Ventilation in Relation to Arterial and Venous Blood Chemistry in Heart Disease

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In a previous report (Gazetopoulos *et al.*, 1966) of this study, the changes in haemodynamics and ventilation with exercise were studied. In this paper we examine the parallel alterations in blood chemistry which take place in patients with various types of heart disease.

There are relatively few published reports of studies of the blood gases in relation to hyperventilation and dyspnoea in cardiac patients, and these are mainly concerned with mitral valve disease. Impairment of lung function, a potential cause of disturbed blood gases, has been shown to occur in such patients by Frank *et al.* (1953) and Riley *et al.* (1956) amongst others, and has been discussed by many authors including Rossier, Bühlmann, and Wiesinger (1960) and Arnott (1963).

In spite of this, Cullen *et al.* (1931) did not find any marked changes of pH and PCO₂ in the arterial blood of exercising patients and concluded that the small changes observed were the result rather than the cause of hyperventilation. The same conclusion was reached by West *et al.* (1953) and Mauck and Shapiro (1961), though the former investigators noted abnormal blood gases in a minority of their patients. Mauck, Shapiro, and Patterson (1964), however, showed an increase of arterial PCO₂ with exercise in 4 out of their 5 patients, sometimes significant in degree, and mentioned the possibility that this could be an additional stimulus to the respiratory centre. Arterial desaturation has also been observed in patients with mitral stenosis by Blount, McCord, and Anderson (1952) and Donald, Bishop, and Wade (1954), and the rise of blood lactic acid during exercise is said to be greater in patients with heart disease than in normal people (Huckabee and Judson, 1958; Donald *et al.*, 1961).

More recently attention has turned to the venous side of the circulation (Armstrong *et al.*, 1961; Riley, 1963). Although experiments in animals

(Cropp and Comroe, 1961; Kao *et al.*, 1963) make it unlikely that the venous blood chemistry acts as a normal controlling mechanism of ventilation, to our knowledge no observations have been published of direct measurements of venous chemistry in human subjects, and the possibility remains that such stimuli may exist, particularly in association with low output states.

The evaluation of humoral factors is of interest in mitral valve disease and left ventricular failure, in that they could serve as stimuli to ventilation additional to that provided by pulmonary congestion; their role in the determination of hyperventilation in patients without pulmonary venous hypertension, e.g. in pulmonary stenosis, is potentially more important. This study has been undertaken to obtain further information about the arterial and venous blood chemistry during exercise in various types of heart disease, in the hope that this might clarify the part played by chemical factors in producing hyperventilation.

SUBJECTS AND METHODS

These studies were performed during mild supine exercise at cardiac catheterization, and also during more severe exercise on a bicycle ergometer up to levels where dyspnoea was present. The clinical material consisted of 40 subjects, 5 of whom were normal; the remainder have been divided into three groups. Group I consists of 9 patients with left ventricular disease, group II of 14 patients in whom mitral stenosis was the dominant or sole lesion, and group III of 12 patients with isolated pulmonary stenosis. Details are given in Table I.

All were exercised during cardiac catheterization apart from Cases 26 and 40 in whom only resting catheterization data are available, and Cases 27 and 28 where no catheterization was performed and the clinical diagnosis of mild mitral stenosis was confirmed at operation. In these 4 patients studies were performed during exercise on the bicycle ergometer.

Received March 12, 1965.

TABLE I
CLINICAL DETAILS OF SUBJECTS STUDIED

Group	Case No. sex, and age (yr.)			BSA (m. ²)	Oxygen capacity (vol. %)	Disability*	Diagnosis
Normal	1	F	18	1.45	18.2	0	Normal
	2	F	17	1.60	15.5	0	Normal
	3	M	29	1.70	20.9	0	Normal
	4	M	14	1.20	15.5	0	Normal
	5	M	11	1.50	18.2	0	Normal
I: Left ventricular disease	6	M	26	1.80	16.1	2	AS
	7	F	24	1.60	17.9	3-A	AS
	8	M	62	1.90	18.2	2	AS
	9	M	59	1.75	16.7	3-A	AS
	10	F	50	1.60	16.9	3-B	AS
	11	M	61	1.70	22.8	3-A	AS
	12	M	33	1.75	22.0	2	AS (complete heart block)
	13	F	35	1.50	18.0	3-A	Cardiomyopathy
	14	M	63	1.67	16.3	4	Left ventricular failure, emphysema (AF)
II: Mitral stenosis	15	F	47	1.35	17.8	3-B	MS
	16	M	39	2.00	18.4	3-A	MS (AF)
	17	F	33	1.50	14.6	3-A	MS
	18	F	51	1.55	17.6	3-B	MS (AF)
	19	F	40	1.50	17.6	3-B	MS, AI (AF)
	20	F	46	1.70	19.2	3-B	MS, MI, TI (AF)
	21	M	26	2.00	22.3	3-A	MS (AF)
	22	M	35	1.50	10.2	3-B	MS, MI, TI (AF)
	23	F	46	1.50	20.9	3-B	MS, MI, hypertension emphysema
	24	F	43	1.65	16.9	2	MS
	25	M	43	1.70	22.1	3-A	MS
	26	F	22	1.75	16.3	2	MS
	27	M	49	1.85	14.7	3-A	MS (AF)
	28	F	40	1.50	15.6	3-A	MS
III: Pulmonary stenosis	29	F	29	1.42	15.5	3-A	PS
	30	M	7	1.00	14.4	I	PS
	31	F	21	1.30	20.3	3-B	PS
	32	F	44	1.70	18.8	3-A	PS
	33	F	14	1.45	20.6	2	PS
	34	M	19	1.85	19.8	I	PS
	35	M	30	1.90	17.6	I	PS
	36	M	15	1.95	21.3	I	PS
	37	M	32	1.95	20.6	I	PS
	38	M	36	1.75	20.9	2	PS
	39	M	58	1.95	20.9	3-B	PS
	40	M	13	1.25	18.7	3-A	PS

* Graduation of disability according to New York Heart Association (1953), Grade 3 being divided into 3-A and 3-B after Donald *et al.* (1954). BSA, body surface area; MS, mitral stenosis; AS, aortic stenosis; MI, mitral incompetence; TI, tricuspid incompetence; AI, aortic incompetence; AF, atrial fibrillation; PS, pulmonary stenosis.

The techniques of cardiac catheterization and the haemodynamic studies were similar to those described in a previous paper (Gazetopoulos *et al.*, 1966), exercise having been carried out in the supine position by means of a spring-loaded leg exerciser. Arterial blood samples were withdrawn at rest, in the third to fourth minute, and the eighth to tenth minute of exercise. They were analysed for pH, PCO₂, bicarbonate, oxygen saturation, lactate, and pyruvate. Samples were also withdrawn simultaneously from the pulmonary artery and analysed for pH, PCO₂, bicarbonate, and oxygen saturation. The pH and PCO₂ were measured by the micro-Astrup method, the oxygen saturations spectrophotometrically, and the lactate and pyruvate by enzymatic methods. Details are given elsewhere (Davies and Gazetopoulos, 1965).

On a separate occasion the 4 patients mentioned above and 6 others were exercised in the upright position on a bicycle ergometer, the initial level being 200 kg./min. Where possible the level was increased by 200 kg./min. at intervals of 10 minutes, exercise being terminated when dyspnoea and fatigue dictated this.

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These patients were thus stressed to their maximum working capacity. Ventilation, oxygen uptake, heart rate, and changes in arterial blood chemistry were measured as previously described (Davies, Gazetopoulos, and Oliver, 1965), blood samples being again withdrawn in the third to fourth minute and eighth to tenth minute of each level. If exercise had to be stopped, a sample was obtained just before this point. It was impossible to measure ventilation in all subjects at the critical levels, but their reactions to the procedures were assessed as carefully as possible.

An untoward reaction occurred in only one patient who developed evidence of pulmonary oedema (Case 16). This responded well to the usual measures, and he has since had a successful mitral valvotomy.

RESULTS

A. Mild Supine Exercise. Table II gives the ventilatory and haemodynamic findings and Table III the arterial and mixed venous blood composition

TABLE II
HÆMODYNAMICS AND VENTILATION AT REST AND ON EXERCISE IN PATIENTS STUDIED

Group	Case No.	$\dot{V}O_2$ (ml./min.) STPD	Heart rate	A-V diff. (vol. %)	CO (l./min.)	Pressures (mm. Hg)				$\dot{V}$ (l./min.) BTPS	Resp. rate	VE
						PCV mean	PA s/d/mean	RV s/d	Syst. s/d/mean			
Normal	1 R	200	100	3.3	6.1	7	18/10/13	23/5	115/75/85	5.6	17	2.8
	E	500	125	6.7	7.5	—	20/10/15	—	100/65/85	15.2	20	3.0
	2 R	250	75	3.0	8.3	12	26/10/14	28/7	130/60/80	4.6	14	1.8
	E	595	115	7.0	8.5	12	26/10/14	25/5	170/90/115	17.2	20	2.9
	3 R	180	72	2.8	7.0	10	25/10/20	30/9	125/50/75	6.4	13	3.5
	E	470	120	6.4	7.4	12	30/10/22	—	110/65/80	14.6	15	3.1
	4 R	175	60	2.9	6.0	10	25/8/14	30/8	95/50/75	4.1	16	2.3
	E	280	94	3.2	8.7	—	—	—	110/60/75	6.6	20	2.3
	5 R	170	76	3.1	5.5	6	22/8/12	25/2	115/70/85	9.0	24	5.2
	E	—	—	—	—	—	30/15/18	—	150/75/95	—	—	—
I: Left ventricular disease	6 R	265	60	5.0	5.3	14	28/18/20	28/8	100/60/80	5.5	10	2.1
	E	720	100	7.4	9.7	18	28/18/20	—	165/80/105	15.4	14	2.1
	7 R	200	75	3.4	5.9	8	20/10/14	25/5	95/65/75	6.0	18	3.0
	E	405	120	4.8	8.4	10	25/10/18	—	100/65/85	11.2	20	2.8
	8 R	190	55	5.2	3.7	17	50/20/35	50/5	100/60/75	6.1	12	3.2
	E	270	83	4.1	5.9	19	55/20/35	—	110/55/80	8.2	14	3.0
	9 R	245	63	4.6	5.5	12	28/13/18	26/6	105/60/85	7.2	11	2.9
	E	580	80	7.7	7.6	18	40/25/30	—	130/75/100	13.9	14	2.4
	10 R	210	94	4.4	4.7	15	35/15/20	35/6	140/80/100	5.5	12	2.7
	E	300	102	5.4	5.5	18	36/12/22	—	150/90/110	7.7	14	2.6
	11 R	210	56	5.7	3.65	12	50/20/26	55/8	150/70/100	6.2	8	2.9
	E	330	84	6.7	5.0	28	80/35/42	—	155/75/100	11.5	21	3.5
	12 R	290	55	5.7	5.1	16	36/16/23	36/15	145/60/88	6.1	13	2.1
	E	665	60	9.4	7.1	14	57/19/33	—	158/66/94	16.5	15	2.5
II: Mitral stenosis	13 R	180	65	4.1	4.4	10	28/12/19	28/8	100/50/70	5.4	13	3.0
	E	270	75	6.2	4.4	—	35/18/24	—	110/65/82	9.6	23	3.5
	14 R	224	80	4.9	4.6	20	55/25/35	55/66	140/60/80	7.1	26	3.2
	E	295	85	6.4	4.6	—	67/30/50	—	—	11.2	21	3.8
	15 R	170	106	3.0	5.6	21	41/23/29	43/8	120/72/95	5.5	20	3.2
	E	255	136	4.2	6.1	26	52/31/38	—	157/90/115	7.5	24	2.9
	16 R	260	88	6.0	4.4	35	90/40/65	90/13	125/80/95	11.2	14	4.3
	E	520	150	10.4	5.0	50	130/70/80	—	150/75/100	32.4	21	6.2
	17 R	215	94	4.7	4.6	23	60/25/40	60/6	140/65/90	5.3	12	2.5
	E	410	108	5.2	7.9	30	75/40/50	75/8	150/70/100	12.3	28	3.0
	18 R	180	60	5.8	3.1	20	50/20/28	50/8	80/90/65	4.9	15	2.7
	E	450	104	9.1	5.0	28	75/35/45	75/10	140/75/100	13.3	24	3.0
	19 R	210	96	5.2	3.75	26	55/25/35	60/7	115/55/70	7.0	22	3.3
	E	370	108	5.6	5.1	36	70/30/45	—	150/90/105	11.0	28	3.0
	20 R	190	70	5.9	3.3	22	60/20/35	60/12	125/50/80	7.0	20	3.7
	E	360	78	8.6	4.2	32	70/20/45	—	160/60/85	16.5	25	4.6
	21 R	250	72	7.1	3.5	22	65/35/45	65/7	140/75/90	7.5	19	3.0
	E	500	125	13.6	3.7	—	74/40/52	—	170/90/110	23.6	30	4.7
	22 R	250	114	6.2	4.0	39	90/55/65	90/15	130/85/100	10.6	21	4.3
	E	460	125	6.5	7.0	50	115/65/85	—	—	22.5	41	4.9
	23 R	195	90	5.9	3.3	20	95/48/62	100/14	215/129/155	6.6	15	3.4
	E	365	120	7.9	4.6	32	125/65/82	—	240/130/180	15.2	23	4.2
	24 R	200	68	3.8	5.2	32	72/25/55	80/8	100/50/70	5.9	18	2.6
	E	450	150	7.6	5.9	55	85/40/65	—	—	23.8	18	5.3
	25 R	215	54	4.2	5.2	13	28/9/16	28/8	125/62/80	5.5	10	2.6
	E	535	86	6.6	7.8	29	42/12/20	—	150/75/95	19.8	20	3.7
	26 R	190	66	4.9	3.8	16	31/16/21	32/9	110/60/82	5.5	14	2.9

TABLE II—continued

Group	Case No.	$\dot{V}O_2$ (ml./min.) STPD	Heart rate	A-V diff. (vol. %)	CO (l./min.)	Pressures (mm. Hg)				$\dot{V}$ (l./min.) BTPS	Resp. rate	VE
						PCV (mean)	PA s/d/mean	RV s/d	Syst. s/d/mean			
III: Pulmo- nary stenosis	29 R	250	120	6.2	4.0	—	40/20/25	210/26	145/90/100	6.3	16	2.5
	E	760	188	11.7	6.5	—	40/20/25	—	150/100/110	22.4	35	3.0
	30 R	175	80	4.5	3.9	9	23/8/15	35/4	95/65/70	3.3	—	1.9
	E	450	120	6.0	7.5	—	23/8/15	65/3	100/67/80	11.1	—	2.7
	31 R	150	—	—	—	—	—	115/10	—	7.9	24	5.3
	E	—	—	—	—	—	—	—	—	—	—	—
	32 R	225	75	4.8	4.6	9	20/10/13	70/9	125/75/105	5.7	15	2.5
	E	560	104	8.5	6.6	—	20/10/13	100/0	140/68/95	26.2	22	4.6
	33 R	196	80	4.8	4.1	7	16/8/11	55/12	105/65/83	5.2	16	2.7
	E	658	150	8.2	8.2	—	17/8/10	130/20	162/87/—	22.2	25	3.4
	34 R	265	65	4.0	6.6	7	25/10/13	50/10	110/60/70	7.0	14	2.6
	E	695	94	7.5	9.3	—	25/12/17	50/10	130/75/85	13.5	15	2.0
	35 R	325	60	4.6	7.0	6	15/8/12	125/10	125/70/85	7.7	14	2.4
	E	700	92	9.0	7.8	—	—	150/10	135/70/88	24.2	18	3.5

$\dot{V}O_2$, oxygen uptake; A-V diff., arteriovenous oxygen differences; CO, cardiac output; PCV, pulmonary capillary venous (wedge); PA, pulmonary arterial; RV, right ventricle; Syst., systemic; V, ventilation; VE, ventilatory equivalent; STPD, standard temperature and pressure, dry (0° C. and 760 mm. Hg); BTPS, body temperature and pressure saturated with water vapour; R, rest; E, exercise.

at rest and on effort in the subjects studied during mild supine exercise on the catheter table.

The changes with exercise in the ventilation and the main components of arterial blood chemistry are illustrated in Fig. 1. The responses to exercise of cardiac output and mixed venous blood composition are illustrated in Fig. 2. The first points in the figure represent the resting values, the second those in the third-to-fourth minute and the last those at about the tenth minute of exercise. In the first column of the figures the corresponding findings in the few normal subjects used for comparison are shown.

In Fig. 1 it is seen, as anticipated, that the ventilatory response to exercise is greater in the patients with cardiac lesions, particularly those with mitral disease. The systemic arterial oxygen saturation was lower than normal in some patients in all three groups. Only 3, however, showed an oxygen saturation below 90 per cent on effort, one of those (Case 16) being the patient who developed pulmonary oedema, another having mitral valve disease with additional lung disease (Case 23), the third (Case 33) being a patient with pulmonary stenosis and a small shunt through a patent foramen ovale.

The levels of the arterial PCO_2 showed no marked

differences between the groups, and certainly no tendency to rise in the group with the greatest increment in ventilation. In most cases the highest ventilatory response was associated with low values of PCO_2 as shown in Fig. 3. Only three patients had an exercise PCO_2 higher than 45 mm. Hg (Cases 11, 14, and 23). The findings in those 3 suggested the presence of lung disease, and this was confirmed by lung function studies in the 2 patients in whom these were performed; both showed a restrictive ventilatory defect and evidence of gaseous maldistribution in the lung.

The arterial pH also showed no apparent correlation with the ventilation, and patients with higher ventilation were usually the more alkalotic ones (Fig. 4).

The arterial lactate is plotted in Fig. 5 against the excess ventilation. The patients with greatest deviation of ventilation from normal have higher lactates, but the relationship is not significant ($p > 0.1$). We noted, moreover, that in cases with a ventilation as much as 100 per cent above the normal for the exercise load, the lactate levels lay within the wide normal range. This will be discussed later.

Finally in Fig. 6 the relationship is shown between

TABLE III
SIMULTANEOUS ARTERIAL AND MIXED VENOUS BLOOD COMPOSITION AT REST AND DURING STEADY-STATE
MILD SUPINE EXERCISE

Group	Case No.	Arterial Blood						Venous Blood			
		SAO ₂	pH	Pco ₂ (mm. Hg)	Bicarb. (mEq/l.)	Lact. (mM/l.)	Pyr. (mM/l.)	SvO ₂	pH	Pco ₂ (mm. Hg)	Bicarb. (mEq/l.)
Normal	1 R E	96.4	7.500	27.5	25.5	0.98	0.09	78.4	7.470	31.0	24.0
		97.1	7.470	30.0	24.0	1.95	0.16	54.2	7.380	46.0	23.5
		94.7	7.410	36.0	23.0	2.15	0.18	62.1	7.389	42.0	22.0
	2 R E	98.7	7.435	36.0	24.5	0.91	0.06	79.7	7.410	43.0	25.0
		28.2	7.405	36.0	23.0	1.95	0.13	55.0	7.345	41.0	20.5
		95.5	7.395	35.0	22.0	2.02	0.17	51.5	7.335	45.0	20.5
	3 R E	96.5	7.400	41.0	24.3	1.04	0.11	81.5	7.370	47.0	24.0
		98.6	7.400	38.0	23.3	2.34	0.14	63.9	7.365	46.0	23.0
		96.5	7.400	39.0	23.5	2.08	0.14	70.5	7.360	49.0	23.5
	4 R E	98.6	7.375	44.0	23.5	1.18	0.12	80.0	7.340	52.0	24.0
		98.6	7.370	44.0	23.5	2.60	0.18	78.0	7.335	54.0	23.5
		98.6	7.380	45.0	24.5	2.08	0.18	78.0	7.360	51.0	24.5
	5 R E	98.0	7.455	36.5	—	0.75	0.07	74.6	7.415	39.5	23.0
		—	—	—	—	—	—	—	—	—	—
		98.0	7.415	40.0	—	1.04	0.09	—	7.410	—	—
I: Left ventricular disease	6 R E	98.4	7.400	44.5	25.4	0.46	0.10	67.5	7.390	50.0	25.4
		96.2	7.365	48.0	25.0	1.24	0.18	50.4	7.350	52.0	24.6
		95.6	7.375	42.0	23.5	1.89	0.18	50.5	7.335	54.0	20.5
	7 R E	97.0	7.380	32.5	20.0	1.30	0.04	78.5	7.360	40.0	22.0
		95.6	7.390	33.0	21.5	1.30	0.14	68.8	7.340	48.0	22.5
		97.6	7.400	33.0	22.0	1.47	0.14	71.6	7.340	46.0	22.0
	8 R E	96.4	7.425	38.0	24.5	1.30	—	67.5	7.410	41.0	24.0
		92.4	7.395	39.0	23.0	1.82	—	68.8	7.370	40.5	21.5
		93.7	7.400	38.0	23.0	2.21	—	63.4	7.390	43.0	24.0
	9 R E	97.5	7.390	35.0	21.5	0.52	—	70.0	7.375	41.0	22.0
		98.0	7.360	38.0	21.0	1.04	—	53.3	7.340	48.0	22.0
		99.2	7.385	36.5	21.5	1.17	—	50.4	7.350	45.0	21.5
	10 R E	91.5	7.405	36.5	23.0	0.97	0.05	65.8	7.395	40.0	23.0
		95.0	7.410	35.0	23.0	1.47	0.07	64.1	7.360	46.0	22.5
		95.8	7.405	36.5	23.0	1.36	—	62.9	7.395	39.5	22.5
	11 R E	93.3	7.382	48.0	25.0	1.17	0.13	68.3	7.315	51.0	21.0
		—	—	—	—	—	—	63.0	—	—	—
		92.5	7.351	46.5	23.0	1.47	0.13	63.0	7.315	49.0	21.0
	12 R E	95.5	7.420	40.0	25.0	0.58	0.07	69.4	—	—	—
		94.2	7.410	40.0	24.5	1.69	0.11	49.9	—	—	—
		96.2	7.420	37.0	24.0	1.43	0.13	53.0	—	—	—
	13 R E	96.2	7.380	41.0	23.0	0.58	0.04	74.4	7.350	44.0	22.0
		97.4	7.370	43.5	23.0	0.97	0.07	62.7	7.325	50.5	22.0
		95.9	7.395	38.5	23.0	0.65	0.06	62.8	7.355	44.0	22.0
	14 R E	91.2	7.420	49.0	28.0	0.65	0.05	61.0	7.390	60.0	29.0
		90.8	7.390	54.0	28.0	1.30	0.06	53.0	7.360	64.0	27.0
		94.6	7.360	55.0	26.0	1.37	0.08	48.0	7.370	59.0	27.5
II: Mitral stenosis	15 R E	95.5	7.380	40.5	23.0	0.84	0.07	78.2	7.360	50.0	24.0
		96.3	7.370	41.5	23.5	1.56	0.12	72.5	7.355	46.0	22.0
		97.7	7.350	44.0	22.5	1.36	0.12	73.7	7.355	47.0	23.0
	16 R E	90.1	7.450	28.0	22.0	0.91	0.11	57.1	7.440	31.0	22.0
		90.9	7.390	34.0	21.0	2.34	0.15	31.3	7.350	45.0	21.0
		84.8	7.395	31.5	20.5	3.58	0.19	32.0	7.350	44.0	20.5
	17 R E	93.2	7.405	35.5	23.0	0.65	0.07	64.5	7.360	45.0	22.5
		91.8	7.380	42.0	23.5	0.98	0.10	57.5	7.350	49.0	22.5
		94.3	7.395	38.0	23.0	0.85	0.09	57.5	7.350	49.0	23.0
	18 R E	93.2	7.430	49.0	29.0	1.36	0.11	60.0	7.395	52.0	26.5
		93.6	7.445	42.0	27.0	2.47	0.13	42.6	7.375	55.0	25.0
		93.3	7.460	35.5	25.5	2.99	0.15	41.0	7.370	55.5	25.0
	19 R E	95.8	7.385	43.0	24.0	0.52	0.06	64.0	7.365	45.0	22.0
		94.5	7.405	40.0	24.0	0.78	0.10	56.0	7.345	49.0	22.0
		98.0	7.465	30.0	24.0	1.17	0.11	56.0	7.385	38.5	22.0
	20 R E	96.0	7.425	40.0	25.5	1.36	0.08	64.5	7.415	46.0	25.5
		95.0	7.425	38.5	25.0	1.82	0.10	44.4	7.370	46.0	23.0
		94.4	7.420	37.0	24.0	1.82	0.12	57.9	7.400	43.0	23.0

TABLE III—continued

Group	Case No.	Arterial Blood						Venous Blood			
		SAO ₂	pH	PCO ₂ (mm. Hg)	Bicarb. (mEq/l.)	Lact. (mM/l.)	Pyr. (mM/l.)	SvO ₂	pH	PCO ₂ (mm. Hg)	Bicarb. (mEq/l.)
II: Mitral Stenosis	21 R E	92.8	7.405	33.0	22.0	0.77	0.08	61.2	7.390	38.0	21.5
		93.3	—	—	—	—	—	—	—	—	—
		95.5	7.395	29.0	21.0	1.48	0.10	33.5	7.325	44.0	19.0
	22 R E	92.0	7.430	27.5	20.5	1.17	0.12	30.0	7.405	37.0	22.0
		94.0	7.460	26.5	21.5	2.08	0.13	28.5	7.365	46.0	23.0
		—	—	—	—	—	—	—	—	—	—
	23 R E	90.5	7.310	49.0	21.5	1.43	0.06	62.3	7.300	59.0	22.3
		—	—	—	—	2.27	0.12	51.8	7.285	61.0	21.5
		89.6	7.300	47.0	20.0	2.08	0.12	53.8	7.265	55.0	18.5
	24 R E	92.7	7.445	33.5	24.0	1.24	0.07	71.4	7.415	40.0	24.0
		94.4	7.430	34.0	23.5	3.57	—	48.2	7.360	48.0	22.5
		93.6	7.475	27.0	22.5	3.64	0.18	49.6	7.375	42.0	22.0
III: Pulmonary stenosis	29 R E	97.1	7.410	34.0	22.5	0.73	0.10	57.0	7.380	39.0	21.5
		97.7	7.345	31.0	18.5	5.58	0.28	22.0	7.265	44.0	17.0
		100.0	7.340	29.5	17.5	5.57	0.34	25.7	7.270	43.0	16.0
	30 R E	94.0	7.400	43.0	25.0	0.65	0.07	66.0	7.365	50.0	25.0
		95.2	7.375	48.0	25.0	1.17	0.14	56.0	7.285	51.0	23.5
		94.0	7.385	46.0	22.0	1.17	0.13	41.0	7.345	51.0	23.0
	31 R E	97.5	7.445	31.5	23.5	1.56	0.17	—	—	—	—
		93.6	7.420	33.5	23.0	3.51	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
	32 R E	94.0	7.430	33.5	24.5	0.52	0.08	68.4	7.415	37.0	23.0
		88.6	7.420	33.0	22.0	1.63	—	42.0	7.350	41.5	20.0
		90.3	7.375	36.0	21.0	2.34	0.11	46.2	7.340	43.0	20.0
	33 R E	98.0	7.410	34.5	22.5	0.94	—	72.7	7.390	38.0	22.7
		89.2	7.400	36.5	22.7	1.65	—	45.4	7.375	45.0	24.2
		88.5	7.405	35.0	22.1	2.35	—	49.8	7.360	46.0	23.5
	34 R E	97.0	7.390	40.0	23.5	0.78	0.10	77.6	7.365	44.0	22.5
		95.6	7.380	40.0	23.0	0.80	0.13	59.0	7.335	48.0	21.5
		99.0	7.370	45.0	23.5	0.98	0.14	60.3	7.340	51.0	22.5
	35 R E	95.0	7.430	33.0	22.5	1.17	0.14	67.8	7.400	39.0	23.5
		95.6	—	—	—	—	—	44.9	—	—	—
		95.6	7.420	33.0	22.0	2.21	0.19	44.4	7.370	40.0	20.5
	36 R E	97.1	7.420	38.0	24.0	0.78	0.05	74.2	7.380	45.0	23.5
		97.0	7.395	35.5	22.2	1.43	0.12	43.0	7.340	47.0	21.0
		96.4	7.400	36.5	22.5	1.56	0.13	56.6	7.350	47.0	21.0
	37 R E	99.0	7.400	33.0	21.0	0.78	0.08	72.0	7.395	40.0	23.0
		96.3	7.340	36.5	20.0	3.25	0.15	50.3	7.340	49.0	21.5
		95.4	7.320	37.0	19.0	2.60	0.17	54.5	7.315	46.0	20.0
	38 R E	95.6	7.365	45.0	23.5	0.65	0.05	72.9	7.345	50.0	23.0
		94.7	7.385	43.0	24.0	1.43	0.09	46.9	7.345	51.0	22.0
		95.8	7.360	43.0	23.0	1.56	0.11	46.5	7.310	45.0	22.0
	39 R E	95.3	7.460	35.5	25.0	1.30	0.10	67.8	7.420	38.5	23.0
		96.1	7.450	36.0	25.0	—	—	52.2	7.380	48.0	24.5
		96.0	7.420	35.5	23.0	1.82	0.12	49.0	—	—	—

Note: During exercise, the observations at the 3rd and 4th minute are shown in the upper line and those in the 9th to 10th minute on the lower.

SAO₂, systemic oxygen saturation; SvO₂, mixed venous oxygen saturation; Bicarb., standard bicarbonate; Lact., lactate; Pyr., pyruvate.

the ventilation and the indirect left atrial pressure on exercise in those patients in whom the latter was measured. A highly significant relationship exists ($p < 0.001$). The 3 patients amongst these with abnormal arterial gases (i.e. PCO₂ more than 45 mm. Hg and/or systemic arterial oxygen saturation less than 90%) are shown in solid symbols. It is seen that their ventilatory response falls into line with the rest and does not suggest that an additional humoral factor is operating.

The changes in the *venous blood chemistry* merit

consideration. Since, with few exceptions, the arterial oxygen saturation showed no significant variations, the venous oxygen saturation for a given exercise load was a direct function of the cardiac output. No significant relationship between the latter and the ventilation was found during mild supine exercise in a much larger series of patients previously reported (Gazetopoulos *et al.*, 1966), and it is, therefore, unlikely that the venous oxygen saturation is related directly to the ventilatory response under those conditions.

FIG. 1.—Ventilation (expressed as ventilatory equivalent, VE) in relation to arterial oxygen saturation, pH, PCO_2 , and lactate concentration at rest and during supine exercise in normal subjects, and several types of heart disease. Group I, left ventricular disease; Group II, mitral stenosis; Group III, pulmonary stenosis. For blood chemistry the three points shown represent, respectively, rest, 3rd to 4th minute, and 8th to 10th minutes of exercise. For ventilation, resting, and steady-state, 5th to 10th minute values are given.

Likewise the mixed venous PCO_2 depends not only on the arteriovenous difference but also on the level of the arterial PCO_2 ; and it is evident from Fig. 2 that there was no significant difference in the former between the several groups. The venous PCO_2 is plotted against the ventilation in Fig. 7. The solid line in this figure shows a postulated normal ventilatory response to increasing venous PCO_2 given by Riley *et al.* (1963). It is clear from our data that patients with the higher ventilation in all groups tended to have lower rather than higher levels of venous PCO_2 . Only a few of our patients have a significantly raised venous PCO_2 during exercise and they include those with chronic CO_2 retention; the ventilation in these patients is in the lower range.

In the upper part of Fig. 2 is shown the mixed venous pH. When this is plotted against the ventilatory response to exercise (Fig. 8) it is seen that the patients with the greatest ventilation were not those who showed the lowest venous pH. From

Fig. 7 and 8 it is also seen that there was no difference in the mixed venous pH and PCO_2 between patients with normal (open symbols) and low cardiac output (closed symbols), in spite of the wider arteriovenous difference in the low-output patients.

B. Upright Exercise. Table IV gives the changes seen in the patients studied on the bicycle ergometer.

Figure 9 illustrates the 4 patients with *mitral stenosis*. Of these, 3 were unable to complete more than a few minutes of exercise at the second level owing to dyspnoea. Accordingly no measurements of the ventilation at that stage could be made in them, though it was clear that considerable hyperventilation was present, certainly more than 40 l./min. The ventilation was also excessive at the first level in these 3 patients. In all the PCO_2 was low, the pH high, and there was no abnormal rise in lactate nor fall in arterial saturation. The fourth patient, who had moderate mitral stenosis,

FIG. 2.—Cardiac output in relation to mixed venous chemistry. Definitions as in Fig. 1. Observations were made simultaneously with those of Fig. 1.

performed the first exercise level with a normal ventilatory response. The mean pulmonary arterial wedge pressure had been 29 mm. Hg at an exercise level corresponding to an oxygen uptake of 530 ml./min. in the supine position during cardiac

catheterization. It is likely that at the first level of exercise when the posture was upright and the oxygen uptake lower (445 ml./min.) the wedge pressure was also lower. Hyperventilation was present when the exercise load was increased and the lactate rose

FIG. 3.—Arterial P_{CO_2} and ventilatory response to exercise in all groups expressed as deviations from mean predicted values (Gazetopoulos *et al.*, 1966). Triangles represent Group I, circles Group II, squares Group III. The P_{CO_2} is seen broadly to vary inversely with the degree of hyperventilation.

FIG. 4.—Arterial pH and ventilation. Symbols as in Fig. 3. Patients with greater ventilation are the more alkalotic.

FIG. 5.—Arterial lactate concentration and ventilation. Symbols as in Fig. 3. No significant relationship is present ($r=0.12$; $p>0.1$).

FIG. 6.—Ventilation and left atrial mean pressure on exercise in patients where blood gas measurements were made. The closed symbols represent those patients with additional hypercapnia or hypoxæmia or both. Despite the abnormal blood chemistry the ventilatory response is not remarkable, suggesting that this does not represent an additional stimulus. Symbols as in Fig. 3. A significant relationship exists between the two variables ($r=0.987$; $p<0.001$).

FIG. 7.—Mixed venous PCO_2 and ventilation. Crosses represent normal subjects, otherwise symbols as in Fig. 3. Open symbols signify normal cardiac output on exercise; closed symbols impaired output (Gazetopoulos *et al.*, 1966). The solid line is the ventilation—venous PCO_2 relationship given by Riley *et al.* (1963). Higher ventilation is associated with lower rather than higher venous PCO_2 .

FIG. 8.—Mixed venous pH and ventilation. Symbols as in Fig. 7. Higher ventilatory levels are not associated with a tendency towards venous acidæmia.

above normal. The arterial PCO_2 at this stage was falling and there was only slight tendency towards acidæmia.

Figure 10 shows our findings in patients with *pulmonary stenosis* studied on the bicycle ergometer. The lowermost part of this figure shows the ventilation, expressed as minute volume, and the heart rate, the limits of normality being those derived from published data and from our own findings (Gazetopoulos *et al.*, 1966). Above that are

illustrated the changes in arterial oxygen saturation, PCO_2 , pH , and lactate. All patients were exercised to their maximal working capacity, at which point they had to stop on account of dyspnoea or fatigue. The ventilatory response was usually excessive at all points up to the highest level. Lactate production was somewhat excessive (see below). We noted a reduction in exercise tolerance in all these patients that seemed to be related to the severity of the stenosis and to their age. In all cases the pH and PCO_2

TABLE IV
ARTERIAL BLOOD COMPOSITION AND OTHER DATA AT REST AND DURING GRADUATED INCREASES OF UPRIGHT EXERCISE ON BICYCLE ERGOMETER

Case No. and diagn.		Ex. load (kg./min.)	$\dot{V}O_2$ (ml./min.) STPD	Heart rate	V (l./min.) BTPS	Arterial blood					
						SAO ₂	pH	PCO ₂ (mm.Hg)	Bicarb. (mEq/l.)	Lact. (mM/l.)	Pyr. (mM/l.)
25 MS	R E	0	200	64	6.3	96.0	7.405	45.0	26.0	1.49	0.08
		200	445	88	15.6	—	7.405	44.0	25.0	2.05	0.10
		—	—	—	—	—	7.415	40.0	24.5	2.14	0.11
		400	1205	120	32.4	—	7.415	37.0	23.0	5.07	0.12
	Rec. (5') (10')	—	—	72	8.6	98.0	7.390	34.0	22.5	5.46	0.20
		—	—	72	6.1	—	7.365	42.0	23.0	4.29	0.35
		—	—	—	—	—	7.380	40.0	23.0	3.08	0.16
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
26 MS	R E	0	190	84	9.5	97.0	7.535	32.5	27.0	1.10	0.08
		200	912	132	28.0	—	7.505	30.5	24.5	2.30	0.11
		—	—	—	—	97.2	7.505	30.5	24.5	2.10	0.13
		400	—	160	—	97.0	7.500	30.5	24.0	2.20	0.16
	Rec. (5')	—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	7.485	32.0	24.5	1.80	0.12
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
27 MS	R E	0	298	80	11.0	97.0	7.470	32.0	24.0	0.65	0.09
		200	920	128	36.0	—	7.460	30.0	22.0	1.36	0.12
		—	—	—	—	—	7.460	28.0	21.0	1.95	0.16
		400	—	136	—	97.0	7.440	29.0	21.0	2.01	0.16
	Rec. (10')	—	—	80	12.0	—	—	—	—	—	—
		—	—	—	—	—	7.450	30.0	22.0	1.49	0.18
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
28 MS	R E	0	200	100	9.0	95.0	7.415	41.0	25.0	1.23	0.07
		200	604	140	33.0	—	7.450	29.5	22.5	2.34	0.12
		—	—	—	—	—	7.460	25.0	21.0	2.73	0.13
		400	—	160	—	95.6	7.470	24.5	21.5	3.12	0.13
	Rec. (5') (10')	—	—	125	—	—	—	—	—	2.14	0.13
		—	—	120	—	—	—	—	—	1.95	0.11
		—	—	—	—	—	7.500	24.0	23.0	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
35 PS	R E	0	350	80	10.0	98.0	7.440	33.0	22.5	1.49	0.12
		200	800	88	18.0	—	—	—	—	—	—
		—	—	—	—	98.0	7.470	30.5	22.5	1.62	0.13
		400	1030	100	20.0	98.0	7.440	32.0	22.0	1.82	0.20
	Rec. (10')	—	—	—	—	98.0	7.460	33.0	23.5	1.75	0.19
		—	—	—	—	96.0	7.425	33.0	22.0	3.05	0.18
		—	—	—	—	96.2	7.400	32.0	20.5	4.03	0.19
		—	—	—	—	92.3	7.360	29.5	17.5	8.45	0.21
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	98.0	7.430	27.0	19.5	5.85	0.31
36 PS	R E	0	250	64	7.8	97.8	7.420	37.0	24.0	0.98	0.06
		200	865	100	21.0	97.6	7.480	25.5	22.5	2.01	0.16
		—	—	—	—	96.1	7.450	28.0	22.0	2.34	0.18
		400	1225	120	30.7	97.3	7.460	27.5	22.5	2.92	0.18
	Rec. (10')	—	—	—	—	96.7	7.425	29.0	21.5	2.93	0.19
		—	—	—	—	95.3	7.415	30.0	21.3	3.30	0.20
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
37 PS	R E	0	270	76	8.5	95.6	7.445	38.0	25.5	1.04	0.06
		200	810	108	19.0	96.9	7.435	30.0	22.5	1.49	0.12
		—	—	—	—	96.6	7.435	30.5	23.0	1.56	0.13
		400	1080	140	29.5	94.4	7.420	29.0	21.0	2.47	0.17
	Rec. (5') (15')	—	—	182	37.4	95.4	7.350	40.0	21.0	3.90	0.17
		—	—	—	—	95.0	7.395	32.0	21.0	4.55	0.18
		—	—	100	10.8	94.0	7.355	37.5	20.5	4.65	0.18
		—	—	95	12.0	95.4	7.395	30.0	20.5	5.46	0.32
		—	—	—	—	92.0	7.420	30.0	21.5	2.86	0.24
		—	—	—	—	—	—	—	—	—	—
38 PS	R E	0	255	98	11.0	94.7	7.460	31.0	23.5	1.04	0.08
		200	625	140	21.6	98.6	7.400	35.5	21.5	1.50	0.10
		—	—	—	—	95.7	7.425	35.0	23.5	1.75	0.11
		400	1125	164	30.7	96.0	7.420	34.0	23.0	2.53	—
	Rec. (10')	—	—	180	43.2	97.0	7.400	34.0	22.0	3.64	—
		—	—	—	—	95.7	7.415	31.0	21.5	46.8	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	96.0	7.425	31.5	22.0	3.60	0.20
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
39 PS	R E	0	408	68	11.9	96.0	7.495	32.0	25.0	0.84	0.07
		200	816	98	27.2	—	7.440	34.0	23.5	2.99	0.12
		—	—	—	—	—	7.450	32.5	22.5	2.73	0.12
		400	1120	176	45.7	—	7.455	32.0	22.5	3.51	—
	Rec. (5') (10')	—	—	80	11.7	96.2	7.460	31.0	22.5	3.90	0.14
		—	—	64	10.1	—	7.415	34.0	22.0	3.64	0.16
		—	—	—	—	—	7.450	32.0	22.5	2.21	0.14
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
40 PS	R E	0	290	108	8.5	96.0	7.445	36.0	25.0	1.82	0.11
		200	700	176	20.5	90.0	7.435	27.0	21.2	3.12	0.22
		—	—	—	—	95.0	7.430	31.0	22.5	3.64	0.19
		—	—	108	8.3	93.0	7.440	31.5	23.4	2.86	0.14
	Rec. (10')	—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—
		—	—	—	—	—	—	—	—	—	—

Note: All patients were exercised to their maximum ability. Recovery figures are also given. Symbols as in Tables II and III.

FIG. 9.—Ventilation, arterial pH, PCO_2 , lactate, and pyruvate in 4 patients with mitral stenosis at two exercise levels performed upright on the bicycle ergometer. In each case abscissa as in lower part of figure. Note that 3 of the patients were unable to complete 10 minutes of exercise at the higher level. See text for discussion.

showed changes that could have been consequent upon hyperventilation, and the oxygen saturation did not change significantly.

DISCUSSION

The object of these studies was to observe whether there were any alterations in the blood

chemistry that were uniformly associated with hyperventilation or dyspnoea.

The results indicate that in all the groups of patients studied, the variations in blood chemistry were those that would be anticipated as a result of hyperventilation rather than as a cause of it.

In the patients with pulmonary venous hypertension, the PCO_2 usually fell and the pH remained

FIG. 10.—Ventilation, heart rate, and blood chemistry in patients with pulmonary stenosis exercised in upright position by graduated increase to maximum working capacity. The normal limits of heart rate and ventilation are shown (Davies *et al.*, 1965). Excessive ventilatory response is usually seen and does not appear to be consequent on changes in blood chemistry.

in the alkalotic-to-normal range, while the lactate, though sometimes higher than is usually seen in normal subjects, was not uniformly excessive when hyperventilation was present. This observation applies to both the arterial and venous sides of the circulation and supports the view that here the dominant stimulus to hyperventilation is the pulmonary congestion, and that the blood chemical changes reflect the effects of the overbreathing. It is true that some exceptions to this general pattern were seen and a few patients showed hypercapnia or arterial hypoxaemia or both, at rest and on exercise. These patients, however, usually had additional lung disease, and their ventilatory response was similar to those in the rest of the group who had equally high left atrial pressures (Fig. 6). This suggests that additional mild hypercapnia or hypoxaemia has little or nothing to do with stimulating ventilation, when the left atrial pressure is raised. This is not surprising since the adaptation occurring in cases with chronic disturbances of blood chemistry is well recognized; the accommodation to chronic hypoxaemia has been discussed in another study of cyanotic patients (Davies and Gazetopoulos, 1965), where it was often found that there was a normal ventilatory response to exercise in spite of marked hypoxaemia. The adaptation to chronic hypercapnia has also been known for many years (Scott, 1920; Donald and Christie, 1949; Fishman, Turino, and Bergofsky, 1957). We note, however, that hypoxaemia and hypercapnia are seen only exceptionally and we believe that the finding of an increase in arterial PCO_2 in a great proportion of the patients of Mauck *et al.* (1964) was due to early sampling (within the first minute of exercise). Such early increases in PCO_2 we have observed both in normal subjects and in patients, representing the increased CO_2 production by the exercising muscles during the period before the ventilation has reached its steady state.

The group of patients with pulmonary stenosis is of particular interest since the factor of pulmonary congestion is excluded. There is no doubt that hyperventilation does occur in such patients in response to exercise (Fig. 1 and 10). One factor distinguishing this group from the patients with pulmonary venous hypertension was that in the latter the exercise limitation was clearly ventilatory, the heart rates being relatively slow at this time (Table IV). In contradistinction, the patients with pulmonary stenosis attained heart rates of about 180 a minute (Fig. 10), representing the maximal effective heart rate; above that level the cardiac output would be unlikely to rise (Remington, 1950; Rushmer, 1959), and the fact that they reached this rate at relatively low exercise loads almost cer-

tainly reflects impairment of cardiac output. The exercise limitation here was circulatory rather than ventilatory, and fatigue rather than dyspnoea stopped them exercising further. Hyperventilation was nevertheless present.

In all patients with pulmonary stenosis, the oxygen saturation, pH , and PCO_2 of both the arterial and venous sides of the circulation do not show changes that would appear sufficient to stimulate ventilation.

We cannot, of course, exclude the operation of some mechanism leading to a lower threshold of response. This could also be present in the patients with pulmonary venous hypertension, but here the stimulus provided by the latter appears to be dominant in leading to the frequently observed over-correction of blood gases. A study of the threshold of the respiratory centre to changes in blood chemistry in low output states would be helpful in this connexion.

The lactate production was on the whole higher than in normal subjects at the same exercise levels, but it is clear (Fig. 10) that it was not sufficient to cause acidemia. We note, moreover, that hyperventilation was often present even at low levels of exercise while lactate concentrations were little raised.

Our results have, therefore, not provided any evidence that the recognized humoral stimuli account for the hyperventilation in patients with pulmonary stenosis on exercise. It is possible that the raised lactate levels may be associated with other manifestations of tissue hypoxia, which could in turn contribute to the non-humoral component of the ventilatory stimulus, for such an association was observed in a study of the effect of exercise in normal subjects (Davies *et al.*, 1965).

The reduction of exercise tolerance, as judged by the rapid heart rates at relatively low exercise loads, indicates impairment of cardiac output as already mentioned. While we have not found a statistically significant relationship between cardiac output and ventilation during mild supine exercise (Gazetopoulos *et al.*, 1966), this may not be true at higher exercise loads or in the upright position when the perfusion of the upper lobes of the lungs is compromised. Another possible explanation for the lack of relation between the impairment of cardiac output and ventilation is that adaptive mechanisms at tissue level may compensate for the former. Other parameters, such as the lactate changes, might therefore be more useful indices of inadequate tissue perfusion than the impairment of cardiac output.

In order to examine the significance of the lactate changes, we have plotted in all groups, in both

FIG. 11.—Arterial lactate concentration and oxygen uptake. Patients have on the whole slightly higher lactate levels than normal subjects at any given oxygen uptake, and those who hyperventilate show a slightly higher level than those who do not, though no clear separation is seen. Details in normal subjects at higher exercise levels are given elsewhere (Davies *et al.*, 1965).

supine and upright exercise, the lactate levels against the oxygen consumption (Fig. 11), as representing the work load. Values taken from another study in normal subjects (Davies *et al.*, 1965) are also included. Patients with a ventilation above the normal range for the given oxygen uptake are shown by solid symbols. The Figure shows that the patients had higher lactate levels than the normal subjects and also that the hyperventilating subjects usually had higher lactate levels than the others. Since the increase of lactate could be secondary to hyperventilation via respiratory alkalosis (Huckabee and Judson, 1958) we have also plotted in Fig. 12 the lactate/pyruvate ratio, which is not affected by those events, and found that a similar relationship exists. As can be seen in Fig. 12, the normal subjects maintain a relatively low lactate-pyruvate ratio below exercise levels corresponding to an oxygen uptake of 1.2 l./min., while in hyperventilating patients it is usually excessive. We have, therefore, plotted the lactate-pyruvate ratios in this range against the degree of hyperventilation in all patients of the three groups (Fig. 13). Although there is some superimposition, the patients with pulmonary stenosis (shown by solid symbols) have, as a rule, higher ratios than patients with pulmonary venous congestion at comparable degrees of hyperventilation. These findings suggest that at low exercise loads tissue hypoxia is more significant in patients with pulmonary

stenosis than it is in normal subjects who show little evidence of anaerobic metabolism, and it is likely that this influences ventilation.

SUMMARY

Simultaneous studies of the effects of exercise on the haemodynamics, ventilation, and arterial and venous blood chemistry have been carried out in normal subjects and in three groups of patients with heart disease.

Changes in arterial blood gases and pH were usually those that would be expected as a result of hyperventilation, and no evidence has been obtained to suggest that the venous chemistry was responsible for excessive ventilatory response.

The findings in patients with pulmonary venous hypertension support the previously-expressed view that this provides a dominant stimulus to the ventilation. In the few cases where as a result of lung disease either chronic hypercapnia or hypoxaemia or both were present, the ventilatory response was not unusual.

Hyperventilation in patients with pulmonary stenosis has been confirmed, and does not seem to be due to changes in arterial and venous blood gases. The lactate production is greater than in normal subjects at the same exercise loads, and the possible influence of inadequate tissue perfusion on the ventilation is discussed.

FIG. 12.—Lactate/pyruvate ratio and oxygen uptake. Symbols as in Fig. 11. The pattern seen is similar to that shown in Fig. 11, the normal subjects showing a lower lactate/pyruvate ratio especially at lower exercise levels.

FIG. 13.—Lactate/pyruvate ratio and ventilatory response to exercise in all patients with an oxygen uptake below 1200 ml./min. Patients with pulmonary stenosis, shown by solid squares, have on the whole higher lactate/pyruvate ratios for a given degree of hyperventilation.

We are grateful to Dr. Charles Baker for permission to study patients under his care; to Dr. M. W. Potts and Mrs. J. R. Samuel for much help with blood-gas determination; and to Miss F. Minnion and Mr. J. F. Gwynn for technical assistance. This work was supported in part by grants from the Guy's Hospital Endowment Fund and Messrs. Boehringer-Ingelheim to whom we are accordingly indebted.

REFERENCES

- Armstrong, B. W., Hurt, H. H., Blide, R. W., and Workman, J. M. (1961). The humoral regulation of breathing. *Science*, **133**, 1897.
- Arnott, M. W. (1963). The lungs in mitral stenosis. *Brit. med. J.*, **2**, 765 and 823.
- Blount, S. G., McCord, M. C., and Anderson, L. L. (1952). The alveolar-arterial oxygen pressure gradient in mitral stenosis. *J. clin. Invest.*, **31**, 840.
- Cropps, G. J. A., and Comroe, J. H. (1961). Role of mixed venous blood PCO_2 in respiratory control. *J. appl. Physiol.*, **16**, 1029.
- Cullen, G. E., Harrison, T. R., Calhoun, J. A., Wilkins, W. E., and Tims, M. M. (1931). Studies in congestive heart failure. XIII. The relation of dyspnea of exertion to the oxygen saturation and acid-base condition of the blood. *J. clin. Invest.*, **10**, 807.
- Davies, H., and Gazetopoulos, N. (1965). Dyspnoea in cyanotic congenital heart disease. *Brit. Heart J.*, **27**, 28.

- Davies, H., Gazetopoulos, N., and Oliver, C. (1965). Ventilatory and metabolic response to graduated and prolonged exercise in normal subjects. *Clin. Sci.* In the press.
- Donald, K. W., Bishop, J. M., and Wade, O. L. (1954). A study of minute to minute changes of arterio-venous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of a steady state during exercise in rheumatic heart disease. *J. clin. Invest.*, **33**, 1146.
- , and Christie, R. V. (1949). The respiratory response to carbon dioxide and anoxia in emphysema. *Clin. Sci.*, **8**, 33.
- , Gloster, J., Harris, E. A., Reeves, J., and Harris, P. (1961). The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease. *Amer. Heart J.*, **62**, 494.
- Fishman, A. P., Turino, G. M., and Bergofsky, E. H. (1957). The syndrome of alveolar hypoventilation. *Amer. J. Med.*, **23**, 333.
- Frank, N. R., Cugell, D. W., Gaensler, E. A., and Ellis, L. B. (1953). Ventilatory studies in mitral stenosis. A comparison with findings in primary pulmonary disease. *Amer. J. Med.*, **15**, 60.
- Gazetopoulos, N., Davies, H., Oliver, C., and Deuchar, D. (1966). Ventilation and haemodynamics in heart disease. *Brit. Heart J.*, **28**, 1.
- Huckabee, W. E., and Judson, W. E. (1958). The role of anaerobic metabolism in the performance of mild muscular work. 1. Relationship to oxygen consumption and cardiac output, and the effect of congestive heart failure. *J. clin. Invest.*, **37**, 1577.
- Kao, F. F., Michel, C. C., Mei, S. S., and Li, W. K. (1963). Somatic afferent influence on respiration. *Ann. N. Y. Acad. Sci.*, **109**, 696.
- Mauck, H. P., Jr., and Shapiro, W. (1961). Dominant role of pulmonary vascular engorgement as a determinant of dyspnea. *J. clin. Invest.*, **40**, 1061.
- Mauck, H. P., Jr., Shapiro, W., and Patterson, J. L., Jr. (1964). Pulmonary venous (wedge) pressure. Correlation with onset and disappearance of dyspnea in acute left ventricular heart failure. *Amer. J. Cardiol.*, **13**, 301.
- New York Heart Association (1953). *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*, 5th ed. New York.
- Remington, J. W. (1950). Relation between length of diastole and stroke index in intact dog. *Amer. J. Physiol.*, **162**, 273.
- Riley, R. L. (1963). The hypernea of exercise. In *The Regulation of Human Respiration: Proc. J. S. Haldane Centenary Symposium*, ed. D. J. C. Cunningham and B. B. Lloyd, p. 525. Blackwell Scientific Publications, Oxford.
- , Dutton, R. E., Fuleihan, F. J. D., Nath, S., Hurt, H. H., Yoshimoto, C., Sipple, J. H., Permutt, S., and Bromberger-Barnea, B. (1963). Regulation of respiration and blood gases. *Ann. N. Y. Acad. Sci.*, **109**, 829.
- , Johns, C. J., Cohen, G., Cohn, J. E., Carroll, D. G., and Shepard, R. H. (1956). The diffusing capacity of the lungs in patients with mitral stenosis studied post-operatively. *J. clin. Invest.*, **35**, 1008.
- Rossier, P. H., Bühlmann, A. A., and Wiesinger, K. (1960). *Respiration*. Mosby, St. Louis.
- Rushmer, R. F. (1959). Constancy of stroke volume in ventricular responses to exertion. *Amer. J. Physiol.*, **196**, 745.
- Scott, R. W. (1920). Observations on the pathologic physiology of chronic pulmonary emphysema. *Arch. intern. Med.*, **26**, 544.
- West, J. R., Bliss, H. A., Wood, J. A., and Richards, D. W. (1953). Pulmonary function in rheumatic heart disease and its relation to exertional dyspnea in ambulatory patients. *Circulation*, **8**, 178.