EFFECTS OF ACUTE ANOXIA ON THE CIRCULATION AND RESPIRATION IN PATIENTS WITH CHRONIC PULMONARY DISEASE STUDIED DURING THE "STEADY STATE" [1]

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INTRODUCTION

The effect of acutely induced anoxia upon the respiration and circulation of man and animals has been repeatedly investigated (1–4). Various circulatory responses have been described, and it is apparent that the observations of different investigators have sometimes been divergent. For example, following the induction of acute anoxia, the minute output of the heart has been noted by individual authors to increase, decrease, or remain unchanged. Grollman (1) reviewed these results and ascribed them to several readily discernible causes: *1*) inaccuracies inherent in the methods used to measure cardiac output; *2*) failure to distinguish between the physiologic responses of anesthetized versus unanesthetized animals; *3*) the variety of species studied, and *4*) dissimilar degrees of anoxia.

A previous report from this laboratory on the effects of acute anoxia on pulmonary artery pressure (3) included measurements of the cardiac output using the "Direct Fick Method" in five normal subjects. It was found in these studies that short periods of anoxia (breathing 10 per cent oxygen for approximately 10 minutes) usually resulted in a decrease of the estimated cardiac output. This response to anoxia which has been observed in normal individuals, merits further consideration in patients with chronic pulmonary disease where spontaneous variations in anoxia and cardiac output incident to their daily activity may contribute to the evolution of cardiopulmonary disease.

It is the purpose of this report to analyze the effects of breathing gas mixtures with various oxygen concentrations upon the circulation of 35 patients with chronic pulmonary disease. Because a "steady state" of the respiration and circulation is essential when one measures cardiac output during cardiac catheterization by the Fick principle, a special attempt has been made to include only studies in which such a state was attained and maintained during the period of observation.

METHODS

All patients were studied in the unanesthetized, postabsorptive, "basal" state. The observations were usually begun approximately one-half hour after arrival in the laboratory, and considerable attention was given to the achievement of complete relaxation during the period of observation. This was facilitated by respiratory measurements and arterial puncture on previous days which served to familiarize the patient with the laboratory, its apparatus and personnel. In some, cardiac catheterization had been previously performed. All determinations were completed within two hours after placement of the cardiac catheter. The methods used were identical with those previously described from this laboratory (5, 6).

The heart rate was observed on the electrocardiogram throughout the entire procedure, including the period of cardiac catheterization and arterial puncture. Lability of heart rate while the subject was at rest and breathing ambient air, supplemented other clinical guides to sympathetic overactivity (tachypnea, moist skin, wide pupils).

The initial series of determinations of cardiac output and blood pressures (pulmonary artery and brachial artery) were made while the relaxed subject was breathing 21 per cent oxygen. After expired gas, mixed venous blood and arterial blood had been simultaneously collected to measure the cardiac output, the entire procedure was repeated with the subject inspiring a higher (if original

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arterial oxygen saturation was less than 90 per cent), or lower oxygen mixture. The blood and expired gas samples were also used to calculate the alveolar-arterial (A-A) oxygen gradient. All determinations were required to check in duplicate. The techniques used are detailed elsewhere (6). The pO_2 of mixed venous blood was obtained by plotting oxygen content (Van Slyke-Neill) on a standard oxyhemoglobin dissociation curve using the corresponding pH determined by the MacInnes-Belcher glass electrode. The oxygen and carbon dioxide tensions of arterial blood were determined directly (7), and the latter was also estimated from the line charts of Van Slyke and Sendroy, using the CO_2 content and the pH of the whole blood. Systolic and diastolic pressures were calculated as averages of two complete respiratory cycles; the mean pressure was obtained by planimetric integration of the area included within these boundaries. Variations were considered significant only if they exceeded limits previously defined in this laboratory (8–10) and include deviations greater than ± 5 mm. Hg for pulmonary artery mean pressure and − 12 to + 18 mm. Hg for systemic artery mean pressure. Similarly under the conditions of these experiments, any cardiac output change exceeding 9 per cent of control was considered significant.

The inspired gas mixtures used in these studies included 100 per cent oxygen and mixtures of 33, 25, 21, 18, 16, 14, and 12 per cent oxygen in nitrogen, administered through demand-type valves or from an anesthesia bag. At least two experiments, each at a different level of arterial oxygen saturation, were completed for each subject. In the following pages, "low oxygen" refers to inspired gas mixtures containing less than 21 per cent oxygen; conversely, "high oxygen" mixtures contain more than 21 per cent oxygen. The specific concentrations used are indicated in the tables.

Criteria used for defining the "steady state"

Three criteria were used as guides to stability of the respiration and circulation (the "steady state") as successive levels of oxygenation. These were *1*) emotional stability, *2*) constancy of oxygen consumption, and *3*) constancy of the respiratory exchange ratio (RQ). Significant deviations in any of these three criteria served to exclude a given subject from this study.

It is known that clinical manifestations of sympathetic overactivity are at best a crude guide to emotional disturbance. However, in response to emotional stimulation, oxygen consumption nearly always increases (11); in absence of such stimulation, oxygen consumption remains remarkably constant from day to day when determined under comparable conditions (12, 13). Neither acute anoxia *per se* nor the hyperventilation induced by it (14–16) causes increase of oxygen consumption. Because of these considerations and in keeping with a large body of data previously gathered in this laboratory during cardiac catheterization (8), any change in oxygen consumption which exceeded + 11 per cent eliminated the experiment from inclusion in this study.

If the oxygen consumption is constant (within the limits defined above) at the two levels of oxygenation, an elevation in respiratory gas exchange ratio (R.Q.) becomes a reflection of respiratory rather than metabolic carbon dioxide liberation (unstable respiratory state). A review of a series of patients previously studied under comparable conditions in this laboratory (8) indicated that all of 20 patients had R.Q. values less than 1.0 during repeated determinations, and that 17 of the 20 deviated from the initial value by less than 0.13 during the second determination performed within one hour. In selecting the group to be presented below, any patient with pulmonary disease with any R.Q. greater than 1.0, or with a second R.Q. which differed from the first by more than 0.11, was excluded.

RESULTS

These data were derived from 45 complete studies on 35 subjects with pulmonary disease. The clinical diagnoses, physical findings, procedures and data concerning the steady state are indicated in Table I.

A. Ventilation

With three exceptions all of these subjects, while breathing ambient air, had a higher than normal respiratory minute volume (Table I). This observation is in accord with similar respiratory studies previously done on the same patients in this laboratory. In the experiments employing high oxygen, there was no significant change in ventilation. However, during low oxygen breathing, the volume of ventilation usually exceeded control levels.

B. Carbon dioxide tension in arterial blood (Table I)

Seventeen of 35 patients, while breathing ambient air, had normal (39.4 ± 2.8) arterial pCO_2. Ten had low pCO_2 values, probably secondary to their chronic hyperventilation. Eight, however, had elevated arterial pCO_2, the two highest values occurring in two subjects with emphysema and cor pulmonale (Cases 32 and 33). Following exposure to low oxygen, the arterial pCO_2 was usually lower than on ambient air. The arterial pCO_2 while the subjects were breathing a high oxygen mixture showed no consistent direction of change.

C. Heart rate

Resting heart rates ranged from 48 to 137. Exposure to high oxygen usually caused slowing or

TABLE I

Physical characteristics, clinical diagnoses, and orienting data in 35 patients studied at successive levels of oxygenation

Case	Sex	Age	BSA m^2	Diagnosis	Concentration inspired oxygen *volumes %*	Ventilation *lit./min./m²*	R.Q.	Oxygen consumption *cc./min./m²*	Arterial pCO_2 *mm. Hg*
				(a) Normal and low oxygen					
1. G. W.	f	38	1.67	Bronchiectasis; interventricular septal defect	21 10	6.6 8.3	.87 .82	113 124	40 31
2. L. K.	m	29	1.80	Diffuse pulmonary infiltration, cause unknown	21 12	5.1 7.2	.86 .97	174 177	34 29
3. M. Mc	f	22	1.42	Diffuse pulmonary fibrosis, scleroderma	21.5 14	5.1 4.8	.85 .85	133 132	42 37
4. J. L.	m	49	1.90	Silicosis; chr. pulm. emphysema	21 12	3.8 5.2	.87 .91	134 148	36 36
5. D. P.	m	36	1.75	Bronchiectasis; diffuse pulmonary infiltration	21.5 18.5	3.5 3.9	.73 .79	127 135	41 38
6. J. R.	m	40	1.38	Acute hematogenous tuberculosis	21 16 21.5 16	4.4 4.2 4.4 5.2	.83 .94 .86 .84	112 102 124 128	40 37 37 36
7. T. Me	f	30	1.59	Chr. pulm. tuberculosis	21 16	4.8 5.6	.86 .86	129 141	43 40
8. E. H.	m	17	1.47	Severe diffuse pulmonary granulomata, cause unknown	21 16 21.5 16	8.3 8.9 7.6 7.0	.86 .83 .95 .96	197 199 172 170	40 34 32 31
9. S. A.	m	60	1.65	Bronchiectasis; chr. pulm. emphysema	21 16 14	6.4 5.8 5.6	.94 .98 .97	123 128 125	41 38 39
10. Q. G.	f	43	1.66	Severe diffuse pulmonary granulomata, Boeck's sarcoid	21.5 17 21 17	6.5 7.2 6.3 6.8	.76 .85 .88 .94	146 141 157 145	39 37 39 35
11. C. D.	m	23	1.67	Chr. pulm. tuberculosis	21 16	4.8 5.2	.72 .80	157 146	34 32
12. H. K.	f	25	1.53	Bronchiectasis; bilateral lobectomy	21 16	5.0 5.0	.79 .84	146 135	34 34
13. E. C.	m	29	1.69	Chr. pulm. tuberculosis	21 16	5.6 5.4	.82 .88	125 120	39 36
14. K. C.	f	31	1.73	Acute hematogenous tuberculosis	21 16	3.7 3.8	.82 .90	112 104	38 40
15. W. H.	m	22	1.90	Diffuse pulmonary granulomata, Boeck's sarcoid	21 16	4.7 6.5	.78 .89	169 167	35 34
16. F. A.	m	48	1.55	Chr. pulm. tuberculosis; acute hematogenous tuberculosis	21 16	7.4 7.4	.85 .83	147 148	35 35
17. F. L.	m	23	1.85	Severe diffuse pulmonary fibrosis, beryllium exposure	21 16	5.8 6.9	.78 .88	140 131	37 35
18. R. S.	m	25	1.85	Moderate diffuse pulmonary granulomata, Boeck's sarcoid	21 16	4.3 4.7	.83 .92	149 146	39 36
19. N. I.	m	31	1.35	Moderate diffuse pulmonary granulomata, Boeck's sarcoid	21 16	4.4 5.4	.82 .91	121 128	34 35
20. C. L.	f	21	1.74	Moderate diffuse pulmonary granulomata, Boeck's sarcoid	21 16	7.0 7.9	.81 .82	166 168	45 43

TABLE I.—*Continued*

Case	Sex	Age	BSA m^2	Diagnosis	Concentration inspired oxygen *volumes %*	Ventilation *lit./min./m²*	R.Q.	Oxygen consumption *cc./min./m²*	Arterial pCO_2 *mm. Hg*
(a) Normal and low oxygen—*Continued*									
21. J. R.	m	23	1.57	Acute hematogenous tuberculosis; 11 days after start Rx with streptomycin	21.5 16	5.5 5.7	.79 .86	147 140	40 36
(b) Normal, low and high oxygen									
22. B. B.	m	52	1.54	Bronchial asthma; chr. pulm. emphysema; cor pulmonale, not in failure	21 16 21 25	6.6 7.2 7.3 6.7	.84 .90 1.0 .90	137 151 150 146	47 42 41 39
23. A. P.	m	49	1.55	Chr. pulm. emphysema; cor pulmonale, in failure	21.5 16 21 30	5.8 6.5 5.4 5.9	.88 .97 .84 .93	141 144 127 128	45 46 42 42
24. D. Mc	m	62	1.61	Carcinoma of bronchus, RML; chr. pulm. emphysema	21 16 21 25	5.7 6.5 5.7 6.1	.80 .88 .80 .83	149 143 149 138	39 39 39 42
25. P. B.	f	42	1.56	Severe diffuse pulmonary granulomata, Boeck's sarcoid	12.5 17.4 21 25	7.4 8.0 7.4 8.3	.92 .96 .92 .98	156 157 156 164	40 36 40 40
26. W. B.	m	46	1.61	Bronchial asthma; chr. pulm. emphysema; cor pulmonale, not in failure	21.5 16 21 30	5.8 6.0 5.8 5.4	.85 .87 .85 .83	138 138 138 135	38 36 40 43
27. P. B.	m	36	1.49	Severe diffuse pulmonary granulomata, Boeck's sarcoid	21 17.4 21 25	8.8 8.8 8.8 8.8	.77 .83 .77 .82	203 184 205 187	35 32 37 36
28. M. L.	f	29	1.32	Severe diffuse pulmonary infiltration, cause unknown	21 17 21 25	7.3 7.3 6.4 6.5	.77 .84 .70 .80	147 141 153 141	29 28 37 39
(c) Normal and high oxygen									
29. J. P.	m	43	1.66	Bronchiectasis; cor pulmonale, in failure	21 100	6.9 —	.75 —	182 206	42 —
30. G. Na	f	52	1.87	Bronchial asthma; chr. pulm. emphysema	21.5 25	5.9 6.6	.72 .74	150 140	52 54
31. P. L.	m	65	1.60	Bronchial asthma; chr. pulm. emphysema	21.5 25 33	6.8 6.7 6.8	.72 .83 .78	141 131 138	30 35 45
32. A. Y.	m	38	1.47	Bronchial asthma; chr. pulm. emphysema; cor pulmonale in congestive failure	21 25	4.8 4.9	.79 .74	157 166	62 58
33. M. C.	m	55	1.54	Bronchial asthma; pulmonary fibrosis; chr. pulm. emphysema; cor pulmonale after treatment	21 25	6.2 6.1	.73 .70	168 161	58 55
34. E. M.	f	60	1.73	Severe diffuse pulmonary infiltration, cause unknown	21 100	5.8 —	.72 —	127 121	39 —
35. M. H.	f	64	1.39	Severe diffuse pulmonary infiltration, cause unknown; cor pulmonale, not in failure	21 30	10.0 9.3	.82 .80	144 140	43 49

TABLE II

The influence of the level of oxygenation upon the circulation in 35 patients with pulmonary disease

Case	Concentration inspired oxygen *volumes %*	Alveolar pO_2 *mm. Hg*	Arterial pO_2 *mm. Hg*	MVB pO_2 *mm. Hg*	Arteriovenous oxygen diff.* *volumes %*	Cardiac index *lit./min./m² BSA*	Heart rate *beats/min.*	Pulmonary artery pressure *mm. Hg*		Brachial artery pressure *mm. Hg*	
								s/d	*m*	*s/d*	*m*
(a) Normal and low oxygen											
1	21	97	73	44	2.1	6.20	100	25/10	18	131/76	99
	10	45	35	27	2.1	6.88	102	25/7	16	108/65	86
2	21	116	100	38	4.6	3.78	85	28/11	18	145/94	114
	12	62	46	31	3.4	5.19	98	32/12	20	123/79	95
3	21.5	100	94	37	3.7	3.60	79	32/13	20	95/57	74
	14	57	29	22	1.8	7.33	98	41/18	27	110/69	84
4	21	111	75	35	5.5	2.43	75	32/11	21	120/68	89
	12	50	36	27	4.0	3.71	88	54/20	36	135/75	103
5	21.5	103	75	33	5.3	2.39	48	36/12	19	136/83	106
	18.5	89	68	31	5.1	2.65	55	41/12	24	134/80	106
6	21	108	102	34	4.2	2.65	85	12/4	9	104/71	84
	16	78	70	33	3.5	2.96	88	17/7	12	111/75	90
	21.5†	108	84	30	4.9	2.38	68				
	16†	69	52	27	4.5	2.67	74				
7	21	107	77	40	3.6	3.68	78	24/6	15	116/64	86
	16	77	63	32	3.7	3.80	75	22/6	14	110/61	81
8	21	107	74	36	4.1	4.80	107	34/18	26	98/64	77
	16	72	43	28	4.1	4.88	115	41/23	31	82/55	67
	21.5†	113	94	38	3.9	6.95	90	39/17	27	132/83	106
	16†	73	56	32	4.1	6.56	100	40/23	31	124/80	98
9	21	107	66	34	4.5	2.67	86	25/12	17	139/77	102
	16	71	47	31	4.4	2.85	88	31/13	20	127/73	92
	14	58	38	30	4.0	3.05	88	35/15	24	127/80	102
10	21.5	107	56	27	4.3	3.39	94	55/27	37		
	17	88	36	25	3.3	4.21	94	67/28	43	115/67	87
	21†	99	71	30	3.7	4.23	106	46/21	32	109/68	85
	17†	78	53	27	3.2	4.52	103	56/23	42	113/67	85
11	21	114	78	37	5.1	3.09	80	18/8	12	122/77	94
	16	74	64	34	4.7	3.10	80	19/7	13	129/83	98
12	21	107	88	36	3.5	3.90	72	26/9	16	126/74	99
	16	72	60	32	3.3	4.10	82	31/10	20	130/77	100
13	21	105	69	35	4.7	2.64	80	23/10	16	114/77	94
	16	64	52	32	4.3	2.80	80	25/11	18	115/72	92
14	21	102	96	38	4.5	2.49	60	23/7	13	128/85	104
	16	72	66	36	3.9	2.68	74	30/9	18	121/82	101
15	21	110	92	40	3.5	4.83	74	17/9	13	124/82	99
	16	75	75	36	3.0	5.58	78	19/10	14	116/80	96
16	21	109	84	32	4.8	3.04	80	24/8	15	118/77	95
	16	67	54	30	5.1	2.90	80	28/10	18	108/71	89
17	21	109	86	36	4.9	2.85	80	30/14	21	116/85	101
	16	71	47	30	4.9	2.68	79	37/17	25	115/83	97
18	21	106	88	42	3.8	3.92	98	20/8	13	151/92	118
	16	78	74	36	4.1	3.82	96	30/10	20	141/88	110
19	21	104	98	30	4.1	2.96	97	22/8	15	111/69	87
	16	83	82	28	3.8	3.37	105	22/9	16	113/67	86
20	21	110	75	34	4.4	3.82	91	32/10	21	127/73	91
	16	75	47	28	4.5	3.73	93	32/14	24	120/76	92

TABLE II.—*Continued*

Case	Concentration inspired oxygen *volumes %*	Alveolar pO_2 *mm. Hg*	Arterial pO_2 *mm. Hg*	MVB pO_2 *mm. Hg*	Arteriovenous oxygen diff.* *volumes %*	Cardiac index *lit./min./m² BSA*	Heart rate *beats/min.*	Pulmonary artery pressure *mm. Hg*		Brachial artery pressure *mm. Hg*	
								s/d	*m*	*s/d*	*m*
					(a) Normal and low oxygen—*Continued*						
21	21.5	105	88	34	3.7	3.97	102	17/7	13	124/76	93
	16	69	66	30	3.1	4.50	102	14/7	11	127/77	93
					(b) Normal, low, and high oxygen						
22	21	94	62	36	4.1	3.33	90	26/11	15	109/62	80
	16	69	55	32	4.1	3.70	103	49/20	32	119/74	92
	21	110	60	37	4.6	3.43	93	39/18	27	142/83	104
	25	141	71	38	4.8	3.20	93	31/17	22	119/76	94
23	21.5	101	60	22	3.9	3.62	95	35/17	24	102/63	79
	16	71	36	18	4.0	3.59	94	49/20	32	119/74	92
	21†	104	61	29	4.7	2.71	68	36/9	19	121/61	85
	30†	189	100	33	4.7	2.71	62	39/12	22	137/67	94
24	21	101	78	34	4.2	3.55	83	29/8	17	143/70	99
	16	72	63	32	3.7	3.86	88	35/9	19	142/72	100
	21	101	78	34	4.2	3.55	83	29/8	17	143/70	99
	25	129	87	36	5.1	2.71	83	31/7	17	153/74	104
25	21.5	118	84	28	5.1	3.07	87	59/27	37	170/105	131
	17.4	94	57	26	4.2	3.74	90	60/23	34	169/109	133
	21	112	84	28	5.1	3.07	90	59/27	37	183/112	135
	25	139	95	30	4.9	3.35	90	52/22	34	190/117	143
26	21.5	107	67	32	5.8	2.39	56	28/7	16	136/79	106
	16	66	40	29	4.8	2.88	66	32/11	20	128/77	101
	21	107	67	33	5.8	2.39	56	28/7	16	136/79	106
	30	167	110	40	5.6	2.41	60	30/9	17	141/80	102
27	21	103	63	19	5.9	3.45	100	50/23	34	91/65	77
	17.4	83	46	16	5.3	3.46	90	59/27	39	91/63	74
	21	103	63	20	5.9	3.45	100	50/23	34	91/65	77
	25	133	81	24	6.0	3.12	100	65/31	42	110/79	92
28	21	114	65	33	4.2	3.12	80	34/16	23	108/71	89
	17	82	40	31	3.2	3.94	80	48/23	33	105/71	87
	21	114	65	34	4.3	3.15	73	36/18	26	97/67	81
	25	142	77	37	4.0	3.14	76	34/17	24	99/66	81
					(c) Normal and high oxygen						
29	21	95	54	37	3.5	5.20	137	42/19	31	129/88	108
	100	—	104	76	4.4	4.68	129	40/17	28	131/88	110
30	21.5	88	48	30	4.5	3.62	75	42/18	28	118/49	75
	25	109	60	31	4.7	3.17	78	42/18	27	124/50	76
31	21.5	116	64	34	4.0	3.53	76	22/7	12	140/82	108
	25	139	75	34	3.9	3.35	74	24/8	15	146/88	114
	33	190	83	34	3.9	3.52	73	20/6	11	138/82	105
32	21	73	46	33	3.4	4.63	106	43/21	30	112/72	84
	25	102	75	38	3.4	4.89	114	51/24	38	139/86	105
33	21	72	33	21	5.6	3.00	115	74/32	46	121/84	99
	25	102	50	28	5.6	2.88	108	77/36	51	114/78	92
34	21	98	82	34	3.9	3.24	91	58/20	34	121/69	91
	100	—	100	111	4.3	2.83	85	—	31	127/69	94
35	21	105	45	26	5.6	2.57	88	67/26	41	120/59	84
	30	194	84	33	5.7	2.46	88	60/28	40	125/62	89

* Using mixed venous blood obtained from the pulmonary artery.
† These observations were made on a second day.

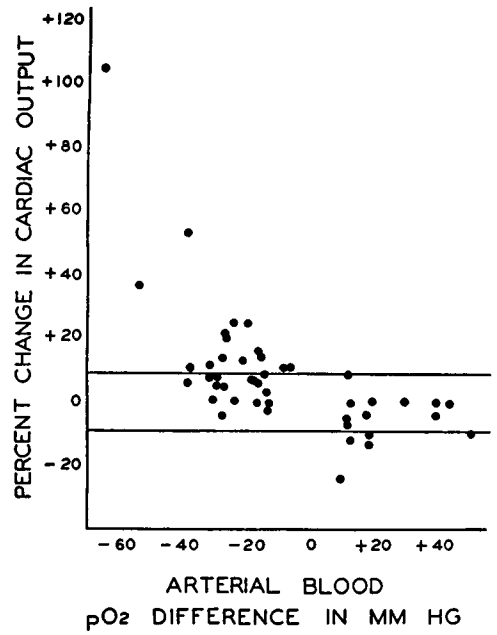

FIG. 1A. RELATION BETWEEN CHANGES IN ARTERIAL OXYGEN TENSION AND CARDIAC OUTPUT

The cardiac output change is expressed in per cent of change from the initial measurement. A change of 9 per cent (above and below the two solid lines) is significant. Note that during anoxia, cardiac output remains unchanged or rises and that increased oxygenation causes no change or a decrease in cardiac output.

insignificant change in heart rate (Table II). A persistent tachycardia was observed in seven of 28 patients during exposure to low oxygen.

D. Cardiac output

There was considerable variation in the level of the initial cardiac index in these experiments (28 normal [3.09 ± 0.5 lit./min./m² B.S.], five low and 12 greater than normal). All 12 with high resting cardiac output had advanced pulmonary disease. Three (Cases 23, 29, 32) were in right heart failure; one (Case 1) had an associated interventricular septal defect. The effects of variation in level of oxygenation on cardiac output are illustrated in Figures 1 and 2. It is apparent that during exposure to low oxygen, the cardiac output either failed to change significantly (less than ± 9 per cent) or increased. There was a significant increase in 14 of the 32 cases. In no instance was there a significant decrease. In 10 additional cases there were small increases, but less than the error of the method. The net experience suggests at least a tendency toward increased cardiac output during moderate anoxia in this series of cases.

On the other hand when we applied the Fick principle to a group of patients with similar clinical diagnoses, but which had been rejected from this study because, according to our criteria, they had failed to achieve a "steady state," the calculated cardiac outputs were found to vary greatly, often with values considerably below control. Since values for cardiac output so obtained are meaningless, we have not tabulated them.

Tables II and III further demonstrate that exposure to high oxygen in the steady state either effected no significant change or a decrease in cardiac output. The degree of change in cardiac output could not be quantitatively correlated with the concentration of oxygen in the inspired gas mixture. This is to be anticipated in the presence of chronic pulmonary disease, particularly in patients with alteration of the alveolar-capillary membrane (for instance Case 3), where decrease in inspired oxygen concentration will cause a greater decrease in arterial oxygen saturation than in normal subjects. The greatest changes in cardiac output were associated with marked changes in

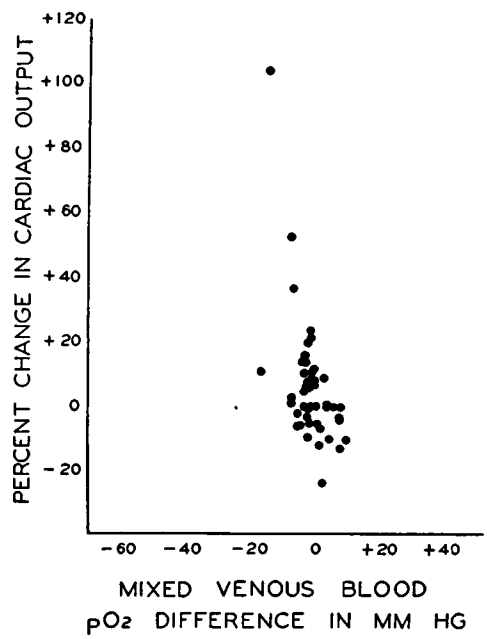

FIG. 1B. RELATION BETWEEN CHANGES IN MIXED VENOUS BLOOD OXYGEN TENSION AND CARDIAC OUTPUT

Note that mixed venous blood oxygen tension is not related to cardiac output.

arterial oxygen tension (Figure 1a). There was no significant relation between mixed venous oxygen tensions and cardiac output (Figure 1b).

E. Pulmonary artery pressure (Table II)

Following increase in the concentration of inspired oxygen, there was no significant change in mean pulmonary artery pressure, except in two subjects (cases 27 and 32), where the mean pulmonary artery pressure rose by 8 mm. Hg.

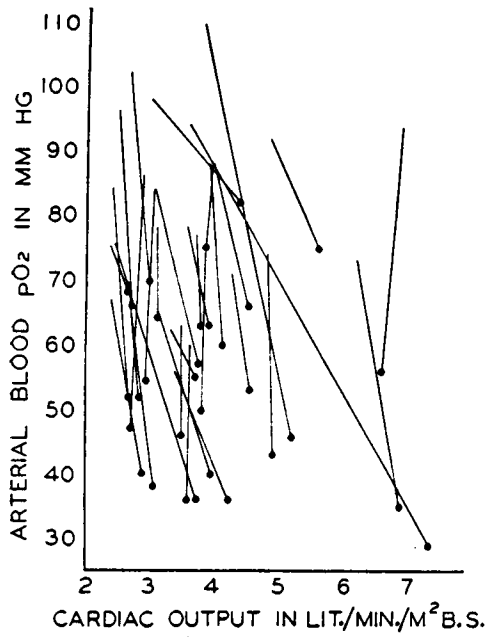

FIG. 2A. THE RESPONSE OF CARDIAC OUTPUT TO ACUTE ANOXIA IN INDIVIDUAL PATIENTS

The upper end of each line indicates the arterial oxygen tension on 21 per cent oxygen; the lower knobbed end indicates the arterial oxygen tension during anoxia.

Note that the slope of the lines indicates that the cardiac output increased or did not change significantly during anoxia.

During low oxygen, mean pulmonary artery pressure rose more than 5 mm. Hg in 10 of 38 experiments. Of the remaining 28 observations, 11 had increases in pulmonary artery pressure, during anoxia, of 3 to 5 mm. Hg. Not all subjects with increased pressures during anoxia had increased cardiac outputs. However, the subjects (Cases 4 and 22) with the largest increases in pulmonary artery pressure had significant simultaneous increases in cardiac output.

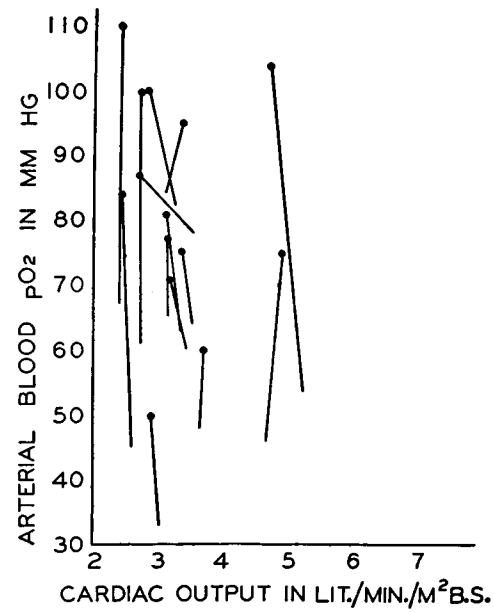

FIG. 2B. THE RESPONSE OF CARDIAC OUTPUT TO INCREASE IN ARTERIAL OXYGEN TENSION IN INDIVIDUAL PATIENTS

The lower end of each line indicates the arterial oxygen tension on 21 per cent oxygen; the upper knobbed end indicates the arterial oxygen tension at the higher level of oxygenation.

Note that at these higher levels of arterial oxygen tension there was either no significant change or a fall in cardiac output.

F. Brachial artery pressure

The changes in brachial artery pressure following high and low oxygen showed no consistent trend. Only one subject (Case 32) underwent a large change in mean pressure (+ 21 per cent) while breathing high oxygen.

DISCUSSION

The importance of achieving the "steady state" when one determines cardiac output by the Fick principle [4] has been emphasized in this presenta-

[4] The Fick principle states that the quantity of any substance taken up by blood perfusing an organ is equal to the amount of that substance in the volume of blood leaving the organ minus the amount contained in the volume of blood entering the organ. For the instantaneous uptake of oxygen by blood in the lungs

$$\dot{V}_{O_2} = \frac{dV_{O_2}}{dt} = [Ca_{O_2}(t) - Cv_{O_2}(t)]Q(t), \quad \text{Equation 1}$$

where Q = instantaneous blood flow *to* lungs = instantaneous blood flow *from* lungs at time (t) and Ca_{O_2}, Cv_{O_2} = instantaneous concentrations of oxygen in arterial

tion. Failure to recognize the importance of this factor may explain some of the discrepancies in previous observations on the effects of anoxia upon the circulation. The difficulty in achieving a "steady state," even in normal subjects exposed to moderate anoxia, is clearly indicated by the data of Rahn and Otis (15). In their studies, normal trained subjects were acutely elevated to simulated altitude, and the time was noted for restoration of heart rate, R.Q., and oxygen consumption to normal. They found that the higher the altitude, the longer the time required for re-equilibration, and at 10 per cent oxygen (roughly equivalent to 18,000 feet) an hour or more was required for these measurements to return to control levels. It is apparent that if our patients had been exposed to these levels of anoxia, a steady state would have been difficult or impossible to approach during the time (15 minutes or more) allotted for equilibration. This is emphasized by the large number of patients who were excluded from this presentation because of their inability to reach a "steady state" even with mild depression of inspired oxygen content.

In our subjects presented above, despite the presence of advanced lung disease, it was possible to approximate a "steady state" by careful selection of the inspired oxygen mixture so as to avoid extreme variations in arterial oxygen saturation. Under these conditions, no significant fall in cardiac output was ever observed during anoxia. This finding led us to re-evaluate the observations on cardiac output previously recorded from this laboratory (3) incident to a study of changes in pulmonary artery pressure in five normal subjects who were exposed to low oxygen mixtures (10 per cent) for brief periods (about 10 minutes). The average cardiac output of the five subjects was reported to have decreased from 5.74 liters to 5.20 liters. A review of the original data from which these results were calculated indicated that these subjects were not in a "steady state" (high initial R.Q., marked variations in successive R.Q. values, and unusually low oxygen intake at the low level of oxygenation). Similar considerations apply to the fall in cardiac output during acute anoxia recently reported from another laboratory (4). Such evidence of an unsteady state invalidates the use of the Fick principle for calculation of cardiac output.

The need for a "steady state" prior to the application of the Fick principle obviously extends to conditions other than acute anoxia, *e.g.*, exercise. Bock, Dill, and their associates (17) stressed the difficulties in reaching a "steady state" during exercise, and urged caution in the interpretation of measurements so made. The evaluation of measurements of cardiac output after exercising patients with heart disease for three minutes is consequently difficult (18).

The other recorded changes in the circulation in man are generally in accord with previous data

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and mixed venous blood respectively, at time (t), from which,

$$Q(t) = \frac{\dot{V}_{O_2}}{Ca_{O_2} - Cv_{O_2}} \qquad \text{Equation 2}$$

and generalizing, the mean flow ($\bar{Q}$) during time (t), becomes

$$\bar{Q} = \frac{1}{T}\int_0^T \frac{\dot{V}_{O_2}}{Ca_{O_2} - Cv_{O_2}}\,dt. \qquad \text{Equation 3}$$

When the quantities V_{O_2}, $Ca_{O_2} - Cv_{O_2}$ remain constant (or do not significantly differ from the mean), then,

$$\bar{Q} = \frac{\bar{\dot{V}}_{O_2}}{\overline{Ca_{O_2} - Cv_{O_2}}}. \qquad \text{Equation 4}$$

In this equation $\bar{Q}$, $\bar{\dot{V}}_{O_2}$, and $\overline{Ca_{O_2} - Cv_{O_2}}$ represent mean values during the time t. This is the form of the Fick principle generally used for calculation of cardiac output. Implicit to its application are the concepts that oxygen is neither secreted nor stored in the lungs.

For substitution in Equation 4, it is assumed that the oxygen uptake, as measured from collection and analysis of expired gas, is equal to the oxygen taken up by the blood in its passage through the lungs; which in turn is equal to the oxygen consumed by the tissues. This relationship does not obtain during the period immediately following the change-over from ambient air to the anoxic mixture. During this period of adjustment to the acute anoxia, the quantity of oxygen in the blood phase and the gas phase is greater than will exist when equilibrium is achieved. Consequently tissue need for oxygen will be met not only from the inspired low oxygen mixture, but also from the surplus oxygen retained in the circulating blood and lungs from the previous level of oxygenation. The oxygen consumption as measured from the spirometer ("apparent oxygen consumption") will thus be lower than both the actual tissue oxygen consumption and the oxygen taken up by the blood traversing the lungs. Cardiac output calculated from this "apparent oxygen consumption" will be lower than the true cardiac output.

Another difficulty in the unsteady state is to relate the measured oxygen uptake to the blood samples responsible for its uptake. Simultaneous and prolonged collection periods for blood and gas do not completely solve this problem, since the proper time relationship is unpredictable.

TABLE III

Summary of changes in circulation and respiration at two levels of oxygenation

Case*	Final concentration inspired oxygen† %	Ventilation‡ %	Oxygen consumption‡ %	R.Q.‡	pO_2 arterial blood‡ *mm. Hg*	pO_2 MVB‡ *mm. Hg*	Heart rate‡ *beats/min.*	Cardiac index‡ %	Pulmonary artery pressure‡ *mean mm. Hg*	Brachial artery pressure‡ *mean mm. Hg*
				(a) From normal to low oxygen						
1	10	+25.8	+11	−.05	−38	−17	+ 2	+ 11	− 2	−13
2	12	+41.2	+ 1.5	+.11	−54	− 7	+13	+ 37	+ 2	− 9
3	14	− 5.9	0	0	−65	−15	+19	+104	+ 7	+10
4	12	+36.9	+11	+.04	−39	− 8	+13	+ 53	+15	+14
5	18.5	+11.4	+ 6.8	+.06	− 9	− 2	+ 7	+ 11	0	0
6	16	− 4.2	− 8.6	+.11	−32	− 1	+ 3	+ 12	+ 3	+ 6
	16	+27	+ 0.5	−.02	−32	− 3	+ 6	+ 8		
7	16	+ 9.2	+ 9	0	−14	− 8	− 3	+ 3	− 1	− 5
8	16	+ 8.3	+ 3	−.03	−31	− 8	+ 8	+ 1	+ 5	− 9
	16	− 7.9	0	+.01	−28	− 6	+10	− 6	+ 4	− 8
9	16	− 8.6	+ 4.4	+.04	−19	− 3	+ 3	+ 7	+ 3	− 4
	14	−12.4	+ 1.5	+.03	−28	− 4	+ 6	+ 14	+ 7	+ 3
10	17	+10.7	− 3.4	+.09	−20	− 2	0	+ 24	+ 6	
	17	+ 7.9	− 5.1	+.06	−18	− 3	− 3	+ 7	+10	0
11	16	+ 8.3	− 7.5	+.08	−14	− 3	0	0	+ 1	+ 4
12	16	0	− 6.2	+.05	−28	− 4	+10	+ 5	+ 4	+ 1
13	16	− 3.6	− 4.0	+.06	−17	− 3	0	+ 6	+ 2	− 2
14	16	+ 2.7	− 7.2	+.08	−30	− 2	+14	+ 8	+ 5	− 3
15	16	+40.0	0	+.11	−17	− 4	+ 4	+ 16	+ 1	− 3
16	16	0	0	−.02	−30	− 2	0	− 5	+ 3	− 6
17	16	+19.0	− 6.4	+.10	−39	− 6	− 1	− 6	+ 4	− 4
18	16	+ 9.3	0	+.09	−14	− 6	− 2	− 3	+ 7	− 8
19	16	+22.5	+ 5.8	+.09	−16	− 2	+ 8	+ 14	+ 1	− 1
20	16	+12.8	0	+.01	−28	− 6	+ 2	− 2	+ 3	+ 1
21	16	+ 3.6	− 4.8	+.07	−22	− 4	0	+ 13	− 2	0

from this laboratory (3), and, in animals, from other laboratories (19). Motley and his associates (3) found that pulmonary artery pressure uniformly increases in normal subjects acutely exposed to 10 per cent oxygen. Approximately one-third of our patients with pulmonary disease manifested a similar response to anoxia. However, the failure of 28 of the 38 to have a significant increase in pulmonary artery pressure at the end of 15 to 20 minutes of anoxia deserves comment. At least three other factors may be considered in evaluating this finding: *1*) The observed tendency of the elevated pulmonary artery pressures to fall towards initial levels in many of these patients as breathing at the low level of oxygenation is continued; *2*) the difference which may exist between the response of the chronically anoxic (acclimatized) and normal subject to acute anoxia; and *3*) the significantly higher pO_2 alveolar level attained in these studies when compared to the previous studies in normal animals and man (3, 19).

Whether a single mechanism is involved in the

TABLE III—*Continued*

Case*	Final concentration inspired oxygen† %	Ventilation‡ %	Oxygen consumption‡ %	R.Q.‡	pO_2 arterial blood‡ *mm. Hg*	pO_2 MVB‡ *mm. Hg*	Heart rate‡ *beats/min.*	Cardiac index‡ %	Pulmonary artery pressure‡ *mean mm. Hg*	Brachial artery pressure‡ *mean mm. Hg*
				(b) From normal to low and to high oxygen						
22	16	+ 9.1	+11	+.06	− 7	− 4	+13	+ 11	+17	+12
	25	− 8	− 2	−.11	+11	+ 1	0	− 7	− 5	−10
23	16	+ 8.3	+ 2	+.09	−24	− 4	− 1	0	+ 8	+13
	30	+ 9.3	0	+.09	+39	+ 4	− 6	0	+ 3	+ 9
24	16	−14.0	+ 0.5	+.08	−15	− 2	+ 5	+ 9	+ 2	
	25	+ 7	+ 7.5	+.03	+ 9	+ 2	0	− 24	0	+ 5
25	17.4	+ 8.1	0	+.04	−27	− 2	+ 3	+ 22	− 3	+ 2
	25	+12.1	+ 5.8	+.06	+11	+ 2	0	+ 9	− 3	+ 8
26	16	+ 3.5	0	+.02	−27	− 3	+10	+ 20	+ 4	− 5
	30	− 6.9	− 2.2	−.02	+43	+ 7	+ 4	0	+ 1	− 4
27	17.4	0	− 9.3	+.06	−17	− 3	−10	0	+ 5	− 3
	25	0	− 8.8	+.05	+18	+ 4	0	− 10	+ 8	+15
28	17	0	− 4.1	+.07	−25	− 2	0	+ 25	+10	− 2
	25	+ 1.6	− 7.9	+.10	+12	+ 3	+ 3	0	− 2	0
				(c) From normal to high oxygen						
29	100		+11		+50	+ 9	− 8	− 10	− 3	+ 2
30	25	+12	− 6	−.01	+12	+ 1	+ 3	− 12	+ 3	+11
31	25	0	− 8	+.11	+11	0	− 2	− 5	− 3	+ 6
	33	0	− 3	+.06	+19	0	− 3	0	− 1	− 3
32	25	+ 1	+ 5	−.05	+29	+ 5	+ 8	0	+ 8	+21
33	25	− 1	− 4	−.03	+17	+ 7	+ 3	− 4	+ 5	− 7
34	100		− 4		+18	+ 7	− 6	− 13	− 3	+ 3
35	30	− 7.0	− 2.7	−.02	+39	+ 7	0	− 4	− 1	+ 5

* As in Tables I and II.
† Second level of oxygenation. Initial level in all instances was ambient or compressed air.
‡ As compared to study with ambient or compressed air.

cases in whom the pulmonary artery pressure increased during anoxia is not clear. Indeed, our data do not provide any information concerning the contribution of the pulmonary veins or left auricle to the elevation in the pulmonary arterial pressure. However, in this group of patients with chronic pulmonary disease, an increase of blood flow in a pathologically restricted vascular bed may cause a rise in pulmonary arterial pressure. This factor could be invoked in seven of the 10 subjects in whom an increase in pulmonary arterial pressure was observed following low oxygen breathing.

Changes in cardiac output greater than 15 per cent at the lower level of oxygenation occurred in nine of the 47 determinations. Such marked changes are of particular importance in the method which Riley, Cournand and Donald (6) have recently described for estimating the oxygen-diffusing capacity and the ventilation-perfusion relationships of the lung. Our data suggest that the assumption of a relatively constant cardiac output in subjects exposed to two levels of inspired oxygen, an assumption which is essential to their method, is most apt to be valid if extreme variation in arterial oxygen tension is avoided by careful selection of inspired oxygen mixtures and the use of an oximeter. However, even with this precau-

tion, a significant, but at the present time unpredictable, increase in cardiac output may occur in some patients with pulmonary disease.

SUMMARY

1. The circulatory responses of 35 patients with pulmonary and cardiopulmonary disease to selected levels of oxygenation (higher and lower than room air) were investigated.

2. Particular care was exerted to arrive at a "steady state" of the respiration and circulation. The criteria for the "steady state" are defined; the relation of the "steady state" to the applicability of the Fick principle for cardiac output measurement is discussed.

3. After the "steady state" was achieved in the patients with chronic pulmonary disease exposed to moderate anoxia, cardiac output remained unchanged or increased. Conversely, an increase in concentration of inspired oxygen caused either no change or occasionally a slight fall in cardiac output. The largest increases in cardiac output during anoxia were associated with marked decreases in arterial oxygen pressure.

4. In response to anoxia, pulmonary artery pressure increased significantly (more than 5 mm. Hg) in a third of these patients with pulmonary disease and remained unchanged in the others.

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