FACTORS INFLUENCING RESPIRATION DURING HEAVY EXERCISE[1]

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The first insight into the control of respiratory function was provided by Haldane and Priestley (1) who concluded that alveolar pCO_2, acting ultimately on the respiratory center, was the ruling factor. The same mechanism was thought to be responsible for the hyperpnea of light exercise but, as pointed out by Douglas and Haldane (2) and by Douglas (3), other factors may come into play during heavy exercise. Since the work of the Haldane school, the CO_2 control theory has been challenged and other factors, both nervous and humoral, have been suggested (4–6).

Among the nervous stimuli that have been considered are direct cortical stimulation (7), reflexes from exercising limbs (8, 9), and reflexes from the great veins and right atrium (10). Serious objections to each of these possibilities have been raised (4, 11, 12).

Humoral factors that have been considered include arterial and venous pCO_2, pH, pO_2, and accumulation of anaerobic metabolites. Investigations by Bannister, Cunningham and Douglas (13), using alveolar CO_2 determinations, lend support to the earlier views of Haldane; other investigators (14, 15) have found either no change or a slight decrease in arterial pCO_2 during exercise. Bannister and Cunningham (16) have also recently postulated decreased arterial pO_2 as a respiratory stimulant during heavy exercise but obtained no data to support the view. A decrease in arterial pH during exercise has been found by many investigators (14, 17, 18), but the phenomenon has never been shown to be causally related to the hyperpnea of exercise. Somewhat along the same lines, the possibility that unidentified metabolites might be so related was suggested by Henderson (19) and was also considered by Asmussen and Nielsen (20).

The following study was designed to examine some of these suggestions, particularly those that are concerned with changes in oxygen and CO_2 tension and with pH alterations in arterial and venous blood.

METHODS

The subjects were normal men, aged 20 to 43 years. All were leading active lives but none were trained athletes. Respiratory data, including maximal oxygen intake, were obtained on 59 men. Blood gas studies, including brachial arterial and peripheral venous samples, were added in 24 subjects, several of whom were studied more than once. Blood samples from all sites, however, were not always obtained on all subjects. Blood from the internal jugular vein was collected, in addition to the other samples, in 4 subjects. In the accompanying Tables I through V, means and standard deviations are followed by the number (in parentheses) of observations on which the data are based. In most instances, the number of observations corresponds to the number of subjects.

Exercise was performed on a motor-driven treadmill in an air-conditioned room at a temperature between 23 and 26° C. Maximal oxygen intake was first determined by a previously published method (21). In studies done some days later, PE 90 (I.D., 0.034 inch) catheters were placed in the left brachial artery and vein, and in the femoral vein. The catheters were attached to three-way stopcocks and were kept filled with normal saline solution containing a small amount of heparin. Blood from the internal jugular vein was collected through a cardiac catheter, the tip of which was in the jugular bulb. In order to permit collection of blood samples during exercise from catheters inserted into the left arm, the subject's left hand gripped a crossbar, placed in front of him and at the level of the lower thorax, throughout the studies. The right arm was allowed to swing normally. The catheter in the femoral vein was long enough to permit the stopcock attached to it to be held steady for sampling, regardless of the motion of the thigh.

Resting studies were carried out with the subject standing in place on the treadmill. He was connected to an Otis-McKerrow two-way breathing valve by means of a rubber mouthpiece and his nose was closed with a nasal

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clamp. Expired air was collected in a Douglas bag. Gas analysis was immediately carried out, using a Beckman E-2 magnetic oxygen analyzer and a Liston-Becker infrared carbon dioxide analyzer. The volume of expired air was measured in a Tissot gasometer and corrected to BTPS. The respiratory rate was determined by means of a strain-gage assembly attached to the respiratory valve and mean tidal volume was calculated by dividing expired volume by respiratory rate. Oxygen intake was determined with the aid of a nomogram (22). Blood samples were collected anaerobically in heparinized syringes from all sites simultaneously.

Oxygen tension was determined polarographically (23). Oxygen and carbon dioxide contents were determined by the Van Slyke and Neill method and per cent saturation was calculated from the oxygen content and oxygen capacity. The pH determinations were performed at 37.5° C. using a Cambridge research model pH meter. Plasma carbon dioxide content was determined from whole blood carbon dioxide content; pH and hematocrit by the nomogram of Van Slyke and Sendroy (24). Carbon dioxide tension was calculated, by use of the Henderson-Hasselbalch equation, from pH and CO_2 content of plasma at 37.5° C.:

$$pCO_2 = \frac{CO_2 \text{ content}}{S[10(pH - pK') + 1]},$$

TABLE I

Ventilatory volume, oxygen intake and respiratory quotient at rest and at exercise loads leading to maximal oxygen intake *

	Rest	Exercise I	Exercise II	Exercise III
Ventilation, *L./min. (BTPS)*	10.15 ± 2.07 (40)*	73.50 ± 10.43 (54)	83.38 ± 11.98 (39)	94.72 ± 15.94 (32)
Respiratory rate/*min.*	17 ± 5 (28)	31 ± 9 (42)	35 ± 10 (31)	38 ± 10 (25)
Tidal volume, *Liters (BTPS)*	0.63 ± 0.21 (28)	2.50 ± 0.67 (42)	2.54 ± 0.64 (30)	2.59 ± 0.57 (24)
Oxygen intake, *L./min. (STPD)*	0.35 ± 0.06 (40)	2.81 ± 0.39 (54)	3.09 ± 0.42 (39)	3.27 ± 0.50 (32)
Oxygen intake, *ml./Kg./min. (STPD)*	4.8 ± 0.8 (40)	38.7 ± 5.2 (54)	42.4 ± 5.8 (39)	44.8 ± 5.7 (32)
Respiratory quotient	0.74 ± 0.08 (40)	1.05 ± 0.10 (54)	0.97 ± 0.09 (39)	0.94 ± 0.09 (32)

* Figures in parentheses refer to number of observations in each category.

TABLE II

Blood gas and pH measurements at rest and at exercise loads leading to maximal oxygen intake in normal subjects *

Site		Rest	Exercise I	Exercise II	Exercise III
Brachial artery	pO_2 (*mm. Hg*)	85 ± 13 (32)	86 ± 14 (34)	89 ± 12 (26)	91 ± 13 (17)
	O_2 Sat. (%)	94.9 ± 2.6 (33)	93.3 ± 5.2 (31)	94.2 ± 3.5 (22)	94.1 ± 2.2 (14)
	pCO_2 (*mm. Hg*)	39 ± 4 (26)	40 ± 6 (23)	38 ± 6 (16)	36 ± 6 (10)
	Plasma CO_2 (*mEq./L.*)	24.0 ± 1.4 (27)	20.4 ± 2.1 (25)	16.3 ± 2.8 (16)	14.1 ± 3.0 (10)
	pH	7.39 ± 0.04 (36)	7.28 ± 0.05 (32)	7.23 ± 0.08 (24)	7.19 ± 0.08 (16)
Brachial vein	pO_2 (*mm. Hg*)	29 ± 8 (22)	24 ± 8 (18)	29 ± 6 (9)	25 ± 5 (9)
	O_2 Sat. (%)	55.0 ± 15.0 (25)	25.0 ± 9.8 (19)	22.1 ± 6.1 (10)	25.0 ± 6.4 (10)
	pCO_2 (*mm. Hg*)	45 ± 5 (20)	71 ± 13 (15)	64 ± 9 (6)	63 ± 9 (8)
	Plasma CO_2 (*mEq./L.*)	26.1 ± 2.2 (20)	26.9 ± 2.2 (15)	25.5 ± 1.4 (6)	23.8 ± 1.5 (8)
	pH	7.36 ± 0.04 (25)	7.21 ± 0.12 (22)	7.19 ± 0.07 (13)	7.14 ± 0.06 (11)
Femoral vein	pO_2 (*mm. Hg*)	26 ± 10 (25)	25 ± 9 (24)	27 ± 5 (12)	30 ± 7 (11)
	O_2 Sat. (%)	40.2 ± 14.4 (27)	24.6 ± 6.6 (27)	24.1 ± 6.2 (13)	20.9 ± 8.0 (12)
	pCO_2 (*mm. Hg*)	47 ± 6 (24)	83 ± 11 (21)	70 ± 8 (7)	74 ± 7 (10)
	Plasma CO_2 (*mEq./L.*)	26.9 ± 2.3 (24)	27.6 ± 2.2 (20)	25.3 ± 2.2 (7)	24.4 ± 1.9 (9)
	pH	7.35 ± 0.05 (29)	7.13 ± 0.08 (28)	7.13 ± 0.06 (14)	7.11 ± 0.05 (13)
Internal jugular vein	pO_2 (*mm. Hg*)	28 ± 8 (4)	30 ± 7 (4)		
	O_2 Sat. (%)	58.3 ± 8.3 (4)	60.3 ± 3.8 (4)		
	pCO_2 (*mm. Hg*)	58 ± 3 (4)	52 ± 4 (4)		
	Plasma CO_2 (*mEq./L.*)	26.8 ± 1.1 (4)	24.2 ± 2.1 (4)		
	pH	7.25 ± 0.02 (4)	7.26 ± 0.04 (4)		

* Figures in parentheses refer to number of observations in each category.

TABLE III

Ventilatory volume, oxygen intake and respiratory quotient during heavy exercise and recovery *

	Exercise	Recovery I*	Recovery II	Recovery III
Ventilation, *L./min. (BTPS)*	73.50 ± 10.43 (54)†	46.46 ± 8.07 (12)	27.93 ± 6.69 (12)	18.28 ± 4.74 (9)
Respiratory rate/*min.*	31 ± 9 (42)	26 ± 6 (10)	23 ± 5 (10)	21 ± 7 (7)
Tidal volume, *Liters (BTPS)*	2.50 ± 0.67 (42)	1.85 ± 0.46 (10)	1.33 ± 0.42 (10)	0.95 ± 0.19 (7)
Oxygen intake, *L./min. (STPD)*	2.81 ± 0.39 (54)	1.08 ± 0.19 (11)	0.59 ± 0.13 (11)	0.45 ± 0.03 (9)
Oxygen intake, *ml./Kg./min. (STPD)*	38.7 ± 5.2 (54)	14.6 ± 2.4 (11)	8.0 ± 0.8 (11)	6.2 ± 0.7 (9)
Respiratory quotient	1.05 ± 0.10 (54)	1.37 ± 0.09 (11)	1.16 ± 0.15 (11)	0.85 ± 0.10 (9)

* The first recovery period is 1 to 2 minutes after cessation of exercise, the second is 4 to 5 minutes, and the third 9 to 10 minutes after cessation.
† Figures in parentheses refer to number of observations in each category.

TABLE IV

Blood gas and pH measurements during heavy exercise and during recovery *

		Exercise	Recovery I	Recovery II	Recovery III
Brachial artery	pO_2 (*mm. Hg*)	86 ± 14 (34)†	87 ± 9 (6)	90 ± 13 (6)	82 ± 10 (5)
	O_2 Sat. (%)	93.3 ± 5.2 (31)	91.8 ± 5.7 (8)	90.6 ± 6.0 (8)	92.7 ± 4.3 (7)
	pCO_2 (*mm. Hg*)	40 ± 6 (23)	36 ± 6 (8)	33 ± 8 (8)	32 ± 7 (7)
	Plasma CO_2 (*mEq./L.*)	20.4 ± 2.1 (25)	15.0 ± 2.4 (8)	13.5 ± 3.7 (8)	14.3 ± 3.6 (7)
	pH	7.28 ± 0.05 (32)	7.20 ± 0.03 (8)	7.19 ± 0.06 (8)	7.23 ± 0.07 (7)
Brachial vein	pO_2 (*mm. Hg*)	24 ± 8 (18)	26 ± 7 (9)	32 ± 7 (11)	34 ± 15 (7)
	O_2 Sat. (%)	25.0 ± 9.8 (19)	39.8 ± 14.5 (9)	49.0 ± 15.7 (10)	48.3 ± 9.1 (7)
	pCO_2 (*mm. Hg*)	71 ± 13 (15)	75 ± 16 (9)	62 ± 22 (10)	51 ± 10 (7)
	Plasma CO_2 (*mEq./L.*)	26.9 ± 2.2 (15)	23.0 ± 2.0 (9)	20.2 ± 3.5 (10)	18.4 ± 3.4 (7)
	pH	7.21 ± 0.12 (22)	7.06 ± 0.12 (10)	7.11 ± 0.13 (11)	7.15 ± 0.14 (8)
Femoral vein	pO_2 (*mm. Hg*)	25 ± 9 (24)	34 ± 8 (13)	38 + 12 (13)	32 ± 12 (11)
	O_2 Sat. (%)	24.6 ± 6.6 (27)	47.0 ± 12.3 (12)	55.9 ± 11.7 (13)	48.8 ± 11.5 (11)
	pCO_2 (*mm. Hg*)	83 ± 11 (21)	82 ± 13 (12)	56 ± 11 (13)	53 ± 9 (11)
	Plasma CO_2 (*mEq./L.*)	27.6 ± 2.2 (20)	22.3 ± 2.8 (12)	17.6 ± 3.6 (13)	18.1 ± 3.9 (11)
	pH	7.13 ± 0.08 (28)	7.01 ± 0.09 (13)	7.07 ± 0.09 (13)	7.11 ± 0.09 (11)
Internal jugular vein	pO_2 (*mm. Hg*)	30 ± 7 (4)	29 ± 6 (4)	29 ± 9 (3)	27 ± 11 (4)
	O_2 Sat. (%)	60.3 ± 3.8 (4)	55.2 ± 6.5 (4)	40.8 ± 10.8 (3)	41.3 ± 20.0 (4)
	pCO_2 (*mm. Hg*)	52 ± 4 (4)	53 ± 3 (4)	57 ± 1 (3)	53 ± 4 (4)
	Plasma CO_2 (*mEq./L.*)	24.2 ± 2.1 (4)	21.4 ± 1.8 (4)	20.9 ± 1.4 (3)	21.7 ± 1.5 (4)
	pH	7.26 ± 0.04 (4)	7.19 ± 0.01 (4)	7.17 ± 0.06 (4)	7.19 ± 0.02 (4)

* The stages of recovery are the same as in Table III.
† Figures in parentheses refer to number of observations in each category.

where

S = solubility factor at 37.5°,
= 0.0304 (25), and

pK′ = factor determined for each value of pH from a nomogram (26).

After the resting determinations were complete, one of two experimental plans was followed. In the first procedure, the subjects were exercised at three increasing workloads with a 10 to 15 minute rest period between each load. Exercise loads were augmented either by increasing the speed or by raising the grade of the treadmill (or by doing both). The three grades included that which had previously produced the maximal oxygen intake. The subjects were exercised for 2.5 minutes at each workload. During the first 1.5 minutes the Douglas bag was flushed with the subject's expired air. During the last minute of the exercise period, expired air was collected and blood samples were drawn from all three sites. After completion of the run, the patient

TABLE V

Ventilatory volume, oxygen intake, cardiac output and "central" blood volume at rest and during three levels of exercise leading to that producing maximal oxygen intake *

	Rest	Exercise I	Exercise II	Exercise III
Ventilation, *L./min. (BTPS)*	10.27 ± 1.19 (11)*	72.64 ± 8.15 (16)	84.94 ± 12.82 (16)	94.91 ± 15.55 (14)
Respiratory rate/*min.*	18 ± 5 (9)	30 ± 5 (16)	34 ± 7 (16)	37 ± 7 (14)
"Central" blood volume, *Liters*	1.65 ± 0.21 (15)	3.09 ± 0.63 (15)	3.15 ± 0.63 (15)	3.52 ± 0.71 (14)
Cardiac output, *L./min.*	5.5 ± 0.9 (15)	21.4 ± 5.4 (15)	21.6 ± 4.3 (15)	23.3 ± 6.0 (14)
Pulse rate/*min.*	88 ± 16 (14)	179 ± 9 (15)	188 ± 9 (15)	190 ± 9 (10)
O_2 intake, *L./min. (STPD)*	0.33 ± 0.05 (11)	2.80 ± 0.25 (16)	3.12 ± 0.34 (16)	3.26 ± 0.43 (14)

* Figures in parentheses refer to number of observations in each category.

rested for 10 to 15 minutes and the study was repeated two more times at higher workloads.

In the second study, carried out at a later date, resting determinations were made and the subjects were exercised for 2.5 minutes at a workload near that producing maximal oxygen intake. Again, the gas and blood collections were carried out during the last minute of the run. After completion of the run, the subject remained standing on the treadmill and recovery studies were performed. Expired air and blood samples from the various sites were collected 1 to 2 minutes, 4 to 5 minutes and 9 to 10 minutes after stopping the treadmill.

In 16 subjects, so-called central blood volume, cardiac output, pulse rate, ventilation, respiratory rate and oxygen intake were studied at rest and at three increasing levels of work. For measurement of central blood volume and cardiac output, 10 mg. of Evans blue dye (T-1824) was delivered at the end of the catheter in the brachial vein of the stationary arm 1.5 minutes after the beginning of exercise. Arterial blood samples were collected from the brachial artery of the same arm at one second intervals using an electrically operated collector or a manual collection device. The dye content of the blood was determined spectrophotometrically. Central blood volume and cardiac output were calculated from the dye dilution curves by the method of Hamilton, Moore, Kinsman and Spurling (27). Expired air was collected simultaneously. Pulse rate was measured electrocardiographically by means of a bipolar precordial lead using needle electrodes at V_1 and V_5 positions, the left hand being grounded.

RESULTS

The mean values for ventilation (BTPS), respiratory rate, mean tidal volume (BTPS), oxygen intake (STPD) and respiratory quotient at rest and during three increasing levels of heavy exercise are shown in Table I (first experimental plan). In Table II, the corresponding changes in arterial and venous blood gases and pH are set out.

The values obtained in the second experimental plan (work and recovery) are shown in Tables III and IV. It will be noted that the exercise data for all subjects at the first level of exercise (near maximal oxygen intake) were utilized in both experimental plans.

In Table V, the mean "central" blood volume, cardiac output and pulse rate at rest and during three subsequent increased workloads with corresponding values for ventilation and respiratory rate are given.

DISCUSSION

These data, and those published previously by our group (21), show clearly that arterial pO_2 does not decline during heavy exercise. In actual fact, there seems to be a slight increase in mean values for arterial pO_2 as exercise loads are made progressively heavier (Table II), and little further change occurs during recovery (Table IV). The discrepancy between these results and those of Lilienthal, Riley, Proemmel and Franke (28) may be attributable to differences in methods or to the level of exercise used.

In Table II, a slight drop in arterial oxygen *saturation* during heavy exercise is seen, a result similar to that reported by Hickam, Pryor, Page

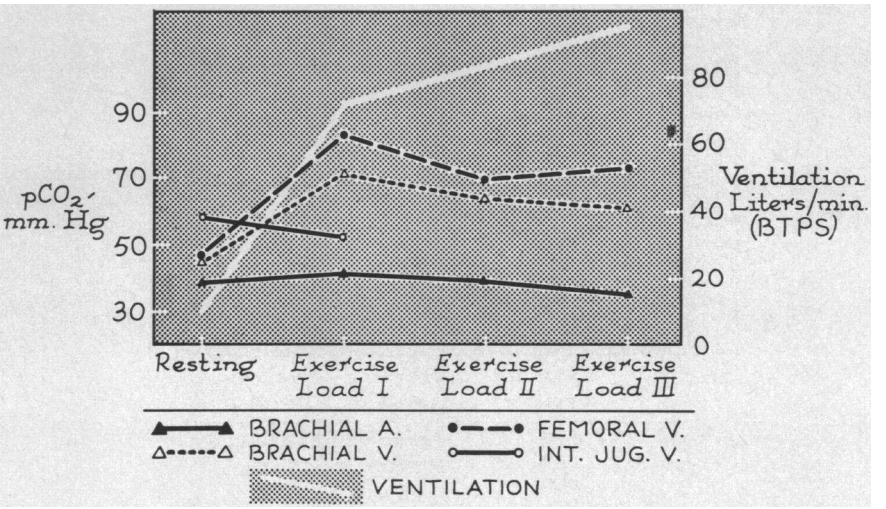

FIG. 1. ARTERIAL AND VENOUS pCO_2 AT REST AND DURING INCREASINGLY HEAVY EXERCISE LOADS AT OR NEAR THAT PRODUCING MAXIMAL OXYGEN INTAKE

Clear line in background indicates course of total ventilation in liters per minute.

and Atwell (14), and by Asmussen and Nielsen (29). A further decline occurs during the first few minutes of recovery (Table IV). The explanation for the divergent behavior of arterial oxygen saturation, as compared with arterial pO_2, has to do in part with changes in arterial pH as shown previously (21).

The behavior of venous pO_2 during progressive exercise loads is also shown in Table II. The differences noted in brachial, femoral and internal jugular venous pO_2 are not significantly different statistically. Whether or not internal jugular venous pO_2 can be taken to represent tissue pO_2 in the respiratory center is doubtful (30) but there is no reason to suppose that exercise produces hypoxia in the respiratory center cells, especially since arterial pO_2 is normal or even elevated during heavy exercise. During recovery, the brachial and femoral venous pO_2 both appear to increase (Table IV) but internal jugular venous pO_2 remains relatively constant.

The original Haldane view on the chemical control of respiration, which by inference invokes changes in arterial pCO_2 during exercise, receives no support (insofar as heavy exercise is concerned) from the present data (Table II and Fig-

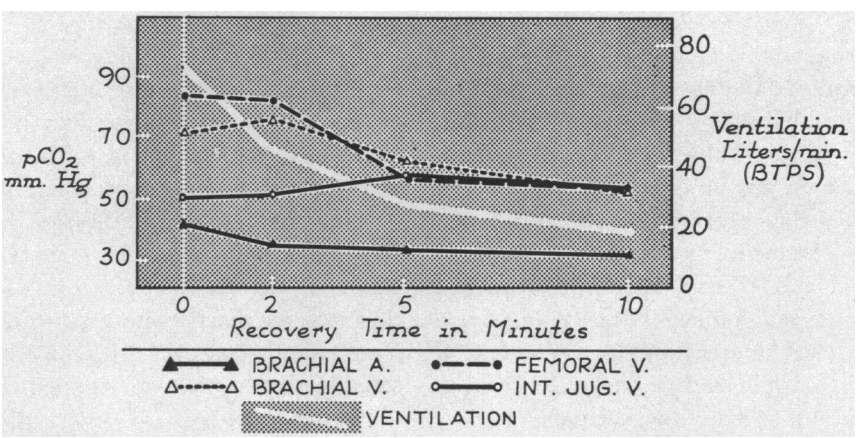

FIG. 2. CHANGES IN ARTERIAL AND VENOUS pCO_2 AFTER CESSATION OF HEAVY EXERCISE

Clear line in background indicates course of total ventilation in liters per minute.

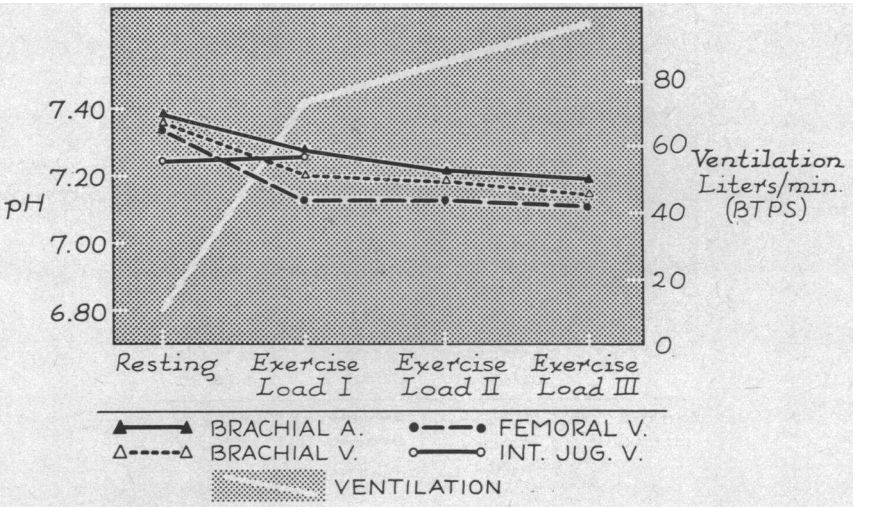

FIG. 3. ARTERIAL AND VENOUS pH AT REST AND DURING INCREASINGLY HEAVY EXERCISE LOADS AT OR NEAR THAT PRODUCING MAXIMAL OXYGEN INTAKE

ure 1) or from the work of Asmussen and Nielsen (29). The study by Filley, Gregoire and Wright (15), who employed the Riley microbubble method, also fails to demonstrate increase in arterial pCO_2 during exercise. The marked increase in ventilation that occurs with heavy exercise cannot, therefore, be due to increased arterial pCO_2. The present study, however, does not rule out the possibility of a change in the CO_2 sensitivity of the respiratory center, but the report by Hickam and co-workers (14) is opposed to it. After the cessation of exercise, arterial pCO_2 decreases below the resting value at a time when ventilation is still increased (Table IV and Figure 2).

Brachial and femoral venous pCO_2 rise markedly during heavy exercise (Table II and Figure 1), the values nearly doubling at the first exercise load and falling slightly as loads are further increased. The resting value for internal jugular venous pCO_2, with the subject standing, is considerably higher than that in the two other systemic veins. The actual mean values were 58 compared to 45 and 47 mm. Hg for the brachial and femoral venous values. During a single heavy exercise load, internal jugular venous pCO_2 was stationary, or fell slightly, instead of rising markedly as it did in the other venous samples. The absence of significant change in jugular venous pCO_2 during heavy exercise is hardly in keeping with the idea that tissue CO_2 tension in the respiratory center rises during exercise unless changes in cerebral blood flow, or other factors, render jugular venous pCO_2 invalid as a guide to CO_2 tension in the respiratory center itself. During recovery from heavy exercise, brachial and femoral venous pCO_2 fell markedly, roughly paralleling the decline in ventilation (Table IV and Figure 2). There was no significant change in the values for internal jugular venous pCO_2 during this period.

It is well established that arterial pH decreases during heavy exercise and that the pH changes are more marked after the cessation of exercise (17, 18). In this study, arterial pH declined, and ventilation increased, during the performance of three exercise loads of increasing severity. During these periods of exercise, an inverse relation between arterial pH and ventilation seemed to exist (Table II and Figure 3). The relation is probably not, by itself, a causal one, since during recovery from exercise it breaks down completely (Table IV and Figure 4). Shortly after the cessation of exercise, arterial pH declined still further and remained quite low for 9 to 10 minutes. Ventilation, however, declined strikingly and steadily after work was stopped.

Brachial and femoral venous pH changes were more marked during three progressive exercise loads than corresponding changes in arterial blood (Table II and Figure 3), the main drop occurring

between the resting value and the first exercise load. The pH changes on the venous side were presumably due to the combined effect of increased anaerobic metabolites and increased pCO_2. Internal jugular venous pH at rest, with the patient standing, was lower than brachial or femoral, the mean value being 7.25 compared to 7.36 and 7.35, respectively. Internal jugular venous pH did not decrease during an initial exercise load but was not measured during progressive exercise loads. During recovery from heavy exercise, brachial and femoral venous pH continued to decline for a few minutes, then began to rise slowly (Table IV and Figure 4). As in the case of arterial pH, the continued fall in brachial and femoral venous pH after cessation of exercise when ventilation was rapidly returning to normal is opposed to the possibility of an inverse relation between these two variables. Internal jugular venous pH decreased only slightly after the cessation of exercise.

"Central" blood volume, as calculated from dye dilution curves by the Hamilton method, was found to increase more or less in a parallel fashion with ventilation as exercise loads of increasing severity were performed. Further evidence on this point was provided by Nowy, Kikodse and Zöllner (31) who, using the same method, also found a slight increase in "central" blood volume in some subjects during light exercise. Whether or not augmentation of "central" blood volume causes increase in ventilation by stimulation of stretch receptors has not been clearly answered. Harrison, Harrison, Calhoun and Marsh (10) have postulated the existence of such receptors, and Yeomans, Porter and Swank (32) produced hyperpnea by means of rapid intravenous infusions. Mills (33) produced hyperpnea by suddenly releasing blood which had been trapped in veins of the legs and suggested that the effect was due to the stimulation of stretch receptors located at the pulmonary capillary level. Asmussen and Nielsen (20) produced more marked increases in ventilation by the release of blood trapped in the legs during exercise but thought the phenomenon to be due to a chemical agent rather than to a volume change. All this work, and the data reported above, are in keeping with the possibility that increased central blood volume, estimated by the dilution technique, may produce an increase in ventilation. The question, however, is far from settled. The reliability of the dilution method for estimating central blood volume, especially when cardiac output is high, is open to question. The main difficulty has to do with errors in extrapolation of dilution curves. This error, as pointed out by Rapaport, Kuida, Haynes and Dexter (34), affects calculation of central blood volume relatively more than cardiac output. It is also probable that the repeatability of the method declines at high output levels. The data presented, however, establish a directional change, indicating an increase in some aspect of central blood volume as ventilation and cardiac output rise.

It seems impossible, therefore, to attribute the hyperpnea of exercise to change of pCO_2, pH, or

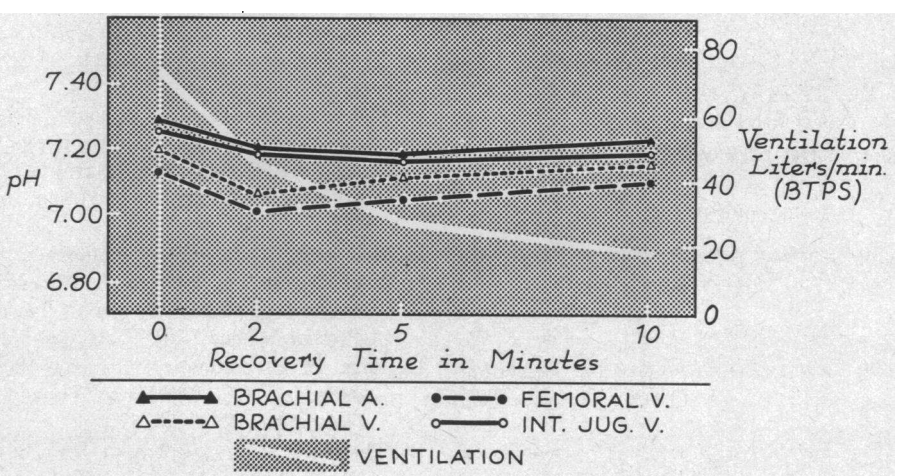

FIG. 4. CHANGES IN ARTERIAL AND VENOUS pH AFTER CESSATION OF HEAVY EXERCISE

pO_2 in the arterial blood. On the venous side, brachial and femoral pCO_2 roughly parallel changes in ventilation during exercise and recovery but tend to fall off as exercise loads of increasing severity are performed. Also, in the recovery period, one to two minutes after exercise, these values remain elevated when ventilation is decreasing. The absence of significant change in jugular venous pCO_2 is opposed to the idea that tissue CO_2 tension in the respiratory center rises during exercise if it be accepted that jugular venous pCO_2 reflects that in the respiratory center itself. The behavior of pCO_2 at the various venous sites, including the internal jugular, does not rule out the possibility that pCO_2 of mixed venous blood parallels, and indeed in part determines, changes in ventilation brought about by heavy exercise. Such a cause and effect relationship would require the presence of CO_2 receptors in the lungs or right heart, a possibility that has been suggested by Pi Suñer (35) but which was not tested in the present study. This possibility, and that having to do with change in "central" blood volume, seem to constitute the most fruitful areas for future studies.

CONCLUSIONS

Arterial pO_2 does not decline significantly during heavy exercise and cannot, therefore, be responsible for the hyperpnea. Neither is there a significant increase in arterial pCO_2. Changes in arterial pH do not bear a predictable relation to changes in ventilation during exercise and recovery. Of the remaining possibilities, changes in mixed venous pCO_2 and in "central" blood volume may be factors involved in the production of hyperpnea during heavy muscular exercise but cannot yet be designated with assurance as the cause or causes of the phenomenon.

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BIBLIOGRAPHY

1. Haldane, J. S., and Priestley, J. G. The regulation of the lung-ventilation. J. Physiol. (Lond.) 1905, **32**, 225.
2. Douglas, C. G., and Haldane, J. S. The capacity of the air passages under varying physiological conditions. J. Physiol. (Lond.) 1912–13, **45**, 235.
3. Douglas, C. G. Pulmonary function: Historical *in* Handbook of Respiratory Physiology, W. M. Boothby, Ed. Project No. 21-2301-0003, USAF School of Aviation Medicine, 1954, p. 1.
4. Comroe, J. H., Jr. The hyperpnea of muscular exercise. Physiol. Rev. 1944, **24**, 319.
5. Grodins, F. S. Analysis of factors concerned in regulation of breathing in exercise. Physiol. Rev. 1950, **30**, 220.
6. Christensen, H. The chemical and nervous control of respiration *in* Handbook of Respiratory Physiology, W. M. Boothby, Ed. Project No. 21-2301-0003, USAF School of Aviation Medicine, 1954, p. 103.
7. Krogh, A., and Lindhard, J. The regulation of respiration and circulation during the initial stages of muscular work. J. Physiol. (Lond.) 1913, **47**, 112.
8. Harrison, W. G., Jr., Calhoun, J. A., and Harrison, T. R. Afferent impulses as a cause of increased ventilation during muscular exercise. Amer. J. Physiol. 1932, **100**, 68.
9. Comroe, J. H., Jr., and Schmidt, C. F. Reflexes from the limbs as a factor in the hyperpnea of muscular exercise. Amer. J. Physiol. 1943, **138**, 536.
10. Harrison, T. R., Harrison, W. G., Calhoun, J. A., and Marsh, J. P. Congestive heart failure. XVII. The mechanism of dyspnea on exertion. Arch. intern. Med. 1932, **50**, 690.
11. Kao, F. F., Schlig, B. B., and Brooks, C. McC. Regulation of respiration during induced muscular work in decerebrate dogs. J. appl. Physiol. 1955, **7**, 379.
12. von Euler, U. S., and Liljestrand, G. The regulation of respiration during muscular work. Acta physiol. scand. 1946, **12**, 268.
13. Bannister, R. G., Cunningham, D. J. C., and Douglas, C. G. The CO_2 stimulus to breathing in severe exercise. J. Physiol. (Lond.) 1954, **125**, 90.
14. Hickam, J. B., Pryor, W. W., Page, E. B., and Atwell, R. J. Respiratory regulation during exercise in unconditioned subjects. J. clin. Invest. 1951, **30**, 503.
15. Filley, G. F., Gregoire, F., and Wright, G. W. Alveolar and arterial oxygen tensions and the significance of the alveolar-arterial oxygen tension difference in normal men. J. clin. Invest. 1954, **33**, 517.
16. Bannister, R. G., and Cunningham, D. J. C. The effects on the respiration and performance during exercise of adding oxygen to the inspired air. J. Physiol. (Lond.) 1954, **125**, 118.
17. Barr, D. P. Studies in the physiology of muscular exercise. IV. Blood reaction and breathing. J. biol. Chem. 1923, **56**, 171.
18. Turrell, E. S., and Robinson, S. The acid-base equilibrium of the blood in exercise. Amer. J. Physiol. 1942, **137**, 742.

19. Henderson, Y. Adventures in Respiration. Baltimore, Williams and Wilkins, 1938.
20. Asmussen, E., and Nielsen, M. The effect of autotransfusion of "work-blood" on the pulmonary ventilation. Acta physiol. scand. 1950, **20**, 79.
21. Mitchell, J. H., Sproule, B. J., and Chapman, C. B. The physiological meaning of the maximal oxygen intake test. J. clin. Invest. 1958, **37**, 538.
22. Dill, D. B., and Fölling, A. Studies in muscular activity. II. A nomographic description of expired air. J. Physiol. (Lond.) 1928, **66**, 133.
23. Sproule, B. J., Miller, W. F., Cushing, I. E., and Chapman, C. B. An improved polarographic method for measuring oxygen tension in whole blood. J. appl. Physiol. 1957, **11**, 365.
24. Van Slyke, D. D., and Sendroy, J., Jr. Studies of gas and electrolyte equilibria in blood. XV. Line charts for graphic calculations of the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. biol. Chem. 1928, **79**, 781.
25. Severinghaus, J. W., Stupfel, M., and Bradley, A. F. Accuracy of blood pH and pCO_2 determinations. J. appl. Physiol. 1956, **9**, 189.
26. Severinghaus, J. W., Stupfel, M., and Bradley, A. F. Variations of serum carbonic acid pK′ with pH and temperature. J. appl. Physiol. 1956, **9**, 197.
27. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Amer. J. Physiol. 1932, **99**, 534.
28. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D., and Franke, R. E. An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. Amer. J. Physiol. 1946, **147**, 199.
29. Asmussen, E., and Nielsen, M. Studies on the regulation of respiration in heavy work. Acta physiol. scand. 1946, **12**, 171.
30. Turner, J., Lambertsen, C. J., Owen, S. G., Wendel, H., Chiodi, H., and Linaweaver, P. Inadequacy of cerebral venous pO_2 as an index of mean brain tissue oxygen tension: Influence of changes in arterial pO_2 upon cerebral venous and calculated mean capillary oxygen tension at fixed reduced arterial pCO_2 (abstract). Fed. Proc. 1958, **17**, 165.
31. Nowy, H., Kikodse, K., and Zöllner, N. Über Bestimmungen des Herzminutenvolumens und zentralen Blutvolumens in Ruhe und bei körperlicher Arbeit mit Hilfe der Farbstaffmethode. Z. Kreisl-Forsch. 1947, **46**, 382.
32. Yeomans, A., Porter, R. R., and Swank, R. L. Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. J. clin. Invest. 1943, **22**, 33.
33. Mills, J. N. Hyperpnoea in man produced by sudden release of occluded blood. J. Physiol. (Lond.) 1944, **103**, 244.
34. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L. The pulmonary blood volume in mitral stenosis. J. clin. Invest. 1956, **35**, 1393.
35. Pi Suñer, A. The regulation of the respiratory movements by peripheral chemo-receptors. Physiol. Rev. 1947, **27**, 1.