RESPIRATORY REGULATION DURING EXERCISE IN UNCONDITIONED SUBJECTS[1]

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INTRODUCTION

The regulation of breathing during muscular exercise has been the subject of much work and speculation. Most of the experience has been gained with subjects in good physical training. In general, blood chemical changes in these subjects have not been great during exercise, and it has been difficult to account for the amount of ventilation on the basis of these changes and other known respiratory stimulants. The present study was done on untrained subjects in only fair physical condition. It seemed likely that the coordination of various respiratory drives would be less smooth in untrained subjects than in trained persons, so that the part played by different stimuli might become more obvious. The conduct of such studies has been simplified by the recent development of techniques for recurrent sampling of arterial blood during the course of exercise. Nearly all past studies have had to rely on indirect means of estimating arterial blood changes.

METHODS

The subjects were 11 male physicians and medical students in normal health but not in physical training. They ranged in age from 22 to 35 years and in surface area from 1.86 to 2.12 sq. m. They were not fasting and came to the experiment directly from their work. Arterial blood samples were taken from the brachial artery through an in-lying Cournand needle attached by flexible plastic tubing to a series of three way stopcocks. Blood was taken into syringes wet with heparin. For pH determinations, sodium fluoride was added as a preservative. The syringes were capped and stored in ice water. Analyses were completed within two to four hours. The subjects breathed through a Douglas valve into a recording spirometer. For determination of oxygen consumption the expired air was diverted into a Douglas bag. Gas mixtures other than air were supplied to the inspiratory side of the system from large Douglas bags. These mixtures consisted of 15% O_2 in N_2, tank oxygen (99.5%), and 5% CO_2, 21% O_2 in N_2. Resting measurements were made with the subject seated. Ventilation was also measured with the subject standing, just before exercise. Exercise was carried out in an airconditioned room at 25° C. on a treadmill at a speed of 5.1 miles per hour on a 3.5% grade. For most of the subjects this exercise rate was fairly severe. Oxygen consumption, measured in eight subjects about five minutes after beginning exercise, was $2,290 \pm 90$ cc./min. (range: $1,760 - 2,610$). Ventilation was recorded continuously and is expressed as ventilation at room temperature (25 ± 1° C.).[3] Arterial blood samples were taken at points during the breathing of various gas mixtures, at rest and exercise, when it became evident from the respiratory tracing that the ventilation rate had been nearly steady for at least 30 seconds. The subjects were studied on two separate days, one of which was devoted to the effects of the carbon dioxide mixture, and the other to the effects of the various oxygen mixtures.

Respiratory gas analyses were done with the Haldane apparatus or with a Pauling oxygen meter. Arterial blood oxygen content and per cent oxygen saturation were determined by a spectrophotometric method (1). The pH of whole blood was measured with a Cambridge Model R pH meter equipped with an inclosed glass electrode. Measurements were made at room temperature, usually 25–26° C., and the result was corrected to 37° C. by Rosenthal's factor (2). This temperature was arbitrarily chosen for all pH measurements on arterial blood. pH determinations were made in duplicate in nearly every case, and duplicate determinations agreed to within 0.02 pH units or less. The stability of the instrument was checked with a pH 4.00 acid phthalate buffer or a pH 7.01 phosphate buffer between each reading. The carbon dioxide content of whole blood was determined by the method of Van Slyke and Neill (3), and the plasma carbon dioxide content was estimated from this value and from the pH and hemoglobin by the line chart of Van Slyke and Sendroy (4). From the pH and CO_2 content of arterial plasma at 37° C., the CO_2 tension of arterial blood was calculated by the Henderson-Hasselbalch equation. For the calculation of CO_2 tension at 37° C., pK′ was taken to be 6.11, as found by Dill, Daly and Forbes (5). Where the method was evaluated, as described below, by equilibration of blood in a tonometer at 38° C., a pK′ value of 6.10 was used, as determined for this temperature by Hastings, Sendroy, and Van Slyke (6).

The determination of CO_2 tension by this indirect means

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[3] Range of barometric pressure: 747–757 mm. Hg.

depends upon several measurements and calculations, of which pH determination and temperature correction seem most liable to error. The validity of the procedure was therefore tested by equilibrating blood samples in tonometers with a variety of CO_2 tensions at 38° C. The actual CO_2 tension or "direct tension" was determined by Haldane analysis of the gas mixture in the tonometer. The blood was then removed from the tonometer, cooled to room temperature, and determination of "indirect CO_2 tension" carried out as described above, except that pH's were corrected to 38° C. In this way, 23 comparisons were made between direct and indirect CO_2 tensions. The direct tensions ranged from 19.5 to 58.1 mm. Hg, and the corrected direct pH's from 7.59 to 7.13. The per cent oxygen saturation of these bloods was between 70 and 100% in 13 instances, and between 25 and 70% in the remainder. The mean indirect CO_2 tension exceeded the direct by 1.62 mm. Hg, with a standard deviation of 2.03, and a standard error of 0.42. This difference, though small, was significant ($P < .01$). In addition, a comparison of indirect arterial CO_2 tension with alveolar CO_2 tension was made in 17 instances. The alveolar airs were collected during rest and exercise with the variations in technique for these conditions described by Dill and colleagues (7, 8), and also during hyperventilation on air and various CO_2 mixtures. Alveolar airs do not provide a satisfactorily exact check on arterial CO_2 tensions, but the comparison was thought to be required by the possibility that changes in the blood during strenuous exercise might seriously invalidate the corrections made in the indirect measurement of CO_2 tension. The alveolar tensions ranged from 17.9 to 76.7 mm. Hg, and the blood pH's from 7.59 to 7.15. The mean indirect arterial CO_2 tension exceeded the alveolar tension by 1.6 mm. Hg, with a standard deviation of 3.7. The difference was not significant. These agreements seem satisfactory. It is not clear why the indirect CO_2 tension is significantly greater than the direct. It seems most probable that the error lies in measurement of blood pH. The difference could be caused by a mean error of approximately .02 units below the true value. The deviations between direct and indirect CO_2 tensions were not more marked at extreme pH ranges than at more ordinary values. This is of importance because Rosenthal's temperature coefficient for whole blood was established for a pH range of 7.25 to 7.45, while the temperature coefficient of serum has been found to vary considerably at extreme pH ranges (6.6 and 7.8) (5). The present results indicate that Rosenthal's coefficient for human whole blood can satisfactorily be extended over the pH ranges encountered in this study.

RESULTS

The data on each subject relating respiratory volume to arterial blood measurements at rest and exercise and during the breathing of various gas mixtures are presented in Tables I and II.

Resting arterial blood

The mean values for resting arterial blood are presented in Table III. Of the 11 subjects, arterial blood was obtained from one on only a single occasion, and from two subjects on three occasions. In the remaining eight, samples were taken during two separate trials. In determining mean values each subject was given equal weight. The arterial oxygen saturation is within the general range of recent reports by Comroe and Walker (97.5%) (9), Wood and Geraci (97.9%) (10), and Drabkin and Schmidt (98.6%) (11). The pH is somewhat lower than that found for arterial blood by Dill, Edwards, and Consolazio (12) (7.40) and by Dill and associates (7.39) (13), but higher than that reported by Barr, Himwich, and Green (7.30–7.36) (14). The CO_2 tension is slightly higher than that reported by Dill and colleagues (41.0, 40.9) (12, 13), higher than that of Lilienthal and coworkers, by Riley's direct method (37.8) (15), close to that of Galdston and Wollack (42 direct, 44 indirect) (16), and less than that of Barr and colleagues (44–45) (14). As noted above, the mean CO_2 tension is probably about 2 mm. Hg too high, and the pH .02 units too low. In addition, the values are probably affected by the small dead space of the respiratory apparatus, and are almost certainly affected by the fact that the subjects were not in a basal state, but came to the experiment directly from their daily activities. Under these conditions the variability in pH and CO_2 tension among normal subjects was quite striking.

Arterial blood changes during exercise

The present observations are not directly comparable to many of those reported in the literature for the reason that the exercise period was too short in most cases for the subject to reach a steady state. In addition, the subjects were untrained, and the exercise accordingly varied in its relative severity. For some subjects it was severe enough to preclude reaching a steady state.

The arterial blood oxygen capacity rose in all subjects, the mean increase being 6%. This is within the general range previously reported (8, 14, 17–19). The increase had reached nearly its full value after three minutes of exercise. The per cent oxygen saturation gradually declined dur-

TABLE I

Effect of 5% CO_2 during exercise

Subject, Surface area	State	Inspired mixture	Time on mixture	Ventilation	% Arterial O_2 saturation	Arterial serum CO_2	Arterial pH	Arterial CO_2 tension
(*sq. m.*)				(*l./min., 25° C.*)		(*vol. %*)		(*mm. Hg*)
R.	Rest	Air		6.1	95.8	53.2	7.41	38
1.93		5% CO_2	2:00	9.6	98.4	57.1	7.34	47
	Exercise	Air	3:25	51.4	95.9	42.9	7.26	37
		5% CO_2	1:38	81.8	95.8	46.2	7.19	53
		Air	1:50	78.6	94.2	34.5	7.20	39
R.	Rest	Air		6.4	97.5	53.5	7.38	41
1.86		5% CO_2	1:50	22.6	99.6	56.2	7.32	49
	Exercise	Air	2:45	71.1	98.8	40.7	7.29	38
		5% CO_2	1:10	122.0	98.2	47.7	7.13	62
		Air	0:54	84.0	97.8	34.5	7.21	38
M.	Rest	Air		9.7	99.3	51.0	7.38	39
1.90		5% CO_2	2:00	11.5	98.7	54.4	7.29	50
	Exercise	Air	3:50	58.0	97.1	43.3	7.20	49
		5% CO_2	1:27	87.0	97.4	49.6	7.13	65
		Air	1:00	67.0	97.5	40.3	7.23	42
K.	Rest	Air		6.5	98.2	58.1	7.38	44
1.88		5% CO_2	2:00	17.5	99.7	60.1	7.32	52
	Exercise	Air	4:00	40.3	97.8	48.5	7.29	45
		5% CO_2	2:00	72.7	99.1	53.1	7.19	61
		Air	2:10	51.1	97.8	45.1	7.27	43
D.	Rest	Air		15.9	99.4	52.6	7.50	31
2.12		5% CO_2	1:50	16.8	99.2	59.5	7.34	49
	Exercise	Air	3:40	49.4	95.1	51.9	7.29	48
		5% CO_2	1:00	66.0	96.8	55.9	7.14	71
		Air	2:10	65.0	94.0	44.6	7.21	49
L.	Rest	Air		8.3	98.4	56.7	7.35	46
1.95		5% CO_2	2:00	15.2	98.7	61.3	7.25	62
	Exercise	Air	3:45	42.0	97.0	51.5	7.20	58
		5% CO_2	1:15	57.0	97.5	53.2	7.10	73
		Air	1:50	59.7	95.6	42.8	7.13	56
C.	Rest	Air		6.3	98.4	56.4	7.36	45
1.92		5% CO_2	1:50	10.7	98.8	60.6	7.29	56
	Exercise	Air	3:30	44.3	98.3	53.2	7.31	47
		5% CO_2	1:45	81.5	98.5	57.6	7.22	62
		Air	1:00	51.0	97.8	50.0	7.32	43
	Rest	Air		7.6	97.4	55.7	7.35	45
		5% CO_2	2:45	17.6	99.2	59.9	7.31	53
G.	Rest	Air		9.1	98.9	60.7	7.40	44
2.04		5% CO_2	1:45	14.0	99.1	63.1	7.33	53
	Exercise	Air	3:15	47.0	96.9	52.7	7.28	50
		5% CO_2	1:00	58.0	97.5	58.7	7.19	67
		Air	1:10	52.4	96.1	53.0	7.27	51
S.	Rest	Air		7.1	97.8	56.4	7.37	44
1.89		5% CO_2	1:50	22.2	98.9	59.2	7.32	51
	Exercise	Air	3:27	37.4	97.3	52.7	7.34	43
		5% CO_2	1:20	72.5	97.6	59.9	7.20	67
		Air	1:03	49.9	97.4	51.4	7.27	49
T.	Rest	Air		6.9	96.7	57.5	7.36	46
2.04		5% CO_2	1:45	11.8	98.9	61.8	7.29	57
	Exercise	Air	3:15	30.0	96.8	58.5	7.29	54
		5% CO_2	1:02	27.3	97.2	64.0	7.19	73
		Air	1:50	31.0	98.1	57.8	7.29	53
	Rest	Air		5.9	97.7	58.6	7.36	47
	Exercise	Air	4:10	20.5	93.1	57.8	7.23	61
		5% CO_2	2:05	34.8	97.3	60.6	7.15	75
		Air	2:46	36.0	95.8	53.6	7.22	58

TABLE II

Effect of 15% O_2 and tank O_2 during exercise

Subject	State	Inspired mixture	Time on mixture	Ventilation	% Arterial O_2 saturation	Arterial serum CO_2	Arterial pH	Arterial CO_2 tension
				(*l./min., 25° C.*)		(*vol. %*)		(*mm. Hg*)
H.	Rest	Air		8.9	99.4	51.6	7.38	39
	Exercise	Air	2:50	66.6	97.7	43.5	7.28	41
		15% O_2	0:54	94.8	86.9	37.2	7.27	36
		Air	1:25	87.4	95.4	33.1	7.15	41
	*Exercise	Air	8:00	84				
		100% O_2	1:15	70				
R.	Rest	Air		7.6	97.6	55.0	7.37	43
	Exercise	Air	3:00	72.0	98.0	43.4	7.23	46
		15% O_2	1:00	97.0	86.9	38.1	7.21	42
		Air	1:10	72.0	95.4	36.5	7.16	45
		100% O_2	1:30	63.0	100.0	36.4	7.18	43
M.	Rest	Air		12.7	99.2	52.1	7.44	35
	Exercise	Air	2:40	65.0	98.0	44.4	7.32	38
		15% O_2	1:24	84.0	89.4	39.4	7.31	35
		Air	1:10	73.0	97.3	40.7	7.25	41
		100% O_2	1:10	49.0	100.0	38.2	7.20	43
K.	Rest	Air		8.3	99.4	54.6	7.32	47
	Exercise	Air	1:36	69.1	99.1	48.8	7.27	47
		15% O_2	1:15	63.0	86.7	41.8	7.25	42
		100% O_2	1:24	64.0	100.0	40.0	7.19	46
		Air	1:15	70.6	94.5	38.4	7.23	40
D.	Rest	Air		13.9	98.7	51.3	7.42	36
	Exercise	Air	3:36	40.7	96.2	50.5	7.23	53
		15% O_2	1:20	61.2	78.0	46.5	7.22	54
		Air	1:15	53.5	95.8	43.7	7.17	52
		100% O_2	1:27	49.9	100.0	44.5	7.14	57
L.	Rest	Air		6.6	98.3	57.9	7.33	49
	Exercise	Air	3:36	40.0	97.1	52.6	7.26	52
		15% O_2	1:46	40.0	88.7	49.8	7.24	51
		Air	1:57	48.0	96.0	49.2	7.21	54
		100% O_2	1:46	43.0	100.0	48.6	7.15	61
		Air	1:45	54.0	95.0	46.9	7.14	60
C.	Rest	Air		7.8	98.0	56.3	7.29	52
	Exercise	Air	2:36	40.6	97.9	50.9	7.29	47
		15% O_2	1:36	56.5	90.4	47.9	7.26	47
		100% O_2	2:00	38.8	100.0	54.7	7.30	49
		Air	1:54	51.0	97.3	49.4	7.32	43
B.	Rest	Air		7.4	99.7	54.0	7.32	47
	Exercise	Air	3:10	37.2	96.6	50.8	7.24	52
		15% O_2	1:36	53.0	88.4	49.2	7.26	48
		100% O_2	2:25	40.6	100.0	49.4	7.24	51
		Air	2:05	47.0	96.5	48.8	7.29	45
G.	Rest	Air		9.6	99.0	57.4	7.38	44
	Exercise	Air	3:51	37.6	97.8	54.0	7.34	45
		15% O_2	1:40	46.0	89.3	53.4	7.36	42
		Air	2:18	40.5	97.1	52.6	7.31	47
		100% O_2	1:39	35.0	100.0	53.1	7.29	49
		Air	1:57	40.9	96.7	53.2	7.31	47
S.	Rest	Air		8.8	95.3	59.3	7.33	50
	Exercise	Air	2:20	36.6	95.3	55.5	7.20	62
		15% O_2	2:10	50.9	84.4	49.8	7.23	52
		100% O_2	2:40	32.4	100.0	54.1	7.18	63
		Air	2:36	29.7	93.0	56.7	7.20	63
T.	Rest	Air		9.9	98.1	58.6	7.35	47
	Exercise	Air	2:36	31.4	97.6	55.2	7.28	52
		15% O_2	1:50	31.4	73.6	54.3	7.23	57
		100% O_2	2:00	36.3	100.0	51.8	7.24	53
		Air	1:20	36.6	95.3	50.0	7.20	56

* Separate study.

TABLE III

Mean arterial blood values of 11 subjects at rest and during exercise

State	Ventilation	Blood CO_2 content	Serum CO_2 content	pH	CO_2 tension	O_2 capacity	% O_2 saturation
	(*l./min., 25° C.*)	(*vol. %*)	(*vol. %*)		(*mm. Hg*)	(*vol. %*)	
Rest	8.7±0.7	46.3±0.7	55.4±0.8	7.37±.01	43.3±1.5	19.51±0.32	98.3
Exercise 3'11"*	47.1±4.0	41.8±1.2	49.9±1.5	7.27±.01	48.2±1.6	20.52±0.37	97.1
Exercise 8'20"*	57.2±4.6	38.1±1.7	45.4±2.1	7.22±.02	47.6±2.1	20.67±0.33	96.1

* Average time. (Ranges: 1'36" to 4'30" and 5'45" to 11'30".) Indicated range following mean values denotes standard error.

ing the exercise period, falling by an average of 2.2%. A similar fall has been reported by Asmussen and Nielsen (20). The arterial oxygen tension has been found to fall during exercise (15). In addition, the pH fall in our subjects would have the effect of shifting the oxyhemoglobin dissociation curve so that the per cent saturation would be less for a given oxygen tension.

For the group as a whole there was a considerable fall in pH and in serum CO_2 content. A large change had occurred by the time of the first sample, and the decline was continued in the second sample. Decreases of arterial pH and CO_2 content during exercise are a reflection of the accumulation of lactic acid (8, 21), and changes of this magnitude indicate that the rate of exercise was severe for the group as a whole. With subjects in better training, exercise rates of this degree or much higher may be maintained without the accumulation of large amounts of lactic acid and without a decline in pH (8, 22). However, with exercise which is severe for the subject, fall in arterial pH and serum CO_2 content of this general magnitude have been reported (14, 21, 23). Our experience is similar to Barr's and Himwich's (23) in the finding that resting pH and CO_2 content may not be restored for many minutes after exercise.

The mean arterial CO_2 tension was slightly increased during exercise. Because of the great individual variation, the difference between the resting and exercising levels is not significant for the group as a whole. Nielsen (22) reported that the CO_2 tension falls during exercise and that the fall is greater with increasing severity of exercise. His observations were made during the steady state of exercise on two highly trained subjects, and the arterial CO_2 tension was calculated from the composition of expired air and the respiratory dead space. Data on this subject are relatively few. The observations of Barr and associates (14), and of Galdston and Wollack (16) showing a fall or no substantial change in arterial CO_2 tension were made on arterial blood drawn shortly after exercise was completed. Lilienthal and colleagues (15), measured CO_2 tension by Riley's method in arterial blood drawn during exercise from six subjects. The sampling time was comparable to that of the present study, but, judging from the oxygen consumption, the severity of exercise was somewhat less. They found an average increase of approximately 3 mm. Hg in arterial CO_2 tension during work. Dill and associates have investigated the arterial CO_2 tension during exercise as measured by "inspiratory" alveolar air. There was considerable individual variation, but the average tension, after a steady state was reached, was not far from the resting value (7, 8). Four trained subjects at graded work rates showed a moderate increase in CO_2 tension with lighter work rates and a gradual decline toward the resting level as the rate was increased (13). Briggs (24) studied subjects under a very large work load. In many of the best performers, there was a high CO_2 content in the expired air (up to 8% in two subjects), indicating a very high arterial CO_2 tension. In short, the available evidence indicates that the arterial CO_2 tension during exercise may rise, fall, or remain nearly unchanged depending upon the individual subject, the work rate, and the duration of work. In four cases in the present study the CO_2 tension within one minute after exercise was found to be substantially the same as the original resting value.

The course of ventilation during exercise

At the start of exercise, as found by Krogh and Lindhard (25), there is an immediate increase in ventilation. With our subjects, this increased ven-

tilatory rate was maintained with relatively minor fluctuations, particularly in the first four to five breaths, for roughly a minute. A rather sharp further increase in ventilation then occurred. This sharp "secondary rise" in ventilation was present consistently except in one subject, T., in whom it appeared in only one of three trials. The secondary rise usually took place within a period of one to three breaths. The time at which the secondary rise occurred varied from 30 to 67 seconds after the onset of exercise, with an average time of 52 seconds. The mean increase at this point was 10.4 ± 1.6 l./min. The ventilation thereafter rose much more gradually and smoothly, reaching a steady state in some cases. This secondary rise seems not to have been commented upon before, although close observations of breathing during early exercise have been made by Krogh and Lindhard (25) and by Asmussen and Nielsen (26). Their subjects were in good physical condition. Continuous recordings of ventilation throughout the course of exercise have been made by Rahn and Otis (27) and by Bruce and coworkers (28), without the finding of a sharp break in ventilation. In these studies the subjects were untrained, but the work rate was quite mild.

It seemed possible that the secondary rise might reflect the beginning of arterial blood changes resulting from exercise. This possibility was examined in two further subjects who showed a well-marked secondary rise on moderate exercise (corresponding to an O_2 consumption of about 1,400 cc./min.). The results are presented in Table IV. It is apparent that there was a rapid fall in pH and a rise in arterial CO_2 tension during early exercise. The total extent of these changes, as measured by the effect on ventilation of breathing CO_2 at rest, could account roughly for the magnitude of the secondary rise. However, the ventilation rise is sharp, while the blood chemical changes are more gradual. This difference may reflect a lag between arterial blood changes and the ventilatory response. It seems possible only to conclude that chemical changes may occur quite early in the arterial blood of untrained subjects even during moderate exercise, and that these changes may be responsible for the secondary rise in ventilation.

On stopping exercise, there was usually a sharp decrease in the ventilation rate, as noted by Asmussen and Nielsen (26). The magnitude of this decrease varied greatly. The mean fall was 8.8 ± 2.6 l./min. Because of individual variation, there

TABLE IV

Ventilation and arterial blood changes during early exercise and while breathing CO_2-enriched air at rest

Subject	Sampling time after starting exercise	Comment	Ventilation	Serum CO_2	pH at 37° C.	CO_2 tension
			(*l./min., 25° C.*)	(*vol. %*)		(*mm. Hg*)
R. M.	Rest		8.8	53.6	7.37	41
	32″–41″		12.7*	55.5	7.34	45
		Secondary vent. rise to 19.8 l./min. begins at 63 sec.				
	71″–82″		19.8	55.8	7.28	52
	3′23″–3′33″		36.5	50.9	7.21	55
	Rest	28 min. after exercise	8.1	49.0	7.32	42
	Rest	Breathing 3–4% CO_2 for 4 min.	15.4	53.7	7.29	49
E. S.	Rest		8.5	56.0	7.38	43
	16″–26″		20.7*	55.5	7.34	46
	45″–55″			56.6	7.32	49
		Secondary vent. rise to 32.5 l./min. begins at 52 sec.				
	2′49″–3′04″		43.6	53.1	7.27	51
	Rest	22 min. after exercise	9.7	51.5	7.34	43
	Rest	Breathing 4–5% CO_2 for 2½ min.	25.2	56.5	7.28	53

* Average after first four to five respirations (about 15 seconds) until secondary rise in ventilation. Treadmill exercise at 4 mph and a 4% grade, subjects in poor training. A sharp "secondary rise" in ventilation is associated with an increase in CO_2 tension. Subjects show normal response to breathing CO_2 at rest.

was no significant difference between the magnitude of the immediate increase at the beginning of exercise and the decrease at the end.

The effect of breathing 5% CO_2

In comparing the effect on ventilation of breathing 5% CO_2 at rest and during exercise, the difficulty arose that a number of our subjects were unable to continue exercise with the gas mixture long enough to reach a steady state. Accordingly, the mixture was given until it was evident from the respiratory tracing that the ventilation was no longer changing rapidly, and arterial samples were then taken. For comparison, the same procedure was adopted in the resting state. The average time on CO_2 at rest was two minutes and during exercise one and one-half minutes. The average time needed to reach a steady state on 5% CO_2 at rest probably exceeds five minutes and in individual cases may be much more (22, 29, 30). However, the breathing time used in the present study covers the period of rapid change in ventilation. In measuring the effect of CO_2 inhalation during exercise, it was necessary to select control levels for ventilation and arterial CO_2 tension. This was complicated by the fact that the subjects were not in a steady state, and ventilation was consequently increasing with time, apart from the effect of CO_2. As shown in Table I, during the same exercise period control measurements were made while the subject was breathing air, both before and after the administration of CO_2. The control value for ventilation while the subject was breathing CO_2 was estimated by assuming that the ventilation time curve would have followed a straight line between these two points if the subject had continued on air. The mean values for the two points on air, before and after giving CO_2, were 46.6 l./min. at three and one-half minutes of exercise, and 58.3 l./min. after seven and one-half minutes of total exercising time.[4] The mean estimated control ventilation during CO_2 breathing was 53.3 l./min., while the mean actual ventilation was 73.0 l./min. The estimated control ventilation is a little too low because the ventilation-time curve is not a straight line but is convex upward. The apparent effect of CO_2 is thereby magnified, but the effect is not great. In the second control period, measurements were made at an average of one and one-half minutes after changing from CO_2 to air. It might have been expected that measurements during this period would still be much influenced by the preceding CO_2 inhalation. However, the mean ventilation at this point (58.3 ± 4.4 l./min.) was not significantly different from that of the last control period in the oxygen experiments (56.0 ± 5.4 l./min.), which are described in the next section. In most of the latter, the preceding gas mixture was tank oxygen, which depresses ventilation instead of elevating it. It is concluded that ventilation in the second control period was not significantly influenced by the preceding gas mixture in either case. The mean CO_2 tension was approximately 47 mm. Hg in each control period. There was very little individual change between periods, and a simple average was taken for the CO_2 tension to be expected if the subject had continued on air. It appears that there is a rapid recovery from the effect of inhaling CO_2 during exercise.

TABLE V

Mean effect on 10 subjects of breathing 5% CO_2 at rest and during exercise

State	Ventilation	CO_2 tension	Ventilation change/CO_2 tension change
	(*l./min., 25° C.*)	(*mm. Hg*)	(*l./min./mm. Hg*)
Rest	8.3±0.9	41.8±1.5	
Rest, 5% CO_2	15.5±1.4	52.6±1.4	.80±.24
Exercise	53.3±4.2*	46.9±2.1*	
Exercise, 5% CO_2	73.0±7.5	65.5±2.0	1.05±.20

* Expected values, calculated from measurements during exercise before and after the administration of CO_2. See text.

The mean results for 10 subjects are presented in Table V. The mean ventilation response to an increase in arterial CO_2 tension during exercise exceeds that at rest, but the difference is not statistically significant ($0.3 < P < 0.4$). It was suggested by Nielsen (22) that the respiratory center becomes more sensitive to CO_2 during exercise, and that this change is an important factor in the regulation of breathing during exercise. Under the conditions of the present experiment, there is no evidence that exercise has sensitized the respiratory center to CO_2 in the sense that the ventilatory response to a given increment in CO_2 ten-

[4] The four minutes between these sampling times included one and one-half minutes each on CO_2 and air, with approximately 30 additional seconds after each period which were occupied in completing the blood sampling and observing the ventilation rate to insure that it was not changing rapidly.

sion becomes significantly greater. The same conclusion was reached by Grodins (31) from an examination of Nielsen's data. The magnitude of the response to 5% CO_2 at rest is somewhat lower than usual, probably because of the short exposure time. The mean pH fall as a result of breathing CO_2 was slightly greater during exercise than at rest. As a corollary to the first conclusion, there appears to be no evidence that exercise produces any marked respiratory sensitivity to a fall in arterial pH.

The effect of high and low oxygen concentrations

In 1920 Briggs (24) observed that breathing oxygen-enriched air during severe exercise decreased the ventilation rate. The effect was greater the more severe the exercise, and for a given exercise rate the effect varied inversely with physical fitness. The finding has been confirmed abundantly (20, 22, 27, 32, 33). Conversely, it is known that ventilation for a given work rate is greater at high altitudes (13, 34, 35) or while breathing low-oxygen mixtures (15, 27, 36, 37) than it is at normal oxygen tensions. In the present study a trial was made of the effect on ventilation of changing from air to 15% O_2 in N_2 and to tank oxygen.

The first control measurements were made after about three minutes of exercise. The subject was then switched to 15% oxygen, and thereafter to air or tank oxygen. In all cases there were two or three control periods on air, as indicated in Table II. The time on each mixture was roughly one and one-half minutes before measurements were made. The subjects did not know the order in which mixtures were given and the changes were made without their knowledge. The method of determining "expected" ventilation and per cent oxygen saturation from the control periods was the same as described in the preceding section. The mean results for 11 subjects are presented in Table VI. Fifteen % O_2 caused a significant increase in ventilation ($P < .05$) and tank oxygen a significant decrease ($P < .01$), with reference to the rate on air. On switching gas mixtures, the change in ventilation rate was extremely rapid. This was particularly true in passing to oxygen, when a marked slowing was often evident within 10 seconds, or four to five breaths. With the ventilation changes there were corresponding changes in arterial CO_2 tension and pH. That is, with the lower ventilation under tank oxygen the CO_2 rose and the pH fell, while reverse changes occurred with 15% O_2. These secondary changes must have limited the extent of the oxygen effect, since they would force ventilation in the opposite direction.

TABLE VI

Mean effect on 11 subjects of breathing 15% O_2 and tank O_2 during exercise

State	Ventilation	% Arterial O_2 saturation	Ventilation change
	(*l./min., 25° C.*)		(*l./min.*)
Exercise, air	52.1±4.8*	96.9*	
Exercise, 15% O_2	61.6±6.5	85.7	9.5±3.1†
Exercise, air	55.8±5.3*	96.1*	
Exercise, tank O_2	47.4±3.9	100.0	8.4±2.3‡

* Expected values, calculated from measurements during control periods. See text.
† $p < .02$.
‡ $p < .01$.

It is of some interest to note that the mean change of CO_2 tension was only about 3 mm. Hg on changing from air to either gas mixture, which was less than might have been anticipated from the change in ventilation. The short exposure time may not have permitted the development of a full change in CO_2 tension. In addition, it is possible that the different gas mixtures may have influenced the rate of bicarbonate breakdown and consequently of CO_2 excretion. From the rate of total blood CO_2 loss, it is apparent that lactic acid was being formed rapidly. The rate of production of lactic acid during work can be markedly slowed by high oxygen mixtures or accelerated by low oxygen (20, 36, 38, 39).

The effect on ventilation of changing arterial oxygen tension is far greater during exercise of this severity than at rest. The effect on ventilation of inhaling high and low oxygen concentrations at rest has been studied by Dripps and Comroe (40). They found a small, immediate drop of 3.1% in ventilation on passing from air to oxygen. On 12% oxygen, which produced a mean fall of 17% in arterial saturation, approximately corresponding to that of the present study, there was an average ventilation increase of 0.5 l./min.

The effect of changes in arterial pH

There has been some disagreement as to the role played by arterial pH in the regulation of breath-

TABLE VII

Arterial blood pH, ventilation, and CO_2 tension in the post-exercise period

Subject	State	Ventilation	Arterial blood pH	Arterial blood CO_2 tension
		(*l./min., 25° C.*)		(*mm. Hg*)
R. M.*	Rest	8.8	7.37	41
	post-exercise 28 min.	8.1	7.32	42
E. S.*	Rest	8.5	7.38	43
	post-exercise 22 min.	9.7	7.34	43
S.	Rest	7.1	7.37	44
	post-exercise 6 min.	8.4	7.33	45
P. S.	Rest	7.8	7.35	45
	post-exercise 18 min.	10.7	7.29	47

* Data repeated from Table IV.

ing during exercise. Barr (14, 41), Dill, Talbott and Edwards (8), and Nielsen (22) found little correlation between pH and ventilation. From studies on diabetic acidosis Kety and associates (42) have suggested that there is a threshold for respiratory response at about pH 7.2. Between this point and pH 7.0, ventilation increased as the hydrogen ion concentration rose. These investigators pointed out that the arterial CO_2 tension of their patients was simultaneously decreased. As emphasized by Gray (43) and Grodins (31) such a change could mask a stimulant effect which might otherwise appear at higher pH levels.

Some data on this point are available from the present study and are presented in Table VII. In the post-exercise period, ventilation and arterial CO_2 tension in these subjects have returned substantially to their former values, while the pH is still .04 to .06 units below the control level. The pH changes are not large, but it seems possible to conclude that small pH changes, produced in this way, do not evoke much respiratory response. No such data are available, from this study, for large pH changes. As pointed out above, the finding that exercise does not generally increase respiratory sensitivity to CO_2 also implies that it does not cause a marked increase in sensitivity to a fall in arterial blood pH, since the pH was decreased considerably both at rest and exercise by CO_2 inhalation.

Individual variation

Individual variation is conveniently examined by reference to Figure 1. There is a striking difference among subjects in response to various stimuli.

The most consistent response is the immediate increase in ventilation on beginning exercise (Figure 1B). Even so, this shows up to 100% variation among subjects, and its magnitude is not closely related to the final ventilation volume. In Figure 1C is presented the abrupt fall in ventila-

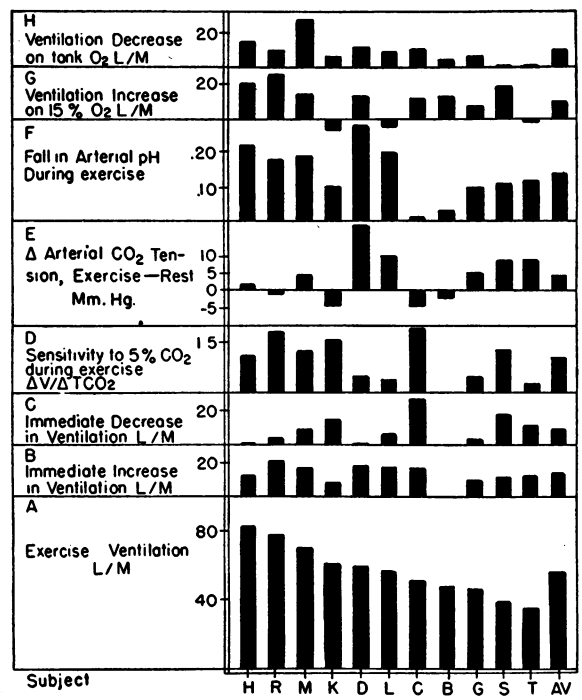

FIG. 1. VARIATION IN PERFORMANCE OF INDIVIDUAL SUBJECTS DURING EXERCISE

Columns at the extreme right represent the mean for each category. The values of categories A, B, C, E, and F are the averages of observations during two separate exercise periods, except for subject B, who had only one exercise period. A: ventilation during arterial blood sampling in the latter part of the exercise period. B: abrupt increase in ventilation on beginning exercise. C: abrupt decrease in ventilation on stopping exercise. D: increase in ventilation (l./min.) per mm. Hg rise in arterial CO_2 tension resulting from administration of 5% CO_2 during exercise. E: difference between arterial CO_2 tensions at exercise and rest. F: fall in arterial blood pH during exercise. G: increase in ventilation resulting from administration of 15% O_2 during exercise. H: decrease in ventilation resulting from administration of tank oxygen during exercise.

tion on stopping work. Here there is even a greater variation. In some subjects there is little or no immediate fall, while others show a fall greater than the original increase. The initial increase, because of its rapidity, has been considered neurogenic from the time of its description by Krogh and Lindhard, and the same etiologic reasoning is evidently applicable to the abrupt fall. Since the discovery by Harrison, Calhoun, and Harrison (44) of respiratory reflexes from passive limb motion, considerable attention has been devoted to this phase of respiratory control, most notably by Comroe and associates (45, 46), who have recently concluded that passive stretch reflexes can play only a minor part in respiratory regulation. Whether peripheral or central in origin, the present effect is of considerable magnitude. It is quite possible that the actual magnitude of this "neurogenic factor" during exercise is not fully measured by the abrupt changes in ventilation on starting and stopping exercise. A preliminary examination of this possibility has been made in subject H., who customarily shows an immediate increase in ventilation of about 12 l./min. on starting exercise and no immediate decrease on stopping, once a large ventilation volume has been reached. This subject was caused to exercise repeatedly for short periods with only brief recovery intervals. The immediate increase on passing from rest to exercise amounted in the first trial to 18 l./min., in the second, to 28 l./min., and in the third to 32 l./min., the last representing an immediate jump from 18 to 50 l./min. The possibility exists that the neurogenic factor may increase during exercise and become much larger than indicated by the average values for starting and stopping effects.

There is a very large range in sensitivity to arterial CO_2 tension, as shown by Figure 1D, representing ventilation increase per mm. of arterial CO_2 tension when 5% CO_2 is administered during exercise. Wide variation among subjects in response to carbon dioxide at rest has also been remarked (29, 30). Figure 1E presents the difference between arterial CO_2 tension during the latter part of exercise and the tension at rest. There is some correspondence between CO_2 sensitivity (Figure 1D) and the behavior of the arterial CO_2 tension during exercise. Where sensitivity is high, the CO_2 tension tends to fall or to rise only slightly during exercise. The large increase shown by D. is probably owing to anxiety and hyperventilation during the resting period, with a resultant subnormal CO_2 tension at rest. An exception is provided by S., who was sensitive to CO_2, but still showed a considerable increase in CO_2 tension during exercise. Evidently, the importance of CO_2 as a respiratory regulator during exercise is subject to considerable individual variation.

The reaction to 15% oxygen and tank oxygen is presented in Figures 1G and 1H. Once more, there was a considerable range of response. In several cases there was much difference in sensitivity to the two mixtures. The response to tank oxygen was a little more consistent than that to 15% oxygen.

DISCUSSION

In 1944 Comroe (47) reviewed the evidence dealing with respiratory regulation during exercise and concluded that a number of factors must act together. Subsequent work, including the present, has confirmed the conclusion. Efforts have been made to quantitate the role played by various of these factors. Most of this work has been done with well-trained subjects. It is generally believed that neurogenic stimuli play some part, although there is disagreement as to whether reflexes originating from the limbs themselves are important or not (46, 48, 49). It has been held, on the one hand, that neurogenic stimuli are of primary importance in light to moderate exercise (50), and, on the other, that they are of little importance. Carbon dioxide has been invoked as a major factor on the ground that exercise increases the responsiveness of the respiratory center to this stimulus (22), and the significance of carbon dioxide as a major factor has been denied on the ground that the alveolar carbon dioxide tension remains unchanged or falls during exercise (47). pH change has not been considered of first-line importance by most observers (8, 22, 41), but its possible importance has recently been asserted (31). Arterial oxygen tension has been dismissed as a regulatory factor because changes in arterial oxygen during exercise are slight, and change in arterial oxygen tension over a considerable range yields little respiratory response at rest (20). A rise in body temperature during exercise may stim-

ulate respiration, but this is slow to develop and probably would not be very effective in less than 10 minutes (51). Because it has often seemed difficult to account for the magnitude of ventilation during exercise, it has been recurrently postulated that an unidentified substance which acts as a respiratory stimulant is produced by working muscles.

In the present study, using untrained subjects, it is apparent that a number of stimuli were operative. Neurogenic factors, of whatever origin, played a significant part in initiating and maintaining ventilation. This stimulus may have been much larger than can be estimated from initial increases and terminal decreases in ventilation.

Arterial carbon dioxide tension appears to have been effective in increasing ventilation during exercise in at least some subjects. Since the respiratory center did not become highly sensitive to carbon dioxide during exercise, the effect as calculated after several minutes of exercise is not particularly large except perhaps in subject S., who was sensitive to carbon dioxide and had a substantial increase in arterial tension during exercise. In those subjects who have a rapid, early decrease in blood CO_2 content, presumably owing to lactic acid accumulation, a rising arterial CO_2 tension early in exercise may assist in increasing ventilation. As pointed out above, this may account for the "secondary rise" in ventilation early in exercise. In trained subjects this secondary rise has not been described, and trained subjects show little, if any, early increase in alveolar CO_2 tension (8, 22) corresponding to that found in the arterial blood of some of our untrained subjects.

The effect of changing the arterial oxygen tension is of considerable interest. The ventilation response is very rapid, and its magnitude is many times greater than at rest. This effect appears in exercise which is severe for the subject, and the effect becomes more pronounced as the severity increases (20, 24). The response is too immediate to make it likely to result from changes in blood concentration of some substance produced by anaerobically working muscles. It has been suggested by Asmussen and Nielsen (20) that an increase in oxygen tension could act by decreasing chemoreceptor sensitivity to such a substance. If so, one would need to postulate that the substance continues to be produced on oxygen at the same rate as on air, although lactic acid production is decreased by oxygen. This is because the results of these investigators show an immediate return of ventilation to the same steady rate as before when the subject is switched back to air. It seems a little simpler to assume that the chemoreceptor system becomes more sensitive to the arterial oxygen tension itself, or that the respiratory center becomes more sensitive to the "tone" which is known to exist at normal oxygen tensions in the resting state (40). In the latter case, the oxygen effect could be regarded as a variety of neurogenic stimulus which becomes more active the more severe the exercise. There is some evidence in animals for a respiratory drive from increased chemoreceptor tone, or increased responsiveness to the existing tone, during electrically induced work (49, 52). The development of this effect during exercise can make a significant contribution to the total ventilation. Normally, it can not provide for a very close regulation of ventilation because the effect does not vary greatly with a small change in oxygen tension. It is probably important in the close regulation of breathing during exercise at high altitudes and in patients with pulmonary disease who have a decreased arterial oxygen tension. For reasons outlined by Bohr (53) and Barcroft (54) and put to experimental trial by Lilienthal, Houston, and others (15, 35, 55), the arterial oxygen tension can fall markedly during exercise when it is already low at rest.

The large falls in arterial pH which occurred during exercise in some of our subjects would be expected to have some stimulant effect on respiration. Our experience, however, is similar to that of others in finding no close correlation between ventilation and pH in a given subject. As pointed out before, we find no evidence that the respiratory response to a fall in pH becomes very great during exercise.

Among the factors known to be operative in the present study, then, are a "neurogenic factor" which may increase during exercise, a changing arterial CO_2 tension, the development of what is provisionally regarded as an increased chemoreceptor tone to oxygen, and a considerable fall in pH. Recently, Gray (43) and Grodins (31) have approached the problem of multiple respiratory stimuli by assigning quantitative values to the stimulant effects of CO_2 tension, hydrogen ion con-

centration, and oxygen tension. If these values are accepted and the quantities measured, it is possible to draw conclusions as to the intensity and mode of action of additional stimuli which are required to account for the ventilation observed in a given situation. One of the most striking findings of the present study is the tremendous variability among untrained subjects in the response to different stimuli, as well as in the extent to which various stimuli develop during exercise. This suggests that any respiratory formula be applied only with reservations to a single subject or even to small groups of subjects, particularly when they are not in good physical training.

This great variability among normal subjects in poor physical condition is in contrast with the much more uniform performance of subjects in good training. It is probable that still greater deviations will occur in the course of disease. Present concepts of the relative importance of various respiratory stimuli in muscular exertion have been gained largely through the study of well-conditioned subjects. It does not appear likely that these concepts can be carried over intact to persons with acute or chronic disease.

SUMMARY

1. Observations have been made on ventilation and arterial blood changes in 11 untrained subjects during short periods of moderately severe treadmill exercise. Particular attention was paid to the ventilation changes at the start and conclusion of work, to the course of ventilation in early exercise, to the effect on ventilation of breathing gas mixtures having, respectively, an increased CO_2 content, a low oxygen, and a high oxygen content, and to associated changes in arterial CO_2 tension, pH and per cent oxygen saturation.

2. With untrained subjects there may be large changes during exercise in arterial CO_2 content, CO_2 tension, and pH, and these may begin to develop very early in exercise.

3. Exercise did not increase significantly the sensitivity of the respiratory center to arterial CO_2 tension, as measured by increase in ventilation per mm. Hg increase in CO_2 tension.

4. An attempt is made to estimate in semi-quantitative terms the role played by various respiratory stimuli in regulating ventilation during exercise. These stimuli are a "neurogenic" effect; an oxygen effect, which is provisionally regarded as an increase in sensitivity of the chemoreceptor system to oxygen tension; fall in blood pH; and arterial CO_2 tension. There is great variation among untrained subjects in the relative importance of these factors.

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