076	—	45
21	-44	—	—	-57	52	0.062	—	46
22	-29	+22	55	-68	50	0.110	6	50
23	-59	—	—	-67	57	—	7	—

Note: Air distribution was measured by the single-breath method (Comroe and Fowler, 1951). Diffusing capacity was estimated by the measurement of the fractional CO uptake (Bates, 1952).

* RV = residual volume; TLC = total lung capacity.

† FEV = forced expiratory volume; VC = vital capacity.

‡ Normal values for distribution are 1–2 per cent and for CO uptake are 35–55 per cent, decreasing with age. The fraction of CO removed is expressed as percentage and is calculated by the formula:
$$\frac{F. \text{Insp. CO} - F. \text{Expir. CO}}{F. \text{Inspir. CO}}$$

however, with the highest pulmonary arterial pressure (Case 2a) shows the least reduction in cardiac output among all patients with primary and thromboembolic pulmonary hypertension.

In Fig. 3 the relation between minute ventilation and oxygen uptake on effort is seen. An obvious exercise hyperventilation is noted in most patients with primary or thromboembolic pulmonary hypertension, though there are some exceptions. The degree of hyperventilation, expressed in litres per minute above the mean predicted value for the given exercise oxygen uptake, was plotted against the pulmonary arterial systolic pressure, the total pulmonary vascular resistance, and the degree of reduction of cardiac output in Fig. 4, 5, and 6, respectively. No relation is seen. Fig. 7 shows the main findings in the two studies of Case 2. Heart failure developed during 3 years between the two studies. Hyperventilation on effort became more pronounced, cardiac output fell, and lactate production increased. In Fig. 8 the degree of exercise hyper-

ventilation has been plotted against lactate levels. For comparison, we have included in this Figure, the relevant findings from patients with isolated pulmonary stenosis where tissue hypoxia, evidenced by lactate production, is likely to be the sole determining factor of exercise hyperventilation (see Discussion). It is seen that in primary and thromboembolic pulmonary hypertension the ventilatory response is, as a rule, much greater than in patients with pulmonary stenosis having a similar degree of lactic acidemia. In the patients with lung disease and in 2 of the 3 with residual pulmonary hypertension the pattern of response seems similar to pulmonary stenosis. The third subject of the last group (Case 10) had evidence of pulmonary embolism. None of the other haemodynamic or biochemical factors seemed to be associated with the degree of hyperventilation.

Discussion

Pulmonary arterial hypertension occurs in a variety

FIG. 1 Cardiac output and oxygen uptake during exercise in primary or thromboembolic pulmonary hypertension (circles), residual postoperative pulmonary hypertension (squares), and pulmonary hypertension secondary to obstructive lung disease (triangles). The normal limits of the relation of the two parameters, obtained from Gazetopoulos et al. (1966b), are shown.

FIG. 3 Ventilation and oxygen uptake during exercise. The normal limits of the relation of the two parameters, obtained from Gazetopoulos et al., (1966b), are shown. Symbols as in Fig. 1.

FIG. 2 Exercise cardiac output expressed as a deviation from the mean predicted normal, in relation to pulmonary arterial systolic pressure. Symbols as in Fig. 1.

FIG. 4 Exercise ventilation, expressed as a deviation from the mean predicted normal, in relation to pulmonary arterial systolic pressure. Symbols as in Fig. 1.

FIG. 5 Excess exercise ventilation in relation to total pulmonary vascular resistance. Symbols as in Fig. 1.

FIG. 7 Ventilation ($\dot{V}$), cardiac output (CO), systolic pulmonary arterial pressure (PAP), total pulmonary vascular resistance (TPR), and arterial blood composition at rest and during stepwise increasing exercise in the two studies performed in Case 2. The time interval between the first (solid line) and the second study (broken line) is 3 years.

FIG. 6 The relation between excess ventilation and degree of impairment of cardiac output during exercise, both expressed as a deviation from the mean predicted normal. Symbols as in Fig. 1.

FIG. 8 Excess ventilation in relation to lactate concentration during exercise. The findings in patients with isolated pulmonary stenosis (X), obtained from Gazetopoulos et al. (1966a), are shown. Otherwise symbols as in Fig. 1. (For discussion see text.)

of conditions of different aetiology, clinical picture, and course. The coexistence of several interacting disturbances in most of these conditions often makes it difficult to evaluate the effects of pulmonary

hypertension on circulatory and ventilatory function. A comparative study of the various forms of pulmonary hypertension would probably lead to a better understanding of the functional significance

TABLE 3 Ventilatory data, haemodynamic data, and arterial blood composition

Case No.	Exercise load (kpm/min)	$\dot{V}O_2^*$ (ml/min) STPD	Heart rate	Cardiac output (l./min)	Resp. rate	$\dot{V}$ (l./min) BTPS	PCV*† mean	Pressures (mmHg)			
								Pulm. art. s/d/m‡	R. vent. s/d	Syst. art. s/d/m	
1	R	0	210	76	3.7	15	9.6	7	90/50/66	92/11	110/70/85
	E	200	565	125	5.2	32	42.3	—	105/55/70	105/10	—
	R	0	330	75	6.8	13	10.5	7	100/50/75	100/10	165/95/110
	E	200	715	100	8.4	25	23.8	—	170/65/95	—	190/105/130
2a	R	0	1100	130	9.1	—	40.7	—	180/80/120	—	195/120/135
	E	200	260	90	2.9	18	10.7	10	140/60/90	140/15	125/90/105
	R	0	665	110	4.9	27	30.5	12	165/60/100	165/25	140/95/110
	E	200	960	155	6.8	34	49.5	—	175/60/110	—	—
3	R	0	220	80	3.2	23	13.5	8	110/45/60	110/13	80/60/70
	E	200	650	128	—	32	44.9	—	—	—	—
4	R	0	230	110	3.5	23	8.8	10	120/50/75	125/16	155/105/135
	E	100	415	125	4.0	28	18.5	—	125/50/80	—	180/130/145
5	R	0	140	58	2.4	22	9.7	5	105/25/55	105/10	100/50/65
	E	100	540	80	4.6	30	31.0	3	125/30/70	125/12	115/60/75
6	R	0	200	75	2.4	16	6.8	—	125/50/75	125/10	95/60/70
	E	100	430	100	3.2	20	16.8	—	150/60/90	—	110/60/75
7	R	0	170	76	2.9	17	4.7	5	100/40/60	100/4	115/75/85
	E	100	345	110	3.6	20	11.0	7	160/70/100	—	—
8	R	0	185	90	—	16	10.5	—	—	—	—
	E	200	580	120	—	26	30.2	—	—	—	—
9	R	0	220	76	4.3	15	6.6	—	110/60/75	110/10	110/65/80
	E	—	—	—	—	—	—	—	—	—	—
10	R	0	250	108	5.1	13	8.6	16	70/35/45	70/12	155/85/100
	E	100	450	136	7.1	36	40.0	21	100/42/50	—	155/85/95
11	R	0	230	65	4.2	15	5.0	9	75/35/55	72/7	130/65/70
	E	200	650	120	6.2	20	17.6	12	110/65/75	110/10	150/85/95
12	R	0	200	80	4.8	20	7.0	10	60/20/35	65/7	125/70/90
	E	100	380	94	5.8	28	12.3	11	65/28/40	68/6	128/75/95
13	R	0	290	90	7.4	15	9.9	10	45/30/34	45/8	135/90/120
	E	200	860	140	10.3	—	29.7	—	70/25/50	70/12	160/100/120
14	R	0	210	64	3.7	16	8.8	16	50/25/35	50/8	180/110/130
	E	200	750	88	9.0	22	22.0	22	75/45/50	—	220/120/170
15	R	0	310	96	8.8	16	8.7	11	40/22/28	38/12	—
	E	300	800	120	—	21	20.4	—	—	—	—
16	R	0	185	76	6.4	18	6.2	7	40/25/32	40/6	95/55/70
	E	200	560	104	7.2	—	17.8	8	65/30/40	65/5	115/60/75
17	R	0	220	80	7.0	14	8.4	10	55/30/35	55/8	165/85/100
	E	200	680	96	8.4	28	20.2	—	72/30/40	—	170/85/100
18	R	0	1080	145	10.2	34	35.8	—	95/35/50	—	—
	E	200	215	94	9.7	22	7.0	8	50/20/30	50/5	130/80/95
19	R	0	405	107	8.1	27	13.0	13	70/30/45	70/8	150/80/100
	E	200	210	95	5.6	24	7.7	7	40/23/27	35/7	110/80/85
20	R	0	575	130	9.1	41	19.1	—	60/37/44	—	110/70/82
	E	200	130	64	3.2	13	4.7	10	70/30/40	68/4	100/60/75
21	R	0	500	100	7.1	24	13.6	—	85/40/55	90/8	100/65/75
	E	100	225	84	9.3	—	8.0	—	50/20/30	50/8	100/50/65
22	R	0	780	120	—	—	30.5	—	—	—	—
	E	300	250	72	4.8	16	9.3	8	58/20/30	55/4	140/80/90
23	R	0	620	138	—	26	25.1	—	—	—	—
	E	200	210	78	6.7	24	7.0	—	100/65/80	100/35	130/75/90

* $\dot{V}O_2$ = oxygen uptake.

$\dot{V}$ = ventilation minute volume.

† PCV = pulmonary capillary venous (wedge).

‡ s/d/m = systolic, diastolic, mean.

STPD = standard temperature, pressure dry; BTPS = body temperature, pressure saturated with water vapour.

R, rest; E, exercise; So_2 = arterial oxygen saturation; Pco_2 = arterial partial pressure of CO_2 .

of increased pulmonary arterial pressure and of the role of coexisting anomalies. Table 4 shows the usual findings in the different situations where increased pulmonary arterial pressure is present.

TABLE 3 (Cont'd)

Arterial blood				
So ₂ %	Pco ₂ (mmHg)	pH	Lactate (mM/l.)	Pyruvate (mM/l.)
87.7	20.6	7.47	0.57	0.07
87.3	21.9	7.46	1.80	0.11
88.8	28.3	7.49	1.00	0.06
88.8	28.3	7.48	1.10	0.09
93.2	26.3	7.48	1.95	0.12
92.3	36.0	7.43	0.90	0.07
85.3	45.0	7.41	1.45	0.10
82.0	32.0	7.39	4.25	0.18
87.5	24.8	7.58	0.76	—
90.5	—	—	2.17	—
80.0	31.5	7.37	1.23	0.14
83.8	32.5	7.36	1.89	0.22
85.7	31.0	7.46	0.59	0.08
83.0	30.5	7.46	2.47	0.14
89.7	36.0	7.42	0.91	0.08
91.5	35.6	7.41	1.62	0.09
96.0	—	—	—	—
96.0	—	—	—	—
98.0	37.0	7.52	1.11	0.06
96.0	30.0	7.51	2.73	—
89.0	—	—	—	—
—	—	—	—	—
93.0	32.5	7.48	0.72	0.08
84.5	30.0	7.44	5.00	0.24
93.2	43.0	7.35	1.10	0.13
96.7	37.0	7.35	2.50	0.19
97.8	40.5	7.42	1.11	0.11
97.6	38.0	7.41	2.15	0.16
84.5	36.8	7.49	0.85	0.04
94.0	34.8	7.47	3.58	0.09
90.5	43.0	7.40	0.82	—
89.0	—	7.34	2.34	—
84.7	39.3	7.45	1.02	—
89.5	40.8	7.41	1.46	—
90.2	43.2	7.40	0.72	0.08
88.0	44.0	7.38	2.30	0.12
90.0	48.0	7.38	0.82	0.07
90.5	51.5	7.35	2.75	0.13
93.2	47.2	7.30	5.21	0.18
86.0	60.0	7.42	0.91	0.05
85.2	50.0	7.40	1.30	0.11
89.6	40.0	7.41	0.84	0.08
82.4	44.0	7.39	1.69	0.14
75.8	61.0	7.33	0.97	0.04
66.1	65.0	7.31	2.60	0.07
80.0	40.0	7.46	0.91	0.10
87.0	42.0	7.35	4.76	0.19
86.0	60.2	7.39	1.16	—
82.8	56.0	7.35	3.25	—
56.0	76.0	7.38	—	—
—	—	—	—	—

In agreement with many others (McIlroy and Apthorp, 1958; Kitchin, Lowther, and Matthews, 1961; Wessel, Kezdi, and Cugell, 1964; Shaw *et al.*, 1965), we have found that the cardiac output is reduced, especially during exercise in primary and thromboembolic pulmonary hypertension, and that it is usually in the low-normal range in pulmonary hypertension due to obstructive lung disease (Fig. 1). Usually, the higher the pulmonary arterial pressure in both these situations, the lower the cardiac output (Fig. 2).

Similar findings were observed in pulmonary hypertension secondary to left heart disease (Gazetopoulos *et al.*, 1966b) and in relation to the systemic blood flow in hyperkinetic pulmonary hypertension (Davies and Gazetopoulos, 1966b). The few existing haemodynamic data in patients with pulmonary interstitial fibrosis (Wade and Bishop, 1962; Sackner *et al.*, 1964) and residual postoperative pulmonary hypertension (Fig. 2), also suggest a similar circulatory disturbance. In the Eisenmenger syndrome, systemic hypertension is in most cases obligatory and the effective pulmonary flow is not as closely related to the level of pulmonary arterial pressure, though it is low.

Pulmonary hypertension is thus associated with reduced cardiac output, particularly on effort, but exceptions occur as is seen in the first study of our Case 2 and probably in residents at high altitude (Penaloza *et al.*, 1963). Other factors, such as the presence of atrial fibrillation and myocardial fibrosis may contribute to the low output. On the other hand, hypoxaemia is likely to have an opposite effect (Shaw *et al.*, 1965).

The effect of pulmonary hypertension on the function of the lungs is variable, and depends on the underlying condition (Table 4). In primary and thromboembolic pulmonary hypertension, routine pulmonary function tests show virtually normal values, and compliance is normal or slightly impaired (McIlroy and Apthorp, 1958; Wessel *et al.*, 1964; Jones and Goodwin, 1965; Storstein *et al.*, 1966; and Table 2). Only more sophisticated measurements, such as the distribution of ventilation and perfusion, indicate how gross the disturbance of lung function may sometimes be (Bass, Heckscher, and Anthonisen, 1967). In left heart disease with pulmonary venous hypertension (Donald, 1959), the lungs are stiff as a result of vascular engorgement and perivascular oedema and fibrosis. Airway resistance is normal or slightly increased. Ventilation-perfusion abnormalities may occur, particularly in the more chronic situations such as mitral stenosis. In left-to-right shunts with hyperkinetic pulmonary hypertension the lung compliance is reduced but other aspects of lung function remain near normal

(Davies, Williams, and Wood, 1962; Woolf, 1963; Davies and Gazetopoulos, 1967). Virtually normal lung function is also seen in the Eisenmenger syndromes (McIlroy and Apthorp, 1958; Davies and Gazetopoulos, 1967), in pulmonary hypertension of high altitude (Hurtado, 1964), and in residual post-operative pulmonary hypertension. Some degree of arterial desaturation, due largely to ventilation-perfusion inequality, is commonly seen in patients with pulmonary hypertension of any cause, but is not an invariable finding.

It is clear that pulmonary hypertension *per se* has no uniform effect on lung function or arterial blood composition; though the physiological disturbance may be considerable, this depends on the nature of the associated disease.

Exercise hyperventilation is usually present in most groups of patients with pulmonary hypertension. Our data and other studies indicate that pulmonary arterial pressure cannot be the determining factor for excessive ventilatory response; they also show that in the majority of cases there are no chemical changes which would act as a ventilatory drive (Cotes, 1955; McIlroy and Apthorp, 1958; Turino *et al.*, 1963; Sloman and Gandevia, 1964; Wessel *et al.*, 1964; Gazetopoulos *et al.*, 1966a, b).

It has been suggested (McIlroy, 1959) that a major cause of hyperventilation in heart disease is low cardiac output, operating through the medium of tissue hypoxia and lactic acidemia. Furthermore, a relation between tissue hypoxia, as evidenced by

lactate production, and the degree of exercise hyperventilation, has been demonstrated in some low output situations, such as isolated pulmonary stenosis, where the lungs are normal and other respiratory stimuli are not present (Gazetopoulos *et al.*, 1966a). The existence of a similar mechanism determining hyperventilation in primary and thromboembolic pulmonary hypertension appears to be supported by Case 2 where the progress of the disease was associated with further reduction in cardiac output, increased lactic acidemia, and increased ventilation (Fig. 7). However, ventilation increased disproportionately to the degree of lactic acidemia in this case, when compared with cases of pulmonary stenosis. Furthermore, other patients with primary or thromboembolic pulmonary hypertension who showed similar degrees of exercise hyperventilation had low lactate levels (Fig. 8). This suggests strongly that factors other than tissue hypoxia are playing an important role in the determination of exercise ventilation in these patients.

In mitral valve and left heart disease, we showed that exercise hyperventilation is also disproportionate to the lactate levels, and is related mainly to the increase in left atrial pressure (Gazetopoulos *et al.*, 1966b). In left-to-right shunts with hyperkinetic pulmonary hypertension pronounced hyperventilation does not usually occur, except when pulmonary venous hypertension is present (Gazetopoulos and Davies, 1966). In the Eisenmenger syndromes, as in other varieties of severe cyanotic congenital heart

TABLE 4 Usual pathophysiological findings in various forms of pulmonary hypertension

Form	Pulmonary flow	Systemic flow	Airway resistance	Lung compliance	Lung diffusion	Arterial oxygenation	Exercise ventilation	Exercise tolerance
Pulmonary venous hypertension	Low	Low	Little increased	Low	Normal or decreased	Normal or little decreased	High	Low
Hyperkinetic pulmonary hypertension	High	Low	Normal	Low	Normal or little increased	Normal or little decreased	Normal or little increased	Little decreased
Eisenmenger syndromes	Low	Normal	Normal	Normal	Normal	Low	High	Low
Primary or thromboembolic pulmonary hypertension	Low	Low	Normal	Normal	Normal or decreased	Normal or little decreased	High	Low
Obstructive lung disease	Normal or little decreased	Normal or little decreased	High	Normal or little decreased	Normal or decreased	Normal or little decreased	Normal or little increased	Low
Pulmonary interstitial fibrosis	Little decreased	Little decreased	Normal	Low	Low	Decreased	High	Low
Pulmonary hypertension of high altitude	Normal	Normal	Normal	Normal	Normal or increased	Normal or little decreased	Normal or little increased	Normal

disease, arterial blood gases are an important determinant of hyperventilation (Davies and Gazetopoulos, 1965). The observation that patients with persistent ductus and the 'Eisenmenger syndrome', in whom the venous blood bypasses the carotid and brain chemoreceptors, do not hyperventilate significantly, indicates the absence of other powerful respiratory stimuli in the Eisenmenger syndromes (Gazetopoulos *et al.*, 1972).

In cor pulmonale due to obstructive lung disease, hyperventilation is not pronounced and is of a degree that would be expected to occur as a result of tissue hypoxia, with a mechanism similar to pulmonary stenosis (Fig. 8). The same mechanism is also likely to determine the ventilatory response in the majority of patients with hyperkinetic pulmonary hypertension (Gazetopoulos and Davies, 1966), in patients with 'Eisenmenger ductus' (Gazetopoulos *et al.*, 1972), and possibly in residual postoperative pulmonary hypertension, as well as in pulmonary hypertension due to high altitude.

The fact that patients with primary or thromboembolic hypertension hyperventilate much more than those with pulmonary stenosis or obstructive lung disease, with similar lactate levels, leads to the conclusion that a low cardiac output with consequent tissue hypoxia is not an important cause of hyperventilation in this group. This brings back the focus of attention from the periphery to the lungs themselves.

It is true that in patients with primary and thromboembolic pulmonary hypertension the pulmonary blood flow is grossly limited and many ventilated alveoli receive no perfusion. It would be reasonable to assume that, in order to cover the oxygen needs of the body, every means available should be used to increase oxygen transport in the lungs by raising the P_{O_2} in the perfused alveoli; it is possible that the observed gross effort hyperventilation is related to this requirement.

However, because of the adaptability in chronic hypoxaemia (Severinghaus, Bainton, and Carcelen, 1966; Edelman *et al.*, 1968) and since other forms of heart disease associated with low alveolar perfusion show no pronounced hyperventilation, one must come to the conclusion that ventilation in these patients is driven by abnormal receptor impulses from the lungs and pulmonary vessels. There is some evidence that such impulses do exist (Guz *et al.*, 1970) though their exact mechanism remains to be elucidated.

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