DYSPNŒA IN CYANOTIC CONGENITAL HEART DISEASE

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Received April 7, 1964

The role of chemical factors in the control of ventilation has been the subject of inquiry ever since Lavoisier at the end of the eighteenth century discovered that oxygen and carbon dioxide are intimately related to respiration. The effects, separately and together, of hypoxia, hypercapnia, and acidæmia have been investigated both in health and sickness.

In the commoner forms of heart disease where dyspnœa is prominent there are often disturbances of lung function due to the altered pressure-flow relation in the lungs, as for example in rheumatic valvular disease, left ventricular failure, or pulmonary hypertension. This makes it difficult to assess with confidence the respective contributions of lung damage on the one hand and chemical changes in the blood on the other in the causation of effort disability. When the pulmonary vascular bed is "protected" by the presence of pulmonary stenosis, however, the variable factor of lung damage associated with pulmonary hypertension is not present. It is then easier to assess the significance of non-pulmonary factors in the genesis of effort dyspnœa.

Shortness of breath on effort is usually considerable and is often severe in cyanotic congenital heart disease. Amongst a large number of patients with cardiac disease in whom we have studied the effects of exercise, there have been a number with morbus cæruleus. This report is concerned with the changes observed in these patients when they were actually dyspnœic.

PATIENTS AND METHODS

Twenty patients with cyanotic congenital heart disease have been studied, and of these 13 had Fallot's tetralogy, the severity ranging from acyanosis at rest in 6, to a resting oxygen saturation of only 58 per cent in one. Four patients had the Eisenmenger syndrome as defined by Wood (1958), two of them with ventricular septal defect, one with ventricular septal defect and patent ductus arteriosus, and one with atrial septal defect. Two patients had pulmonary valve stenosis and atrial septal defect, and one had transposition of the great vessels with pulmonary stenosis. Details are given in Table I. In Cases 12, 16, and 17 Blalock anastomoses had been performed at the ages respectively of 10, 11, and 11 years; in the first two the shunt had become inadequate. Cases 3 and 9 underwent infundibular resection at the ages of 11 and 16 years, the former with great and lasting relief; in the latter case restenosis of the outflow tract of the right ventricle had occurred with reappearance of former symptoms.

For clarity of presentation the cases have been placed in three groups according to their resting arterial oxygen saturation. This appears to be a satisfactory arrangement since with few exceptions they fall into this pattern with respect to their clinical disability and the changes that we have observed on exercise. *Group I* consists of Cases 1-7, with a resting arterial oxygen saturation greater than 90 per cent. All fell within the designation of "acyanotic Fallot's tetralogy" except Case 7: this patient had an "Eisenmenger ASD". *Group II* consists of Cases 8-15, having a resting arterial oxygen saturation between 80 and 90 per cent (inclusive). *Group III* consists of Cases 16-20, with resting arterial oxygen saturations less than 80 per cent.

TABLE I
DETAILS OF 20 CASES OF CYANOTIC CONGENITAL HEART DISEASE

Groups	Case No., sex, and age	Diagnosis	Resting art. O ₂ sat. (%)	Hb (g./100 ml.)	Disability	B.S.A.
I	1 M 38	Fallot	97	14.7	II	1.7
	2 M 29	Fallot	96	17.8	I	1.9
	3 M 19	Fallot	93	15.6	I	1.7
	4 M 18	Fallot	94	17.3	I	1.7
	5 F 18	Fallot	95	14.5	I	1.5
	6 F 16	Fallot	94	13.4	I	1.5
	7 M 35	ASD Eis.	97	16.5	I	1.9
II	8 F 41	PS+ASD	90	15.0	II	1.6
	9 F 27	Fallot	90	17.8	II	1.2
	10 M 34	Fallot	86	17.0	II	1.7
	11 F 23	Fallot	87	15.3	II	1.4
	12 F 26	Fallot	90	16.4	I-II	1.7
	13 M 13	Fallot	90	17.2	I	1.3
	14 M 25	VSD Eis.	86	17.8	II	1.7
III	15 F 28	VSD+PDA Eis.	84	17.7	II	1.5
	16 M 23	Fallot	58	22.4	III	1.6
	17 M 26	Fallot	75	19.0	II	1.6
	18 F 23	VSD Eis.	75	17.1	II-III	1.4
	19 M 15	Transpos. +PS	54	24.0	III	1.4
	20 F 26	PS+ASD	75	21.3	II	1.6

The resting arterial oxygen saturation was measured immediately before bicycle or step exercise, except in Cases 8, 9, and 20, where only catheter data are available. Disability grades according to New York Heart Association (1953). B.S.A.=Body surface area in square metres (DuBois and DuBois, 1915).

Exercise studies were originally performed during the course of cardiac catheterization, using a spring-loaded leg exerciser in the supine position. While this yielded data of considerable interest, it soon became apparent that the exercise level was too low to produce dyspnœa. Accordingly more strenuous forms of exercise, using standard step tests and the bicycle ergometer, were adopted.

For the cardiac catheterization all patients were premedicated, usually with Omnopon and scopolamine. Samples of blood for oxygen and metabolic studies were taken at rest and between the sixth and eighth minute of steady leg exercise, pulmonary and systemic flows being estimated by the Fick principle. The ventilation was measured from the spirometric tracing obtained after the fifth minute of exercise and corrected to BTPS.*

For the step and bicycle exercise the patient was not prepared in any way apart from the insistence that he should have been resting for the previous hour. The nomogram of Hugh-Jones and Lambert (1952) was used to estimate the exercise level on the steps, though this gives only a modest approximation of the work output at lower levels; the same can be said of the bicycle ergometer. Particular attention was paid to the maintenance of a steady level of exercise.

Under local analgesia a Cournand arterial needle was introduced into either the brachial or radial artery. After an interval of three minutes a resting blood sample was withdrawn, and measurements made of resting ventilation, oxygen uptake, and heart rate. The type of exercise was then commenced which was considered most appropriate to the case being studied, and continued until dyspnœa was present, as judged by the patient's statements and the evidence of considerable hyperventilation and tachypnœa. The level of effort chosen depended on the severity of the clinical disability; if after 10 minutes at the given level there was no dyspnœa, the exercise load was increased by 100–200 kg. m./min. In a few cases the effects of walking before the other levels of effort were assessed.

Blood samples were withdrawn usually in the fourth and tenth minute of exercise at each level. Of the 10 ml. taken, 6 ml. were immediately transferred to test-tubes containing 6 per cent perchloric acid for lactate and pyruvate estimation by the methods respectively of Scholz *et al.* (1959) and the modification of the

* BTPS="Body conditions" for gas volumes (body temperature, ambient pressure, water vapour saturated at body temperature).

TABLE II

DATA OBTAINED DURING CARDIAC CATHETERIZATION

Case No.		O ₂ uptake (l./min.) STPD	Vent. (l./min.) BTPS	Heart rate	Pressures (mm. Hg)		Oxygen %			Flow (l./min.)			Shunt (l./min.)		Arterial blood				
					P.A.	B.A.	P.A.	B.A.	Mixed venous	Pulm.	Syst.	Effec.	L-R	R-L	pH	P _{CO₂} (mm.)	Stand-ard bicarb. (mEq/l.)	Lac-tate (mM/l.)	Pyru-vate (mM/l.)
3	Rest	0.246	7.0	75	18/6	130/60	82.8	95.8	76.5	10.2	6.9	6.9	3.3	0	7.440	42.0	27.0	0.68	0.12
	Ex.	0.657	17.6	108	20/5	130/70	71.7	92.0	66.6	14.6	14.0	12.2	2.4	1.8	7.455	37.0	26.0	1.50	0.12
4	Rest	0.264	8.8	75	17/7	125/75	74.7	88.2	78.2	6.0	10.5	6.0	0	4.5	7.430	33.0	22.0	0.98	0.11
	Ex.	0.620	19.8	115	17/5	130/70	61.9	81.9	61.9	7.6	13.2	7.6	0	5.6	7.420	33.0	22.0	1.56	0.09
7	Rest	0.180	8.2	72	80/30	80/45	64.5	80.9	60.7	2.7	4.5	2.4	0.3	2.1	4.420	33.0	21.0	1.17	—
	Ex.	0.675	24.8	110	110/40	110/55	57.0	75.5	43.5	7.9	9.4	6.3	1.7	3.1	7.410	32.0	20.5	1.63	0.12
8	Rest	0.160	6.2	65	15/5	110/60	65.8	90.2	65.5	2.4	3.1	2.4	0	0.7	7.430	38.0	24.5	0.91	0.10
	Ex.	0.355	11.5	80	17/7	—	52.4	82.1	53.0	3.8	5.8	3.8	0	2.0	7.420	35.0	23.5	1.56	0.13
9	Rest	0.100	4.5	65	15/5	100/60	70.2	88.0	62.0	1.7	2.0	1.3	0.4	0.7	7.410	33.0	21.5	0.78	1.00
	Ex.	0.245	13.8	96	15/5	110/70	50.1	76.2	50.1	2.3	4.0	2.3	0	1.7	7.420	30.5	21.0	1.37	1.00
14	Rest	0.216	7.4	68	95/50	95/60	74.7	89.5	64.8	4.5	3.6	3.1	1.4	0.5	7.365	47.0	24.0	0.59	0.07
	Ex.	0.630	30.8	94	125/65	125/80	50.2	70.0	48.4	5.9	12.1	5.7	0.2	6.4	7.380	41.0	23.0	1.30	—
18	Rest	0.194	6.6	80	120/60	120/70	66.5	65.0	47.6	2.9	4.6	1.7	1.1	2.9	—	—	—	—	—
	Ex.	—	—	136	—	135/70	—	—	—	—	—	—	—	—	—	—	—	—	—
20	Rest	0.190	7.2	79	18/12	130/80	66.0	75.3	66.1	2.2	6.3	2.2	0	4.1	7.400	34.0	21.0	1.24	0.11
	Ex.	0.464	15.8	100	20/10	160/80	51.2	68.0	53.2	3.6	9.9	3.6	0	6.3	7.355	35.0	19.0	3.00	0.19

STPD=standard conditions for gas volumes.

BTPS=body conditions for gas volumes.

P.A.=pulmonary artery.

B.A.=brachial artery.

Warburg technique as described by Landon, Fawcett, and Wynn (1962). The remainder of the blood sample was analysed for pH, P_{CO₂}, and bicarbonate content by the micro-Astrup technique, applying the interpolation method of Andersen and Engel (1960). Oxygen saturation was measured in a Brinkman haemoreflexor. P_{O₂} was calculated from the nomogram of Severinghaus (1958).

It was intended to measure ventilation in all cases, but in the more disabled patients interference with respiration by the mouthpiece made this unsafe at higher ventilatory levels. Where measurements were made, a Wright anemometer was used and the expired air was collected in a Douglas Bag for analysis by the Haldane method. The ventilation was measured between the fifth and tenth minute of each exercise level. When measurements of ventilation were not made dyspnoea was assessed on a clinical basis as severe (Grade III), moderate (Grade II), or mild (Grade I).

There were no untoward effects from these tests apart from feelings of nausea either during or after the exercise in a few cases. It is stressed that during such studies the patient must be watched carefully at all times and the exercise terminated as soon as there are any signs of distress. This is particularly so in the Fallot group, where severe dyspnoea may appear very quickly after a period of apparent comfort at the same exercise level.

Where necessary, information derived from the study of other patients in this laboratory over the past five years has been drawn upon.

RESULTS

The data obtained are presented in Tables II and III. Table II shows the results of exercise during cardiac catheterization, and Table III those at bicycle, step, or walking exercise.

Figure 1 summarizes the changes in the main factors studied at higher exercise levels where dyspnoea was present.

Arterial Oxygen. (a) *At rest.* This depended on the nature and severity of the lesion. In 4 out of 5 cases in whom arterial oxygen estimations were made both during cardiac catheterization and before bicycle or step tests there were differences in the resting saturations on the two occasions. The values at catheterization were lower in three cases, by 10 per cent in Case 7, 16 per cent in Case 18, and 6 per cent in Case 4; Case 3 showed no difference, while Case 14 had a slightly higher level at catheterization.

(b) *During exercise.* The arterial oxygen saturation fell in all cases. At catheterization the fall was modest; during bicycle or step exercise very low values were seen at times, e.g. 25 per cent in

TABLE III
DATA OBTAINED DURING STEP AND BICYCLE EXERCISE

Case No.	State	Work	Duration	Vent. (l./min.) BTPS	O ₂ uptake (l./min.) STPD	Heart rate	Dyspnœa grade	Arterial blood							
		(kg.m./ min.)	(min.)					O ₂ %	pH	Po ₂ (mm.) (calcu- lated)	Pco ₂ (mm.)	Standard bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P
1	Rest			9.25		84	(Group I)	97	7.440	96	33.0	23.5	1.04	0.12	8.6
	Ex. steps	400	4 7	34.0		120 130	II III	63 60	7.410 7.405	32 31	35.0 34.0	22.0 21.0	2.73 3.44	0.15 0.15	18.2 23.0
	Recovery		5 10	24.0				79 88	7.420 7.445	43 55	29.0 31.0	20.5 22.5	3.0 1.82	0.18 0.11	16.7 16.5
2	Rest			7.6			0	96	7.452	84	36.0	25.0	0.83	0.10	8.3
	Ex. steps	400	3 10	28.0			I II	87 80	7.405 7.395	45	38.0 33.0	23.5 21.0	3.51 4.75	0.12 0.18	29.2 26.4
3	Rest			7.6		92	0	93	7.455	67	34.0	25.0	0.91	0.10	9.1
	Ex. cycle	300	3 7	21.4	1.07	110 120 120	I I I	86 85 81	7.455 7.460 7.465	50 49 45	36.0 30.0 36.0	25.0 23.0 26.0	1.24 1.30 0.91	0.10 0.14 0.12	10.3 9.3 7.6
	cycle	500	3	45.0	1.34	160	II	73	7.460	37	30.0	24.0	1.36	0.12	11.3
4	Rest			6.5		82	0	94	7.420	72	27.0	19.0	1.04	0.10	10.4
	Ex. walking	200	10	18.2	0.58	100	0	78	7.420	42	28.0	20.0	1.17	0.09	13.0
	cycle	300	4 10	25.6	0.83	120 126	I I	69 56	7.410 7.420	36 28	31.0 31.0	20.5 21.0	2.53 2.73	0.10 0.17	25.3 16.0
	cycle	400	4 10	40.2	1.160	160 164	II II	50 47	7.395 7.375	26 26	33.0 23.0	20.5 18.5	3.18 4.42	0.17 0.19	18.7 23.3
	Recovery		10			104		86	7.400	54	28.0	18.5	—	—	—
5	Rest			4.3	0.11	76	0	95	7.480	74	33.5	25.7	0.55	0.07	7.9
	Ex. cycle	200	4 10	11.3	0.38	135 140	I I	89 83	7.445 7.450	56 51	33.2 30.5	24.5 23.0	1.69 2.08	0.09	18.8
	cycle	400	4 10	25.8	1.03	160 160	II II	80 81	7.410 7.395	45 46	32.2 30.5	22.0 20.5	3.90 3.84	0.13 0.17	17.3 22.6
	Recovery		5 10	8.2 5.0		100		94	7.395 7.425	73	32.5 28.0	21.0 21.0	2.99 2.40	0.18 0.17	16.6 14.1
6	Rest			6.0		84	0	94	7.505	65	28.0	23.0	0.72	0.08	9.0
	Ex. walking	200	6	13.5	0.58	96	0	93	7.495	64	29.0	23.0	0.85	0.07	12.1
	cycle	300	3 9 12	19.7	0.87	120 132 130	I I I	88 69 68	7.435 7.390 7.440	55 37 34	30.0 36.0 33.0	20.5 20.5 21.4	1.82 2.40 2.40	0.15 0.15 0.16	12.1 16.0 15.0
	cycle	400	4			150	II	51	7.410	26	36.0	21.4	2.34	0.16	14.6
	Recovery		5			84	0	72	7.435	37	33.0	20.5	2.15	0.22	9.8
7	Rest			10.2	0.36	80	0	97	7.485	91	27.0	22.0	1.82	0.13	14.0
	Ex. cycle	400	4 10	38.0	1.24	120 136 160	I II II	81 70 66	7.454 7.390 7.400	44 37 34	29.0 32.0 31.0	21.0 19.0 19.0	2.67 3.64 4.29	— 0.18 —	— 20.2 —
	cycle	600	3			96 98	0 0	97 98	7.420 7.510	98 99	26.0 22.0	19.0 22.0	3.38 1.82	— —	— —
	Recovery		5 10												

Table III continued overleaf.

TABLE III *cont'd.*

Case No.	State	Work	Duration	Vent. (l./min.) BTPS	O ₂ uptake (l./min.) STPD	Heart rate	Dyspnea grade	Arterial blood												
		(kg.m./min.)	(min.)					O ₂ %	pH	Po ₂ (mm.) (Calculated)	Pco ₂ (mm.)	Standard bicarb. (mEq/l.)	Lactate (mM/l.)	Pyruvate (mM/l.)	L/P					
10	Rest	300	4 10 6 10			78	(Group II)	86	7.425	52	29.5	21.0	0.78	0.09	8.7					
	Ex. cycle					108	II	70	7.395	37	35.8	21.0	2.34	0.14	16.7					
	Recovery					120	III	40	7.375	21	38.5	19.5	2.73	0.13	21.0					
							I	85	7.395	52	35.0	21.0	2.15	0.15	14.3					
11	Rest	300	5			84	0	87	7.440	53	28.0	22.4	0.88	0.07	12.6					
Ex. steps	125					II	55	7.375	30	31.0	20.5	3.58	0.16	22.4						
12	Rest	200 200 300	10 4 10 4 7 10 5 10	10.1 16.9 24.7 34.1 13.4 10.0	0.29 0.53 0.62 1.08	68	0	90	7.440	59	30.0	21.5	1.04	0.11	9.5					
	Ex. walking cycle					96	I	83	7.410	49	30.0	20.0	1.24	0.10	12.4					
						108	I	82	7.415	48	30.0	20.0	1.43	0.10	14.3					
	cycle						I	82	7.400	48	29.0	19.5	1.79	0.13	13.8					
						120	II	78	7.405	43	32.5	20.0	1.95	0.16	12.2					
	Recovery					120	II	73	7.390	39	32.0	19.5	2.15	0.13	16.5					
						120	II	51	7.370	27	36.0	19.0	3.06	0.16	19.1					
							96	0	79	7.390	44	29.0	18.5	2.60	0.17	15.3				
		72	0	68	7.400	36	31.0	19.0	—	—	—									
13	Rest	400	1 3 5 7 10 5 10	6.5 31.5 9.6 7.0	0.21 1.15	70	0	90	7.480	57	29.0	24.5	1.45	0.16	9.0					
	Ex. cycle					120	I	59	7.454	31	33.0	22.5	3.00	0.17	17.6					
						136	II	62	7.375	32	36.0	20.0	4.42	—	—					
	Recovery					140	II	55	7.390	29	32.5	19.5	5.33	0.19	28.0					
						154	II	57	7.365	30	31.5	18.5	5.72	0.23	24.9					
	Recovery					156	III	33	7.340	20	35.0	17.0	5.33	0.24	22.2					
						114	0	79	7.400	44	26.5	19.5	3.90	0.27	14.5					
						120	0	83	7.435	49	24.0	20.0	3.38	0.22	15.4					
14	Rest	400	4 7 10 2	8.0 53.4	1.19	100	0	86	7.455	51	34.7	24.5	1.37	0.12	11.4					
	Ex. cycle					150	II	48	7.370	26	43.3	2.15	5.26	0.17	31.0					
							II	45	7.315	27	44.0	20.0	8.06	0.18	44.9					
	Recovery						III	46	7.295	28	46.5	20.3	—	—	—					
15	Rest	200 300	5 3 5 10 15	6.9 22.0 40.0 11.0 9.8 7.9	0.19 0.59 1.06	64	0	84	7.435	49	32.5	22.0	1.09	0.08	13.6					
	Ex. walking steps					90	I	68	7.440	30	33.0	22.0	1.07	0.10	10.7					
						140	II-III	43	7.380	24	35.5	19.0	3.38	0.10	33.8					
	Recovery							79	7.380	45	30.5	18.5	—	—	—					
								79	7.400	44	30.0	19.5	1.82	0.15	12.1					
							82	7.415	47	30.0	20.5	—	—	—						
	16					Rest	200	4 6 2 5 10 24			(Group III)									
						Ex. cycle					96	0	58	7.362	31	42.0	21.0	1.04	0.09	11.6
135		II	31	7.350	19						46.0	20.0	2.79	0.11	25.4					
Recovery		132	III	25	7.275	18					53.0	17.5	3.51	0.12	29.2					
		120	II	18	7.272	14					55.5	17.0	—	—	—					
Recovery		106	II	27	7.245	19					46.5	16.0	3.12	0.16	19.5					
		120	II	36	7.310	22					46.0	17.5	2.73	0.14	19.5					
		120	I-II	21	7.315	15					49.5	18.5	3.20	—	—					
17	Rest	200 200 300 300 400	4 10 4 7 10 1 4 10 2 4 5 10	6.1 18.7 14.4 21.0 19.1 16.2 17.3 24.3 7.8 4.5	0.192 0.584 0.576 0.813	84	0	76	7.400	41	38.0	22.0	0.60	0.07	8.6					
	Ex. walking					100		59	7.405	31	37.0	22.0	0.52	0.07	7.4					
						100		50	7.380	26	35.0	19.0	0.91	0.07	13.0					
	cycle						I	50	7.370	26	38.5	20.0	1.04	0.07	14.9					
								45	7.390	24	36.0	20.0	2.01	0.11	18.3					
	cycle							45	7.385	24	36.5	20.0	1.50	1.10	15.0					
								30	7.360	18	39.0	19.0	2.99	0.11	27.2					
	cycle							48	7.370	26	36.0	19.5	3.25	0.16	20.3					
								48	7.345	26	39.0	19.0	3.51	0.18	19.5					
	Recovery							40	7.380	22	36.0	19.5	2.73	—	—					
								20	7.360	14	38.0	18.0	3.12	—	—					
							71	7.380	37	33.0	19.5	2.15	—	—						
		88		74	7.420	39	35.0	22.0	1.11	—	—									
18	Rest	300	2			100	0	75	7.430	39	33.0	22.0	—	—	—					
	Ex. walking					160	III-IV	34	7.241	23	54.0	20.0	—	—	—					
19	Rest	200	4 6			110	0	54	7.375	29	30.5	20.0	1.89	0.15	12.6					
	Ex. steps					140	II	46	7.330	26	34.0	19.0	3.09	0.12	25.8					
						130	III	32	7.300	19	49.0	18.0	2.93	0.11	26.6					

BTPS. STPD. L/P=Lactate/pyruvate ratio.

TABLE IV

Case No.	1	2	3	4	5	6	7	10	11	12	13	14	15	16	17	18	19
Rest arterial O ₂ %	97	96	93	94	95	94	97	86	87	90	90	86	84	58	76	75	54
Rest arterial P _{O₂} (mm.) ..	95	85	67	73	74	65	91	52	53	59	57	51	49	31	41	39	29
Exercise arterial O ₂ %	60	80	81	47	81	51	66	40	55	51	33	46	43	25	20	34	32
Exercise arterial P _{O₂} (mm.)	31	45	37	26	46	27	34	21	30	27	20	28	24	18	14	23	21

Arterial O₂ saturation and partial pressure at rest and at peak of exercise in subjects exercised to point of dyspnœa.

Case 16 and 20 per cent in Case 17. Table IV shows the saturations and partial pressures of oxygen that were found in the arterial blood at the peak of exercise, which represents in almost all cases the point at which it had to be terminated.

The lowest saturation seen was 18 per cent in Case 16, Corresponding to a P_{O₂} of 14 mm. (Table III). This occurred shortly after the cessation of exercise. Symptoms varied considerably in relation to the level of arterial oxygen, from Cases 1 and 2 who were incommoded when their saturations were 60 and 80 per cent respectively, to Case 17 who was content to carry on when his arterial oxygen saturation was 20 per cent. Clearly the oxygen saturation is not the only factor that determines disability.

Figure 2 shows the fall in partial pressure of arterial oxygen on exercise as a function of its resting value. It enables us to derive an approximate estimate of the level that might be attained during exercise leading to dyspnœa in any cyanosed patient whose resting level is known. For example, if the resting saturation were 80 per cent (P_{O₂} of 45 mm. at pH 7.4), the exercise value would be likely to fall to around 35–40 per cent (P_{O₂} of about 22 mm. at pH 7.3) before dyspnœa would prevent the patient from exercising any further.

FIG. 1.—Changes in arterial oxygen saturation, P_{CO₂}, lactate, and pH on exercise in normal subjects and three groups of patients with cyanotic congenital heart disease. Group I, resting arterial oxygen saturation above 90 per cent; Group II, 80–90 per cent; Group III, below 80 per cent. The first point represents the resting value, the second that after approximately three minutes of exercise, and the third that at the highest level of exercise when dyspnœa was present.

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FIG. 2.—The relation between the resting arterial P_{O₂} and the fall below that value which occurred when exercise was continued to the point of dyspnœa.

The average arterial P_{O_2} on effort in Group I was 35 mm. Hg, in Group II 25 mm. Hg, and in Group III 22 mm. Hg, the resting values being 79, 54, and 35 mm. Hg respectively. There was thus a fall of 44 mm. in Group I, 29 mm. in Group II, and 13 mm. in Group III.

On cessation of exercise, the rise in arterial saturation was usually prompt. In Case 16, however, the level continued to fall for several minutes before rising again. Eight minutes later it fell once more (Table III). Both these episodes were accompanied by manifestations of excessive vagal activity, *viz.* nausea, sweating, and bradycardia.

Arterial P_{CO_2} . (a) *At rest.* At cardiac catheterization the values were very variable, ranging from 33 mm. in Cases 4, 7, and 9, to 38 and 42 mm. in Cases 8, and 3, to 47 mm. in Case 14.

Before the bicycle or step tests the circumstances were very different in that the patients were not sedated and there was necessarily a measure of anxiety accompanying the insertion of the arterial needle, the measurement of ventilation, etc. The P_{CO_2} values found in the patients, as in those of Campbell, Hunt, and Poulton (1923), were lower than those usually seen under similar conditions in normal subjects and in others without central cyanosis. It would be tempting to relate this to the fact that there is in most of them a lowered arterial oxygen tension, since hypoxæmia has been so widely held to be responsible for hyperventilation and consequent hypocapnia (Morse and Cassels, 1953). However, on examining the relation of the arterial oxygen to the CO_2 levels, it is clear that the more cyanosed patients do not in fact have the lower values of P_{CO_2} (Table III and Fig. 3). All that can be said is that the cyanosed patients had on the whole a lower arterial P_{CO_2} than normal, but that the lowering was not proportional to the degree of hypoxæmia.

The finding of a lower-than-normal arterial P_{CO_2} in a patient with a right-to-left shunt must mean that the pulmonary venous P_{CO_2} is particularly low. This was measured during cardiac catheterization in Case 20, with severe pulmonary stenosis and reversed inter-atrial shunt, and shown to be 26 mm. Hg. Gootman, Scarpelli, and Rudolph (1963) have recorded the pulmonary venous P_{CO_2} in hypoxic patients and found it to be low (18–27 mm. Hg).

(b) *On exercise.* The behaviour of the arterial P_{CO_2} during exercise was significantly different in the three groups (Fig. 1 and Table III). In Group I, the acyanotic group, the level rose initially and then fell below the resting value. In Group III, the most cyanosed, there was a progressive rise in P_{CO_2} , uninterrupted by any fall. In Group II the pattern of change was intermediate between that of the other two groups.

Campbell (1934) found a diminished output of carbon dioxide in the early minutes of exercise in patients with heart disease. Davison, Armitage, and Arnott (1953) found a delay in the ventilatory response in the early minutes of exercise in patients with cyanotic congenital heart disease, and noted that there must be considerable retention of CO_2 at this time. We have confirmed an

FIG. 3.—The resting P_{CO_2} in relation to the degree of arterial hypoxæmia.

FIG. 4.—The resting arterial lactate concentrations related to P_{O_2} .

FIG. 5.—The exercise arterial lactate concentration related to the resting P_{O_2} .

FIG. 6.—The pH and P_{O_2} in the arterial blood at rest.

early rise of arterial P_{CO_2} , but must note that it occurred not only in cyanosed patients but also in normal subjects (Rahn and Otis, 1949; Suskind *et al.*, 1950; Matell, 1963).

Arterial Lactate and Pyruvate Concentration. (a) *At rest.* These were on the whole within the normal range, confirming the findings of Hallock (1939) and Havel and Watkins (1950). Fig. 4 shows that there is no relation between the actual level of P_{O_2} and arterial lactate concentration.

(b) *On exercise.* Arterial lactate and pyruvate tended to be a little higher than those of normal subjects at the same exercise level (Davies and Gazetopoulos, to be published). The most striking feature, however, was that the most profound hypoxæmia could exist with only a slight increase of arterial lactate, as in Cases 16, 17, and 19. This is surprising in the light of the known association between oxygen lack and lactate production (Hill and Lupton, 1923; Meakins and Long, 1927; Jervell, 1928; Huckabee, 1958). Presumably the fact that the intensity of effort was limited by other factors in severe cases, as will be discussed later, was responsible for the low lactate levels which tended to be lower in the most disabled group (Fig. 5). The peak lactate levels were attained at the point of maximum effort in these patients, and we never saw a late release after the end of exercise.

Pyruvate rose in the usual fashion, the maximum values being reached a few minutes after the end of exercise. The actual levels reached were not remarkable.

Arterial pH. (a) *At rest.* These were within the upper normal to alkalæmic range, though there was some tendency towards acidæmia in the more hypoxæmic patients (Fig. 6). Of these, Case 16 had a higher than usual resting P_{CO_2} , while Case 19 had a somewhat raised blood lactate. These findings are in keeping with those of Bing *et al.* (1948) and Morse and Cassels (1953).

(b) *On exercise.* The arterial pH fell in all cases except 3 in the acyanotic group. The levels reached were lowest in the most disabled patients. It is of considerable interest that since the lactate levels were low in the latter group, the acidæmia was in the main hypercapnic rather than metabolic in origin. The lowest value seen was 7.24 in Case 18, who had Eisenmenger's complex.

Ventilation. (a) *At rest.* It has been widely accepted that patients with cyanotic congenital heart disease hyperventilate at rest, in the sense that their minute volume of ventilation is higher than normal. Bing *et al.* (1948) found that this was so in 29 out of 30 cases, that the arterial P_{CO_2} and alkaline reserve were reduced, and that the arterial pH was normal. There appears to be some lack of agreement, however, in the published figures for normal subjects. Baldwin, Cournand, and Richards (1948) and Matheson and Gray (1950) stated that in resting young adults the average ventilation was 4.0 l./min./m.², but Bucher (1949) found in 27 cases an average of 6.3 and Shephard (1955) gave the figure as 4.2. Shephard found that the minute ventilation was increased in most forms of congenital heart disease, both in the cyanotic group and in the acyanotic group with increased pulmonary blood flow. Davison *et al.* (1953) confirmed the resting hyperpnœa of cyanosed patients, though they doubted whether hypoxæmia was the main factor responsible.

FIG. 7.—The resting ventilation in normal subjects and in three groups of patients with cyanotic congenital heart disease. Open circles represent Fallot's tetralogy; closed symbols Eisenmenger syndrome (circles: ventricular septal defect; squares: atrial septal defect; triangles: patent ductus arteriosus).

FIG. 8.—The ventilation in relation to the oxygen uptake in six cases of Fallot's tetralogy at rest and on exercise. The dotted lines represent the limits of normality obtained from patients studied in this laboratory and from published cases ($\dot{V}$ =ventilation in l./min.).

In an attempt to clarify this, we have examined the records of ventilation in a large number of patients during cardiac catheterization. Normal subjects have been compared with cyanosed patients in the Fallot and Eisenmenger groups. Fig. 7 shows the results. It is seen that there is a slightly higher mean level of ventilation in the cyanosed group, but the difference is not significant (mean 4.7 in normals as against 5.5 in the cyanosed patients). The difference between the means in these groups is not significant ($p > 0.2$). Here, allowance must also be made for the fact that there is a higher proportion of small people, young and undersized, in the severer groups, the ventilation per square metre being of course greater in smaller subjects (Shock and Soley, 1939; Mannheim, 1949). In the sedated state, therefore, there is scant evidence of hyperventilation, in the sense of increased minute ventilation, in patients with cyanotic congenital heart disease.

Without sedation the resting ventilation also seems to be within the normal range, though we would not wish to draw firm conclusions from the relatively few measurements that we have at our disposal. We have reservations about accepting the frequently-quoted statements about the resting hyperventilation of cyanotic congenital heart disease, though it is conceivable that under conditions of stress such patients may show an excessive ventilatory response as compared with normal subjects. Patients with the Eisenmenger syndrome are not apparently separated from the Fallot group in respect of their resting ventilation.

(b) *On exercise.* The first relevant observation is that, as in normal subjects (Åstrand, 1960), the amount of exercise rather than its type is the more important in determining the ventilation. This is well seen in Case 4 (Table III), where the ventilation at similar levels of exercise can be compared, first at catheterization and then during walking; also in Case 17 ventilation while walking and during the lowest level of bicycle exercise is seen to be comparable (leg exercise has always been used during these studies).

A second general observation is that in most cases the ventilatory response is normal up to a certain level of exercise. Above this level the ventilation is greater than expected. With others we use for this the term "relative hyperventilation".

This is seen clearly in patients exercised at more than one level. Fig. 8 shows that in patients with Fallot's tetralogy the relation between ventilation and oxygen consumption is normal at values of $\dot{V}_{O_2}$ (oxygen uptake) less than about 800 ml./min. STPD.* Above this relative hyperventilation occurs. The more severe the cyanosis the lower is this "critical level" (i.e. the level at which relative hyperventilation begins). Generally the acyanotic group was able to attain an

* STPD="standard conditions" for gas volumes (0°C., 760 mm. Hg, dry).

exercise level of 400–600, the intermediate group 300–400, and the most severe cases less than 300 kg. m./min., but there was a notable exception in Case 17 with a functioning Blalock anastomosis which will be discussed later.

The normal ventilatory response of the Fallot group to sub-critical exercise is accompanied by biochemical changes which, oxygen saturation apart, are similar to those in non-cyanosed patients and normal subjects at the same exercise levels. Above the critical level it appears that there are disturbances in the other humoral factors and the level of oxygen tension is not by itself a potent determinant of relative hyperventilation. In Fig. 9 the level of exercise is related to the ventilation and to the measured variables during stepwise increases in exercise in representative cases from each group and one normal subject for comparison. While ventilation is normal up to a certain point, relative hyperventilation begins at lower levels in the patients, according to the severity of the disease as judged by the arterial oxygen saturation at rest.

Oxygen Consumption and Carbon Dioxide Output. (a) *At rest.* Most authors (Holling and Zak, 1950; Burchell *et al.*, 1950; Ernstring and Shephard, 1951; Davison *et al.*, 1953) have found the basal oxygen consumption to be normal in patients with cyanotic congenital heart disease. Likewise we have seen no abnormality of the oxygen consumption either at cardiac catheterization or before bicycle or step tests. Fig. 10 illustrates the findings in 114 patients and 29 normal subjects drawn from our laboratory records; it is seen that there is no significant difference between the groups.

(b) *On exercise.* Taking as the basis for comparison the figures of Åstrand (1960), we have found no abnormality of the oxygen uptake for a given work load in our patients. Doubtless at higher exercise levels a limit would be imposed by the restriction of pulmonary blood flow, but other factors cause a cessation of exercise before this point is approached. These findings appear to provide further testimony to the fact that adaptive mechanisms are highly effective in preserving the oxygen economy in such cases.

The CO_2 output was measured in only a few patients, but in them it was found that at rest and at sub-critical exercise levels the respiratory quotient lay within the normal range. On effort it rises above unity in the patients in whom the arterial P_{CO_2} drops, but we have no figures in cases where the latter rises. Our data indicate therefore that the resting oxygen consumption is normal in these patients, and that it increases normally with effort at least up to the critical level of exercise.

Heart Rate. This is higher for a given amount of exercise than in normal subjects (our data), but there are wide individual differences.

FIG. 9.—Changes in arterial oxygen, pH, P_{CO_2} , lactate, and ventilation measured at different exercise levels in a patient from each of the three groups and a normal subject. The three solid lines, in order of decreasing heaviness, represent Case 16 in Group III, Case 12 in Group II, and Case 4 in Group I. The broken line represents a normal patient. The intervals on the abscissa in each diagram are as in the lowest one. (Ventilation could not be measured in Case 16.)

FIG. 10.—The resting oxygen uptake per square metre of body surface area at cardiac catheterization in normal subjects and in three groups of patients with cyanotic congenital heart disease. Symbols as in Fig. 7.

The heart rate cannot be used as an index of exercise limitation or of physical working capacity. Thus in the most severely disabled patient (Case 16) the rate rose no higher than 135 at the point of maximum effort and dyspnoea. This aspect of the circulatory adjustment to exercise is discussed by Kjellberg *et al.* (1959).

DISCUSSION

In normal subjects during exercise the ventilation and oxygen uptake increase in linear fashion with the load at lower levels of effort. After a certain point, ventilation increases disproportionately, and at this point there is evidence of lactate accumulation and metabolic acidosis (Dejours, 1959; Cotes, 1963).

Severe effort hyperventilation leads to a fall in P_{CO_2} to levels that may be well below those of the resting state. The tendency towards alkalæmia, which is the consequence of the release of CO_2 , only partially compensates for the acidæmia associated with lactate production, and the arterial pH falls. There are no significant changes in P_{O_2} of arterial blood of normal subjects on effort (Asmussen and Nielsen, 1958; Mitchell, Sproule, and Chapman, 1958).

Whether or not ventilation is a factor limiting exercise in normal subjects, dyspnoea is usually accompanied by considerable relative hyperventilation, though of course there are wide individual variations in the exercise level needed to produce this, depending on sex, age, body habitus, and state of training.

In normal subjects at the lower levels of exercise, of the order of those to which we have subjected our cyanosed patients, there are biochemical changes of only relatively small degree. The arterial lactate increases to only about 2 mM./l., and the pH and the P_{CO_2} remain close to their resting values (Dejours, 1959 and our unpublished data). It is against these relatively minor changes that the response of the cyanosed patients must be judged.

In patients who are acyanotic at rest but are cyanosed on effort the metabolic changes with exercise, oxygen saturation apart, are not far removed from normal; the lactate rises to levels a little higher than in normals at the same exercise load, but the increase is not as great as that which we have seen in normal subjects at exercise levels sufficient to produce relative hyperventilation. The "acyanotic" patient has a pulmonary blood flow sufficient to lower the arterial P_{CO_2} on effort, and hypoxæmia and slight metabolic acidosis appear to be the main humoral disturbances; he can continue exercising without distress in the presence of relative hyperventilation. Thus Case 3, who was almost totally disabled before pulmonary valvotomy and infundibular resection, had a good pulmonary blood flow after operation (Table II). The metabolic changes with effort were small. The main humoral disturbance was hypoxæmia. In Cases 1 and 2, particularly the latter, lactic acidæmia was greater and hypoxæmia relatively mild. It may be significant that they were amongst the older patients, and were unique in this series in that they suffered from angina pectoris.

Where the pulmonary blood flow is adequate, therefore, hyperventilation leads to a fall in arterial P_{CO_2} to levels below the resting ones. The severely cyanosed patients, on the other hand, show a different pattern of response. On account of the considerably restricted pulmonary blood flow, hyperventilation is ineffectual in clearing the body of carbon dioxide. The changes in lactate are on the whole smaller than those in the acyanotic group for a given degree of disability, and the oxygen saturation is lower. It is of considerable significance that the arterial P_{CO_2} rises, and that the pH indicates that there is an acidæmia which is more hypercapnic than metabolic. These facts are fundamental to the understanding of the disability of the cyanosed patients.

The changes in arterial P_{CO_2} are also of importance in the intermediate group. We have been able to study somewhat more closely the minute-by-minute changes in a few such patients. As shown in Fig. 11 (Case 13), in the first minute of exercise the arterial oxygen fell and the P_{CO_2} rose as the ventilation increased to its steady-state level. The arterial pH fell at this stage partly due to the rise in CO_2 and partly to the increase of lactate. By the third minute the oxygen had reached a steady level, the P_{CO_2} was at its first peak, and the pH was falling in response to the rising lactate.

In the fifth minute the oxygen was at the same level, but the P_{CO_2} now fell in response to the hyperventilation. At this stage the ventilation was 31.5 l./min. and the oxygen uptake 1.15 l./min. The situation did not then alter materially until at the tenth minute he became dyspnoeic rather suddenly. The oxygen saturation at this time fell again, the P_{CO_2} rose once more and the pH fell, the lactate now being unchanged or a little lower than its peak value. It is likely that such changes accompany the sudden access of dyspnoea that is often seen at about this stage of steady exercise.

Thus, of the three classical humoral stimuli to respiration, hypoxia, hypercapnia, and acidæmia, only the latter is present during severe exercise in normal subjects, whereas all three operate in the more disabled cyanosed cases even on mild effort.

Nielsen (1936) and Nielsen and Smith (1952) showed clearly in normal subjects the interrelation of hypoxia and hypercapnia in the determination of ventilation. At normal alveolar oxygen levels the effect of increasing P_{CO_2} is apparent above a level of 36 mm. When the alveolar P_{O_2} is 47 mm., there is little response from increasing P_{CO_2} until its level reaches 33 mm., after which a further increase of 5 mm. in P_{CO_2} leads to a trebling of the ventilation. At a P_{O_2} of 37 mm. the threshold lies at a P_{CO_2} of about 31 mm. Thereafter an increase of as little as 2 mm. increases the ventilation by 30 l./min. (Nielsen and Smith, 1952).

As Asmussen (1963) points out, the increased response to CO_2 under conditions of hypoxia was discussed by Miescher-Rüsch in 1885, and formulated more precisely by Lindhard, in 1911.

Nielsen (1936) also investigated the influence of acidæmia on ventilation. The lowering of the CO_2 threshold following acidæmia caused by ingestion of ammonium chloride was shown clearly. Whether CO_2 and acidæmia are separate and cumulative stimuli to respiration is beyond the scope of this paper to discuss, but this concept forms the basis of the multiple-factor theory of Gray (1946) and the later mathematical refinements of the ventilatory equation (e.g. that of Cunningham (1963) and Lloyd (1963)).

Of especial interest was Case 17. This patient with severe Fallot's tetralogy treated by a Blalock anastomosis had a resting arterial oxygen saturation of 76 per cent dropping to 20 per cent with exercise on the bicycle. Despite this gross fall, he was content to carry on at a level of 400 kg. m./min., was not dyspnoeic, and was stopped on account of his gross cyanosis. This case illustrates well the measure of adaptation to hypoxæmia, and confirms the view that other factors than this are the special ones related to severe dyspnoea; the arterial P_{CO_2} did not rise above its resting level, and the pH dropped only a little by virtue of mild lactic acidæmia.

The general adaptations to hypoxæmia are too well known to require emphasis. On the enzymatic and metabolic levels, adaptation to chronic hypoxia has been shown to exist in animals. Tappan *et al.* (1957) found that guinea-pigs under those conditions have increased glycolysis and adenosine triphosphatase capacities, and accumulate higher levels of high-energy phosphates. Myoglobin stores, desoxyribonucleic acid, and succinoxidase activity are significantly higher. Hurtado (1963) states that natives of the Andes carry out muscular activity with less production of lactate than sea-level man. Such adaptive mechanisms may be operative in patients with chronic hypoxæmia and the lactate-pyruvate metabolism be correspondingly altered. On the other hand the normal oxygen uptake and the low lactate production of these cases suggests that there is little or no deficiency of oxygen supply to the tissues.

FIG. 11.—The effect of exercise on the arterial oxygen saturation, pH, P_{CO_2} , and lactate in Case 13 (see text).

In 1958 Wood pointed out that in the Eisenmenger syndrome the patient with a patent ductus arteriosus was significantly less disabled than his fellow with a communication at atrial or ventricular level, and gave it as his opinion that this might be due to the fact that the head and neck were supplied with highly oxygenated blood from the left ventricle, the deoxygenated blood entering the aorta through the ductus distal to the origin of the carotid vessels. This observation gains in significance when it is realized that the oxygenated blood, being essentially pulmonary venous in origin, is low in CO_2 content. Not only is there differential cyanosis in the patient with the "Eisenmenger ductus", but more significantly to the patient's symptomatology there is "differential hypercapnia".

Miescher-Rüsch in 1885 concluded from his studies that only dissolved carbon dioxide, and not oxygen, was the humoral stimulus to ventilation, though hypoxia could alter the excitability of the respiratory centre. As quoted by Asmussen (1963), he finished his discussion with the sentence, "So carbon dioxide spreads its protecting wings over the oxygen needs of the body." This appears to be particularly appropriate to the patient with morbus cæruleus.

While dyspnoea is a symptom, its objective expression is hyperventilation. Any stimulus to ventilation is, in the appropriate circumstances, a stimulus towards dyspnoea. It is likely that the chemical changes occurring in these cyanosed patients, acting in the milieu of hypoxæmia, are the special ones related to the severe dyspnoea which they suffer.

SUMMARY

Twenty patients with cyanotic congenital heart disease have been studied at rest and during exercise. All patients showed a fall in arterial oxygen levels on effort, but in those who were acyanotic at rest metabolic changes were slight and arterial pH and P_{CO_2} behaved normally. Severely disabled patients who were cyanotic at rest showed on effort a marked rise in arterial P_{CO_2} and fall in pH which was in part hypercapnic and in part metabolic. The lactate changes, though greater than normal, were not striking in view of the profound hypoxæmia sometimes present.

The influence of these changes on the ventilatory drive is discussed. It is suggested that, acting in the presence of hypoxæmia, the rise in arterial P_{CO_2} and the fall in pH may be the cause of the considerable dyspnoea of the centrally cyanosed patient, and that the magnitude of the pulmonary blood flow, in determining the rate at which carbon dioxide can be cleared from the body, determines also the critical point at which relative hyperventilation and dyspnoea occur.

We wish to thank Dr. C. G. Baker and Dr. D. C. Deuchar for having so readily allowed us to study their patients and put facilities at our disposal for doing so. Dr. M. W. Potts and Mrs. J. R. Samuel of the Department of Anaesthetics have given invaluable assistance with the investigations and the determinations of pH and P_{CO_2} , and to them we are very grateful. The work was supported in part by a grant from Messrs. Boehringer-Ingelheim.

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