STUDIES IN CONGESTIVE HEART FAILURE.

XIII. THE RELATION OF DYSPNEA OF EXERTION TO THE OXYGEN SATURATION AND ACID-BASE CONDITION OF THE BLOOD^{1, 2}

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(Received for publication June 18, 1931)

In a previous study (Harrison, Turley, Jones and Calhoun (1931)) it has been shown that the degree of dyspnea produced by muscular effort is directly proportional to the ventilation and inversely proportional to the vital capacity. For a constant amount of exertion this

ratio $\frac{\text{Ventilation}}{\text{Vital Capacity}}$ was higher for patients with cardiac disease than for normal subjects. These results involve two problems:

(1) Why does the individual with cardiac disease usually ventilate more than the normal does for the same exertion?

(2) How does decreased vital capacity tend to produce dyspnea?

The most generally accepted theory of respiratory control is that the increase in ventilation must be due to either an increased hydrogen ion concentration or increased CO₂ tension of the blood or respiratory center or of both. This in turn is supposed to be caused by insufficient aeration of the tissues or respiratory center because of decrease in cardiac output. In support of this are the conclusions of Sir James MacKenzie (1925), Means (1924), and Meakins and Davies (1925), that cardiac dyspnea is due to decreased blood flow through the brain.

If these views are correct it should be possible to find changes in oxygen saturation and acid-base condition in the blood, especially in the blood flowing through the brain. The present paper presents the

¹ Aided by a grant from the National Research Council.

² Presented in abstract at the Meetings of the Federation of American Societies of Experimental Biology, April 9, 1931, at Montreal, Canada.

results of a study of these variables made with modern methods upon a series of patients with cardiac dyspnea.

EXPERIMENTAL

Plan. The study included analysis of blood for O₂ capacity and content, of blood serum for pH and total CO₂ content; the determination of the ventilation of the subject, before, during and after a fixed amount of exertion; and the determination of the vital capacity. The source of blood varied as the work progressed. The first series was done on venous blood from the arm, the second series on arterial blood from the brachial artery and the third series on venous blood from the internal jugular vein. The details of blood sampling and the results for each series are grouped in accordance with the source, i.e., arm vein, brachial artery and internal jugular vein.

Subjects. The subjects studied included seven normal males between the ages of twenty-five and forty, and twelve patients with cardiac disease of various types (usually hypertensive or syphilitic) in various stages. Some of the patients had only slight symptoms, others had had repeated breaks in compensation. The patients were classified according to the degree of cardiac disease, "+" refers to those individuals whose only symptom was dyspnea on exertion, "++" and "+++" designate respectively subjects with slight and moderate degrees of congestive failure.

Blood Analyses. Approximately twenty to twenty-five cubic centimeters of blood were taken (the syringe containing mineral oil) for each sample. Part of this—six to eight cubic centimeters—was expelled into a small bottle containing sodium oxalate and mineral oil. This was used for determination of oxygen content and capacity by the Van Slyke-Neill technique (1924). The remainder of the blood was placed in a centrifuge tube under oil, the oil was replaced by melted paraffin, and the tube centrifuged. After centrifuging 20 to 30 minutes, mineral oil was run over the paraffin plug, the plug removed and the serum removed with a pipette containing oil to a Pyrex tube containing oil. The hydrogen ion concentration of the serum was determined by Cullen's method (1922) using the refinements reported by Earle and Cullen (1929). All readings were made at 20° C. in a constant temperature room with constant ("Daylight") source of light and were corrected to

38° by subtracting 0.23 pH. All readings were made independently by two observers. In addition to the values read against the phosphate color standards, the individual tubes of each series were compared against each other so that with these checks a difference of 0.02 pH may certainly be considered as true difference. The carbon dioxide content of the serum was determined by the manometric extraction apparatus of Van Slyke and Neill (1924).

Carbon dioxide tensions were calculated from the Hasselbalch formula (1912), using Van Slyke and Sendroy's (1927) absorption coefficients and a pK' value of 6.10.

Ventilation. These findings were obtained with a Tissot spirometer which was connected to a fairly comfortable face mask with the regular arrangement of valves. The vital capacity was measured on a Benedict-Roth spirometer.

A. The findings in the venous blood obtained from the arm.
(Tables 1 and 2.)

Procedure. The observations were made in the resting post-absorptive state. The subject came to the laboratory without breakfast and rested in a comfortable chair for ten or more minutes. A face mask was applied and the expired air was collected for a five minute period. Venipuncture at the elbow was then performed, after injection of novacaine into the subcutaneous tissue, with a needle which had a well fitting stilette. (For this purpose a sixteen gauge lumbar puncture needle was cut off to a length of about 4 cm. and re-sharpened.) Stasis was usually necessary for the puncture. After the needle was well in the vein the tourniquet was removed, the stilette inserted, and the needle fixed in place with small strips of adhesive plaster. Several minutes later blood was drawn into a syringe containing mineral oil, no stasis whatever being used. The subject then stood up and walked up and across and down from a platform two steps high and 64 cm. broad at a rate of one "round-trip" in twenty seconds for two minutes. [More complete details of the exercise are given in the previous paper by Harrison, Turley, Jones and Calhoun (1931). The exercise referred to in the present paper as "mild" is the exercise I of their paper, whereas "moderate" exercise is the exercise III of their paper.] He then sat down and a second blood sample was taken immediately.

A record was kept of the time at which the blood first appeared in the syringe and of that at which the sample was completed. It was usually possible to obtain the necessary twenty cubic centimeters of blood within the first minute after the end of the exercise. The ventilation was measured for each minute of the exercise and for each of the succeeding five minutes. The value in the table for "ventilation after exercise" refers to the ventilation during the minute in which the blood was obtained, while the value for resting ventilation is the average of the five minute fore-period.

In all subjects the first exercise performed was slight, almost equivalent to walking at a slow pace. Severer exercise was usually not done by the patients, but several of the normals repeated the performance at a faster rate (one "round-trip" over the platform and back in seven and one half seconds) this being equivalent to rapid walking. Immediately after this exercise a third blood sample was taken.

In this technique of obtaining venous blood three points are emphasized.

(a) There was absolutely no stasis present during the sampling.

(b) No pain was experienced when the sample was drawn. For this reason psychic factors due to pain can be excluded. In this entire study whenever the subject was disturbed by pain incidental to blood sampling, or when there was any evidence of apprehension or other psychic disturbance the experiment was abandoned.

(c) The arm did not partake of the exercise.

Results

Ventilation. That the exercise employed in this series is sufficient to markedly increase the ventilation is evident from the tables. The normals increased their ventilation from 18 to 104 per cent while the patients increased their ventilation from 32 to 121 per cent. This increase in both groups is sufficiently great so that chemical changes of sufficient magnitude to account for it should be detectable.

Oxygen saturation. The range of oxygen unsaturation in volumes per cent O_2 i.e., the O_2 utilized during capillary flow varies over the same range in the cardiac patient as in the normal both at rest and following exercise. The average increase for exercise (Table 1) for the normals was only 0.5 volume per cent O_2 and for the patients only

TABLE 1

The ventilation and acid-base condition of venous blood of the arm at rest and after mild exercise

Subject	Date	Diagnosis	Degree of cardiac disease*	Control period—rest						After mild exercise						Change from resting value after mild exercise					
				Vital capacity per square meter	O ₂ capacity	Ventilation		O ₂ unsaturation	Serum CO ₂ content	CO ₂ tension	pH	Ventilation per minute per square meter	O ₂ unsaturation	Serum CO ₂ content	CO ₂ tension	pH	Ventilation increase per minute per square meter	O ₂ unsaturation	Serum CO ₂ content	CO ₂ tension	pH
						liters	volumes per cent														
	1980			liters	volumes per cent	volumes per cent	volumes per cent	mm. Hg		liters	volumes per cent	volumes per cent	mm. Hg		liters	volumes per cent	volumes per cent	mm. Hg			
T. R. H.	Nov. 10	Normal	0	2.57	18.00	3.46	6.74	62.5	35.7	7.50	6.41	4.56	61.4	32.1	7.54	2.95	+2.18	-1.1	-3.6	+0.04	
J. A. C.	Oct. 29	Normal	0	2.28	17.65	3.07	4.18	67.1	40.9	7.47	6.27	4.07	67.6	37.7	7.51	3.20	+0.11	+0.5	-1.1	+0.04	
G. E. C.	Oct. 22	Normal	0	1.99	18.58	3.75	6.06	68.2	43.5	7.45	6.61	8.23	69.7	43.5	7.46	2.86	-2.17	+1.5	0	+0.01	
W. E. W.	Oct. 21	Normal	0	2.38	19.10	4.28	4.45	66.5	38.8	7.49	6.23	5.42	66.1	38.5	7.49	1.95	-0.97	-0.4	-0.3	0	
E. J.	Oct. 21	Normal	0	2.18	16.88	3.07	4.23	67.6	47.1	7.41	4.65	5.93	68.8	42.8	7.46	1.58	-1.70	+1.2	-4.8	+0.05	
J. T. J.	Nov. 18	Syphilitic aortic insufficiency	+	1.45	16.05	4.72	5.15	63.4	37.0	7.49	10.45	5.27	63.8	37.2	7.49	5.73	-0.12	+0.4	+0.2	0	
L. C.	Nov. 3	Hypertension	+	1.34	13.88	3.54	5.15	62.8	38.3	7.48	6.80	5.15	64.9	38.7	7.49	3.26	0	+2.1	+0.4	+0.01	
A. C.	Oct. 31	Hypertension	+	1.63	16.55	6.31	6.73	75.0	45.7	7.47	8.16	8.31	77.6	46.2	7.48	1.85	-1.58	+2.6	+0.5	+0.01	
A. B.	Nov. 12	Syphilitic aortic insufficiency	++	1.59	14.12	4.98	2.97	63.7	38.0	7.48	7.53	5.17	61.8	34.0	7.50	2.55	+2.20	-1.9	-4.0	+0.02	
R. J.	Nov. 6	Hypertension	++	1.59	14.85	3.38	6.37	7.20	42.0	7.49	7.48	5.64	71.7	40.9	7.50	4.10	+0.73	-0.3	-1.1	+0.01	
W. C.	Oct. 28	Hypertension	++	1.27	15.10	4.40	5.65	60.3	32.2	7.53	9.30	7.83	62.0	33.9	7.52	4.90	-2.18	+1.7	+1.7	-0.01	

* See text.

TABLE 2

Change from resting value produced by moderate exercise

(Six of the experiments with mild exercise reported in Table 1 were continued with moderate exercise resulting in the changes tabulated in this table.)

Subject	Ventilation increase per minute per square meter	Oxygen unsaturation	Serum CO ₂ content	CO ₂ tension	pH
	<i>liters</i>	<i>volumes per cent</i>	<i>volumes per cent</i>	<i>mm. Hg</i>	
T. R. H.	5.42	+2.79	-1.9	-3.3	+0.03
J. A. C.	4.17	+1.33	-3.2	-1.1	+0.02
G. E. C.	7.21	-3.64	+2.0	+1.8	0
W. E. W.	4.96	—	-2.8	+0.9	-0.03
L. C.	9.14	+0.42	+1.9	+3.8	-0.03

0.9 volume per cent. The results for oxygen utilization afford no adequate explanation for the marked increase in ventilation.

Carbon dioxide content of the serum. The range for the patients was greater than for the controls but all values were within normal limits. The mean values were almost exactly the same for the two groups. It is evident that these patients showed no evidence of diminished alkaline reserve, and hence that the difference in ventilation cannot be ascribed to changes in bicarbonate content.

As a matter of fact, in review of the eleven observations, the CO₂ content was slightly *greater* after exercise and the average figures were an *increase* of 0.3 volume per cent for the normal and 0.8 volume per cent for the cardiac.

Hydrogen ion concentration of the serum. At rest the values were on the average slightly more alkaline in the patients than in the controls, but here again overlapping occurred and with one exception all were within the normal limits of pH, reported for normal individuals in Nashville by Earle and Cullen (1929). After mild exercise four of the five normal subjects had an increase in pH, the fifth showing no change. Of the six patients, four had a slight rise in pH, one a slight decrease and one no change. After mild exercise the pH was on the average 0.03 more alkaline in the normals and 0.01 more alkaline in the patients than in the control determinations. After moderate exercise the normal subjects were often slightly more alkaline—average 0.01—than in the control period.

From these results it is clear that such differences in pH as were found after exercise must be looked on as *effects* rather than causes of the changes observed in ventilation.

Carbon dioxide tension of the serum. The resting values were usually somewhat lower in the patients, the average being 39 mm. as opposed to 41 mm. in the normals. However, two of the patients had values above the average for the normals and one of the controls had a value below the average for the patients. After mild exercise the carbon dioxide tension of the normal subjects was decreased in three instances and practically unchanged in two. In the patients the carbon dioxide tension was decreased in two, increased in one, and practically unchanged in three observations. (Differences of less than 1.0 mm. are almost certainly not significant as an error of 0.2 volume per cent in carbon dioxide content plus an error of 0.02 in pH would cause a difference of approximately 2 mm. in the calculated carbon dioxide tension. However, since the above errors are maximal for the methods used, changes of more than one millimeter are possibly significant.) The average change was -2.3 mm. in the normal subjects, and -0.4 mm. in the patients. After moderate exercise the carbon dioxide tension returned almost to the resting level.

It can therefore be stated that insofar as conclusions can be drawn from the venous blood of the arm, neither the increased ventilation after exercise in both the normal and diseased subjects, nor the increased ventilation in the latter as compared to the former under similar conditions can be attributed to changes in carbon dioxide tension. On the contrary such changes in the latter function as have been found are probably to be considered as results of increased ventilation.

B. The findings in arterial blood. (Table 3)

Plan. The observations of Haldane (1922), of Winterstein (1911), and of Hasselbalch (1912) have indicated the great importance of the hydrogen ion concentration of the arterial blood in the control of respiration. Other authors, Hooker, Wilson, and Connett (1917), and Scott (1918), have believed that the arterial carbon dioxide tension has a more or less specific function in respiratory control. Since it is possible that the absence of any definite changes in venous blood from the arm might have been due to the buffering action of the muscles of the arm it seemed necessary to study arterial blood.

TABLE 3

The ventilation and acid-base condition of arterial blood of the arm at rest and after mild exercise

Subject	Date	Diagnosis	Degree of cardiac disease*	Vital capacity per square meter	O ₂ capacity	Control period—rest					After mild exercise					Change from resting value				
						Ventilation per minute per square meter	O ₂ saturation	Serum CO ₂ content	CO ₂ tension	pH	Ventilation per minute per square meter	O ₂ saturation	Serum CO ₂ content	CO ₂ tension	pH	Ventilation change per minute per square meter	O ₂ saturation	Serum CO ₂ content	CO ₂ tension	pH
	1980			liters	volumes per cent	liters	per cent	volumes per cent	mm. Hg		liters	per cent	volumes per cent	mm. Hg		liters	per cent	volumes per cent	mm. Hg	
F. Q.	November 19	Hypertension	±	1.91	18.75	2.60	91.8	63.4	33.9	7.53	7.64	96.9	62.5	35.0	7.48	5.04	+5.1	-0.9	+1.1	-0.05
A. C.	November 25	Hypertension	+	1.76	17.92	4.30	94.6	69.2	40.4	7.49	9.56	98.7	69.1	41.1	7.48	5.26	+4.1	-0.1	+0.7	-0.01
	December 13			1.72	16.60	5.04	91.3	68.8	39.3	7.50	6.57	97.8	68.9	38.4	7.51	1.53	+6.7	+0.1	-0.9	+0.01
J. P. W.	December 15	Hypertension	+	1.74	17.80	3.44	96.0	55.4	31.6	7.50	9.03	100.0	55.1	32.2	7.49	5.59	+4.0	-0.3	+0.6	-0.01
		Arterio-sclerosis																		
R. J.	November 24	Hypertension	++	1.76	16.95	4.10	93.7	63.0	30.1	7.58	6.94	99.3	64.4	32.2	7.56	2.84	+5.6	+1.4	+2.1	-0.02
W. C.	November 21	Hypertension	++	1.54	16.82	4.70	93.0	58.0	27.1	7.59	9.03	95.7	56.1	27.9	7.56	4.33	+2.7	-1.9	+0.8	-0.03
	December 12			1.62	16.95	4.62	92.1	58.8	28.2	7.57	9.41	97.3	58.4	31.2	7.53	4.79	+5.1	-0.4	+3.0	-0.04
Al. C.	December 3	Syphilitic	++	1.28	18.12	5.52	92.9	60.9	34.0	7.51	9.10	98.8	58.1	33.1	7.50	3.58	+5.9	-2.8	-0.9	-0.01
	December 19	aortic insufficiency		1.84	18.75	4.86	96.3	57.9	33.0	7.50	10.98	98.8	55.8	29.2	7.54	6.12	+2.5	-2.1	-3.8	+0.04

* See text.

The experimental procedure was the same as that previously described except that brachial arterial punctures were done before and immediately after the exercise. The punctures were made with local anesthetic, novacaine. Whenever there was any pain or any difficulty in obtaining any sample the experiment was abandoned. Blood usually appeared in the syringe within twenty seconds after the end of the exercise and in most instances the entire sample was obtained during the first minute of the after period. The values for ventilation after exercise in the tables are those for the minute during which the blood samples were drawn.

The *oxygen capacity* of the blood was usually determined only once, a mixed sample consisting of equal parts of the blood drawn before and that drawn after exercise being used. In the one experiment in which capacity was determined both before and after exercise an increase of approximately one volume per cent was found. This is in agreement with the findings of Harrison, Robinson and Syllaba (1929), who reported increase in oxygen capacity during exercise.

The *oxygen saturation* varied between 90 and 100 per cent, all values being therefore within, or nearly within, normal limits. In most instances a small rise in oxygen content was noted after exercise. Similar results were obtained by Himwich and Loebel (1927) on normal subjects. It is evident that the changes in arterial saturation are the results rather than the cause of the increase in ventilation produced by exercise.

It was noted in the previous paragraph that pooled blood was used for the determination of the oxygen capacity. Since the oxygen capacity is greater after exercise, the effect is to increase the apparent oxygen saturation in exercise blood and to decrease it in resting blood. This effect is negligible in these experiments, but should be considered in using these data for absolute values.

The *carbon dioxide content of the serum* was unaltered (change of less than 0.2 volume per cent) twice, increased once and decreased six times. All changes were of relatively small degree. The average for the nine observations was a diminution of 0.8 volume per cent. Such a change could be explained either by a slight increase in non-volatile acid or by over-ventilation.

The *hydrogen ion concentration of the serum* was unchanged after excess exercise (change of 0.02 or less) in five instances, decreased in

three and increased in one. The mean change was a decrease of 0.01 pH which is almost the average error of the method. It is to be noted that in the resting cardiac patients there is a definite tendency toward alkalinity. This is in agreement with the observations of Fraser, Harris, Hilton and Linder (1928).

The carbon dioxide tension was not appreciably altered in five instances (change of less than one millimeter) was increased in three and decreased in one. The average change was an increase of 0.3 mm. which is much less than the error of the method.

It may be noted that there was on the average a very slight shift toward acidity as regards carbon dioxide tension and in respect to hydrogen ion concentration. These changes were so slight that in six of the nine observations, they might have been considered in any given instance as due to error. However, the question arises: could such slight changes account for the observed change in ventilation, which was usually increased by more than fifty per cent and often was more than double the resting value? Expressed otherwise this question becomes: Is the respiratory center sensitive to changes in carbon dioxide tension or hydrogen ion concentration of such small magnitude as to be scarcely detectable by our present methods? As Gesell (1925) has pointed out, that theory of respiratory control which assumes that the hydrogen ion concentration of the arterial blood is the sole or chief factor in respiratory control necessitates the assumption that such an extreme sensitivity exists. Hence, one might assume that increase in acidity of the arterial blood was the cause of the increased ventilation observed in our patients after exercise. If this be true one has to assume first that in four instances a decrease in pH of less than 0.02 was sufficient increased acidity to stimulate the center and secondly that the two cases of increased pH were due to errors in technique. Since changes in blood pH can only affect the center by resultant changes in the center itself as has been emphasized by Gesell (1925), it seems extremely unlikely that the increased ventilation in these instances was due to the changes in blood pH. However, additional attempts were made to determine the relative sensitivity of the breathing to change in arterial pH. The well known fact that ammonium chloride causes an acidosis was utilized for the following experiment.

C. *Observations on arterial blood before and after the administration of ammonium chloride*

The usual measurements of ventilation and the usual analysis of arterial blood were made on two patients in the fasting resting state. They were then given ammonium chloride by mouth, two grams every half hour for four doses and the observations were repeated. The data are seen in Table 4. Their oxygen saturations decreased, probably due to a lowering of the oxygen dissociation curve. In both patients the carbon dioxide content diminished markedly, the pH decreased and the carbon dioxide tension was also reduced. It should be noted that the decline in pH was greater than that found after the mild exercise of this study. The ventilation of both patients increased very slightly—to a much less degree than that which occurred after the exercise. Neither patient complained of any dyspnea; in fact, both volunteered the information that they felt better after taking ammonium chloride. We are forced to conclude from these observations that the respiratory center is much less sensitive to changes in hydrogen ion concentration than has been generally believed to be the case. These experiments also indicate that the slight shift toward acidity which was found in the arterial blood of some—not all—of our patients after exercise can in no sense be regarded as the cause of the marked increase in ventilation during and after exercise.

D. *Time curves of the gases in arterial blood before, during, and after exercise*

It seemed possible that blood samples obtained after exercise might not represent the state of the blood during exercise, and hence that the increase in ventilation might have been due, in the first instance, to chemical changes which were not detectable in blood drawn two to three minutes after the beginning and one-half to one minute after the end of the exertion. It might be argued that there was an immediate increase in either hydrogen ion concentration or CO₂ tension sufficient to stimulate respiration and that this increased respiration caused enough over-ventilation to bring the pH back to, or above, its initial level. The only answer to this argument appeared to lie in studying the blood continuously. The subject lay in bed. Resting ventilation was measured. The needle was then inserted in the brachial artery

TABLE 4
The effect of ammonium chloride on ventilation and on acid-base condition of arterial blood

Subject and chief diagnosis	Date	Vital capacity per square meter	Time at which blood was taken	Ventilation per minute per square meter	O ₂ capacity	O ₂ content	O ₂ saturation	Serum CO ₂ content	CO ₂ tension	pH	Remarks
E. G. Syphilitic aortic insufficiency Cardiac failure +	1980 December 20	1.86	Before NH ₄ Cl	4.04	14.28	14.05	98.4	61.9	mm. Hg 36.9	7.48	No dyspnea following NH ₄ Cl
			After 8 grams NH ₄ Cl	4.14	16.22	14.53	89.6	48.6	33.8	7.41	
A. C. Syphilitic aortic insufficiency Cardiac failure ++	December 20	1.87	Before NH ₄ Cl	4.54	15.74	14.88	94.7	58.4	30.1	7.53	No dyspnea following NH ₄ Cl
			After 8 grams NH ₄ Cl	4.84	18.40	16.70	90.8	45.4	26.6	7.49	

and a resting sample of blood was obtained. The syringe was then detached from the needle which was held *in situ* in the artery. Exercise, consisting of alternately flexing and extending the opposite thigh and leg was then performed. This exercise was continued for two minutes at a rate of thirty complete movements—flexion and extension—per minute. During each of these two minutes and also during the first minute after the work had ceased, successive blood samples were obtained.

Four such observations were made on three patients. The findings are shown in Table 5. In none of the patients were significant reductions in the pH or increases in carbon dioxide tension observed. Such slight changes as did occur in these functions were more often in the direction of increased alkalinity, but most of the changes were within the limit of error of the methods used. However, ventilation was increased in every case.

The changes noted in the arterial saturation, although of slight degree, are of some interest. There was a tendency toward slight diminution during, and slight increase after, exercise. A possible explanation is as follows: During exercise the cardiac output probably increases relatively soon, when the pumping action of the muscle begins. However, the ventilation increases more slowly, being always greater during the second, than during the first, minute of exercise. At the cessation of effort, the pumping action of the muscles ceases and a rapid diminution in venous return and in cardiac output probably occurs. However, the ventilation remains elevated for a longer time. At the time when the increase in circulation is relatively greater than that in ventilation, one would expect a tendency for the arterial oxygen to decrease, whereas, when the reserve was true, an increased saturation would be expected.

In any case the changes in oxygen, like those in carbon dioxide and hydrogen ion concentration, are much too small and too inconstant to account for the changes in ventilation.

TABLE 5
Time relationship of exercise and acid-base condition of arterial blood

Sub- ject	Chief diagnosis	Date	Degree of cardiac disease *	O ₂ capacity	Time of blood specimen	O ₂ content	O ₂ satura- tion	Serum CO ₂ content	CO ₂ tension	pH	Ventilation per minute per square meter	Vital capacity per square meter
P. H.	Asthma Emphysema Syphilitic aortic insufficiency	1930 December 23	++	volumes per cent 18.27	Before exercise During 2nd minute of ex- ercise 1st minute after exercise	volumes per cent 16.34 15.85	per cent 89.5 86.8	volumes per cent 55.2 54.8	mm. Hg 29.2 28.7	7.55 7.54	liters 4.46 7.33	liters 1.65
		December 26	++	16.35	Before exercise During 1st minute of ex- ercise During 2nd minute of ex- ercise 1st minute after exercise	15.36 15.36	94.0 94.0	51.4 51.1	28.7 28.5	7.51 7.51	5.66 7.40	1.56

* See text.

TABLE 5 (continued)

Sub- ject	Chief diagnosis	Date	Degree of cardiac disease *	O ₂ capacity	Time of blood specimen	O ₂ content	O ₂ satura- tion	Serum CO ₂ content	CO ₂ tension	pH	Ventilation per minute per square meter	Vital capacity per square meter
A. C.	Syphilitic aortic insufficiency	1950 December 24	++	volumes per cent 17.92	Before exercise	volumes per cent 16.70	per cent 93.2	57.0	mm. Hg 33.3	7.49	liters 4.76	1.97
					During 1st minute of ex- ercise	16.70	93.2		33.3	7.49	5.89	
					During 2nd minute of ex- ercise	16.95	94.6	55.1	28.1	7.55	7.03	
					1st minute after exercise	17.20	96.0	55.1	32.2	7.49	6.68	
W. C.	Hypertension Arterio- sclerosis	December 27	+	18.28	Before exercise	17.50	95.7	58.3	28.5	7.57	4.26	1.82
					During 1st minute of ex- ercise	16.88	92.4	58.2	27.2	7.59	6.80	
					During 2nd minute of ex- ercise	17.32	94.8	57.7	28.2	7.57	8.76	
					1st minute after exercise	17.44	95.5	56.6	27.7	7.57	8.76	

E. The findings in the blood from the internal jugular vein

As a result of the observations which have been given it is evident that the increase in ventilation brought on by exercise cannot be explained by changes in the chemical composition of the arterial blood or of the venous blood from the arm. However there remains the possibility that decreased blood flow through the brain might be present and account for the dyspnea. Is cardiac dyspnea due to decreased blood flow through the brain? Some authors seem to think so. Means (1924) ascribed cardiac dyspnea to diminished output of the heart, and presumably meant more specifically, decreased cerebral blood flow. Meakins and Davies (1925) discuss the complicated nature of cardiac dyspnea, and they, too, are inclined to regard decreased blood flow as being the most important factor. These conclusions have been, in each instance, based on very indirect evidence. Gesell (1925) has demonstrated the great importance of the blood flow through the brain in the control of respiration. But is the flow of blood through the brain decreased in patients with cardiac dyspnea?

In order to obtain evidence on this point studies were made on the blood from the internal jugular vein. This was obtained according to the technique described by Myerson, Halloran and Hirsch (1927) and by Lennox (1930). Otherwise, the experimental procedure was exactly the same as that already described. Observations were made before and after the mild exercise described under "methods" on three subjects and in each of them the taking of the second jugular sample was completed within the first one and one-half minutes after exercise. The data are shown in Table 6.

The oxygen content after exercise was the same as at rest in one patient, rose in another and fell in the third. Values for mean unsaturation were 6.98 and 6.81 volumes per cent for rest and exercise respectively. These values are close to the average of 7.3 volumes per cent unsaturation found by Lennox (1930) in the internal jugular blood of sixty patients without cardiac or pulmonary disease. It is therefore evident that, unless one is willing to make the unlikely assumption of diminished metabolic rate in the brain during exertion, the dyspnea brought on by mild exercise in patients with cardiac disease cannot be attributed to decrease in cerebral blood flow.

TABLE 6
Ventilation and acid-base condition of blood from internal jugular at rest and after mild exercise

Subject	Date	Diagnosis	Degree of cardiac disease*	Vital capacity per square meter	O ₂ capacity	Control period—rest					After mild exercise					Change from resting period				
						Ventilation per minute per square meter	O ₂ saturation	Serum CO ₂ content	CO ₂ tension mm. Hg	pH	Ventilation per minute per square meter	O ₂ saturation	Serum CO ₂ content	CO ₂ tension mm. Hg	pH	Ventilation increase per minute per square meter	O ₂ unsaturation	Serum CO ₂ content	CO ₂ tension	pH
				liters	volumes per cent	liters	per cent	volumes per cent	mm. Hg		liters	per cent	volumes per cent	mm. Hg		liters	volumes per cent	volumes per cent	mm. Hg	
E. M. E. G.	1980 December 9 December 5	Hypertension Syphilitic aortic	++ ++	2.01	17.68	5.30	59.8	67.0	38.2	7.50	10.16	56.2	66.5	38.0	7.50	4.86	+0.72	-0.5	-0.2	±0
				1.51	16.70	4.58	54.4	70.2	42.7	7.47	8.30	54.4	70.2	40.1	7.50	3.72	±0	±0	-2.6	+0.03
R. J.	December 8	insufficiency Hypertension	++	1.70	16.71	4.12	62.4	69.0	40.3	7.49	6.37	69.6	69.6	38.8	7.51	2.25	-1.21	+0.6	-1.5	+0.02

* See text.

The carbon dioxide content did not undergo significant changes and this is further evidence against diminished cerebral circulation. The pH was unchanged in one patient and increased slightly in the other two. The tendency was for the blood to be more alkaline after exercise but the degree of change was too slight to be significant. The *carbon dioxide tension* was less after exercise in two patients and unchanged once. Such small changes as did occur in the acid-base state of the blood were in the direction of increased alkalinity and are therefore to be regarded as effects rather than causes of the increased ventilation.

F. Changes in the arterial blood of normal subjects and patients with cardiac disease before and after maximal exercise

In order to determine whether patients with cardiac disease are able to exercise sufficiently severely to become acidotic to any marked degree, observations were made before and immediately after an exertion which was as severe or nearly as severe as the subject could perform. In these instances ventilation was not measured as it was felt that the face mask might hinder the respiration and hence limit the severity of the exercise. As can be seen in Table 7, the arterial saturation increased. The changes in carbon dioxide content and in hydrogen ion concentration were much less marked in the patients than in normal subjects who performed much severer exercise but had about the same degree of distress. Despite relatively striking diminution in pH and carbon dioxide content, the carbon dioxide tensions were only slightly affected by the severe exercise.

As the patients were doing all, or nearly all, they could do, it seems fair to conclude that individuals with cardiac failure are unable to perform severe enough exercise to markedly affect their acid-base balance. *Their dyspnea checks them before acidosis has become severe.*

In view of this finding certain conclusions drawn in a previous paper in this series (Harrison and Pilcher (1930)) must be revised. It was found that patients with cardiac failure are unable to exert themselves sufficiently severely to acquire a large oxygen debt. Believing that the limiting factor of exercise in such patients, as in normal subjects, was the dyspnea due to the rise in hydrogen ion concentration of the blood, Harrison and Pilcher, who did not study the blood, assumed that their patients had, on the performance of relatively slight exercise, and hence following the production

TABLE 7
The effect of maximal exercise on the acid-base conditions of arterial blood

Sub- ject	Date	Diagnosis	Degree of cardiac disease *	O ₂ capacity	Time of blood sample	O ₂ content	O ₂ satura- tion	Serum CO ₂ content	CO ₂ tension	pH	Exercise performed	Remarks
G. C.	1931 January 10	Normal	0	volumes per cent 20.70	Before exercise 1st minute after exercise	volumes per cent 19.60 20.70	per cent 94.7 100	volumes per cent 60.2 41.5	mm. Hg 32.1 30.2	7.53 7.39	Standing run- ning 220 high steps per min- ute for two minutes	Maximal exercise
F. T.	January 10	Normal	0		Before exercise 2nd minute after exercise			58.1 32.6	27.6 27.0	7.59 7.33	Standing run- ning 220 high steps per min- ute for two minutes	Maximal exercise
E. G.	January 8	Syphilitic aortic insufficiency	+	15.75	Before exercise 1st minute after exercise	14.30 14.78	90.4 93.9	64.7 53.8	33.1 33.5	7.55 7.46	Stair climbing up and down 48 steps per minute for two minutes	Maximal exercise
A. C.	January 7	Syphilitic aortic insufficiency	++	18.06	Before exercise 1st minute after exercise	17.10 17.34	94.7 95.8	59.8 58.7	30.5 32.8	7.55 7.51	Standing run- ning 180 low steps per min- ute for two minutes	Severe exer- cise almost maximal

* See text.

of a relatively small amount of lactic acid, a marked acidosis of the blood stream. From this they concluded that the buffering power of the tissues was diminished in such patients. However, the present work shows that one of their premises was incorrect, because the limiting factor in exercise in patients with cardiac failure is not acidemia. Hence the inability of the patient with cardiac failure to acquire a large oxygen debt can no longer be considered as indicative of diminution in muscle buffers. (The other evidence for diminished muscle buffers is of course not affected by this study. It may be also said that the findings in the present work are in no sense contrary to the data of Harrison and Pilcher, but only to the conclusions which they drew.)

DISCUSSION

Application of data to cardiac disease. At the beginning of the paper it was stated that our main object was to attempt to ascertain (1) why patients with cardiac disease usually have a greater ventilation than normal individuals upon the performance of a given exercise and (2) how decreased vital capacity tends to produce dyspnea. From the foregoing data it seems clear that the present researches have failed entirely to furnish an adequate answer to either question. All of our findings point toward the conclusion that such small changes as do occur in the composition of the blood are usually to be considered as effects rather than as causes of increased ventilation. The absence of any consistent alteration in the blood also seems to indicate that diminution in vital capacity predisposes to dyspnea by some mechanism other than changes in the oxygen saturation or acid-base condition of the blood. At the present time we are unable to state what this other mechanism may be. Studies on the subject are in progress.

The observations which have been made confirm those of Peters and Barr (1921); Eppinger, Kisch and Schwarz (1927); and Fraser, Harris, Hilton and Linder (1928). These investigators have reported similar more or less negative results in their attempt to correlate cardiac dyspnea with changes in blood composition. They found increased acidity occasionally and increased alkalinity more frequently. Most of their values were within normal limits. Fraser and his co-workers, having found normal or slightly alkaline values for the hydrogen ion concentration and the carbon dioxide tension of arterial blood in patients with cardiac dyspnea, concluded that the dyspnea was probably to be attributed to decrease in blood flow through the respiratory center and

postulated alterations in the blood draining the brain. Our findings in jugular blood seem to invalidate this hypothesis. It must be admitted that an adequate explanation for cardiac dyspnea is entirely lacking at the present time. Such an admission seems to us to be a distinct step forward. So long as it is assumed, on insufficient evidence, that the symptoms of cardiac failure are essentially and primarily due to constantly diminished cardiac output, the various problems of the subject are likely to be considered as solved and further progress in the subject will be delayed.

It is our belief that very little is known concerning the causes of cardiac dyspnea.

Certain other features in connection with the present study may be mentioned as requiring further elucidation. It is of some interest to note that the venous blood (both jugular and cubital) usually becomes slightly more alkaline after mild exercise, whereas the arterial blood less commonly exhibited this change. The carbon dioxide content of the venous blood of the arm was in the majority of instances slightly greater after than before exercise; whereas, that of the arterial blood tended to be slightly less. These facts suggest that the blood was buffered in some way as it passed through the tissues. Either a shift of chloride from serum to cells or a passage of base from tissue to serum would explain the findings. Further observations on this point are needed.

In a previous paper (Pilcher, Clarke and Harrison (1930)) examples of patients with cardiac failure and acidemia were presented. It should be remembered that our earlier studies, which dealt particularly with edema were necessarily carried out on severely decompensated patients, and several of them had diminished alkaline reserve of the blood. As a result of those studies, it was concluded that edema tends to cause tissue acidosis by interfering with the diffusion of oxygen. The fact that cardiac dyspnea of the type here studied is not essentially and primarily due to diminished blood alkalinity does not mean that acidosis never occurs in patients with cardiac failure. Patients with extensive edema may have diminution in the reserve alkali; low values for pH have been found in individuals dying from cardiac disease (Pilcher, Clark and Harrison (1930)) but as the present studies indicate, acidosis is usually only a very late manifestation of congestive failure,

and cannot be regarded as the essential cause of dyspnea in patients with relatively early cardiac disease.

Application of data to general subject of respiration. Complete data for normal individuals was obtained only in the first series of experiments on venous blood from the arm. The evidence there obtained was that the chemical changes in the blood of the normal were not essentially different from those of patients with early cardiac disease.

This evidence and the cumulative data of both arterial blood and internal jugular blood from the brain in the subjects with early cardiac disease indicate (1) that the respiratory mechanism is not as sensitive to changes in acid-base condition as has been generally assumed and (2) that changes in the acid-base condition and oxygen saturation constitute only one factor in the control of respiration. This conclusion is substantiated more fully in the following report on orthopneic dyspnea. (Calhoun, Cullen, Harrison, Wilkins and Tims (1931)).

The results reported here and those found concurrently in Dills' laboratory (Myerson, Loman, Edwards and Dill (1931)) are in entire agreement. Dill and his associates studied simultaneously blood from the jugular vein, femoral vein and femoral artery during partial anoxemia and found no accumulation of lactic acid or other fixed acid. Blood from the brain was within the normal range in most subjects.

SUMMARY

Measurements of the ventilation, oxygen content, hydrogen ion concentration and carbon dioxide content of the blood before, after, and in a few instances during mild exercise have been made on patients with cardiac disease with relatively mild congestive failure and on normal subjects. Although the exercise was mild it was sufficient to cause slight subjective respiratory distress in the majority of the patients and to cause an increase of 50 to 100 per cent in ventilation. The following results have been obtained.

In *arterial blood* neither during nor immediately after mild exercise were there observed significant alterations in the hydrogen ion concentration, carbon dioxide content or carbon dioxide tension. The changes which occurred are to be interpreted as being, in the main, effects rather than causes of increased ventilation.

At rest the *venous blood* of the arm of the patients was almost identical with that of the normal subjects in regard to oxygen unsaturation, and

carbon dioxide content. As an average the pH was slightly higher and the carbon dioxide tension slightly lower in the patients, but the differences were too slight to be significant. After the mild exercise the blood of both groups tended to be slightly more alkaline and the oxygen unsaturation was slightly greater in the patients than in the normal subjects. Any chemical changes in the blood are to be regarded in both groups as effects rather than causes of the increase in ventilation.

In blood from the *internal jugular* of subjects at rest the oxygen unsaturation in the patients was slightly but not significantly less in the patients than the average values found by other investigators for jugular blood in normal subjects. After mild exercise the oxygen content was not altered. The carbon dioxide content, pH and carbon dioxide tension of the jugular blood were unchanged or slightly altered in the direction of alkalinity after exertion.

Ammonium chloride, administered by mouth caused relatively great decrease in pH and carbon dioxide content of the arterial blood and relatively slight increase in ventilation, whereas mild exercise caused slight or no change in blood gases and marked increase in ventilation.

Maximal exertion in normal subjects caused marked reduction in carbon dioxide content and pH of arterial blood. In patients with cardiac failure maximal exertion which, although actually less than that performed by the normal subjects was accompanied by comparable respiratory distress, was attended by less marked reduction in carbon dioxide content and pH of the arterial blood. The limiting factor in exertion in such patients is not acidosis, but some other mechanism.

The respiratory mechanism is less sensitive to changes in acid-base condition of the blood than has been generally believed. It appears that both in normal subjects and in patients with cardiac disease delicate respiratory adjustments to mild exercise are made quite independently of changes in the oxygen saturation and the acid-base condition of the blood.

The observations do not lend support to the notion that the blood flow through the tissue is significantly less than normal in patients with slight cardiac failure either at rest or upon the performance of mild exercise. The findings are contrary to the idea that dyspnea in patients of this type is due to diminution in cerebral blood flow. Cardiac dyspnea is apparently due to some other, as yet unknown, cause.

BIBLIOGRAPHY

- Calhoun, J. Alfred, Cullen, G. E., Harrison, T. R., Wilkins, W. E., and Tims, M. M., *J. Clin. Invest.*, 1931, x, 833. Studies in Congestive Heart Failure. XIV. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood.
- Cullen, G. E., *J. Biol. Chem.*, 1922, lii, 501. Studies in Acidosis. XIX. The Colorimetric Determination of the Hydrogen Ion Concentration of Blood Plasma.
- Earle, I. P., and Cullen, G. E., *J. Biol. Chem.*, 1929, lxxxiii, 539. Studies of the Acid-Base Condition of Blood. I. Normal Variation in pH and Carbon Dioxide Content of Blood Sera.
- Eppinger, H., Kisch, F., and Schwarz, H., *Das Versagen des Kreislaufes*. Berlin, 1927, p. 43.
- Fraser, F. R., Harris, C. F., Hilton, R., and Linder, G. C., *Quart. J. Med.*, 1928, xxii, 1. Arterial Carbon Dioxide Pressure in Cardiac Dyspnea.
- Gesell, Robert, *Physiol. Rev.*, 1925, v, 551. The Chemical Regulation of Respiration.
- Haldane, J. S., *Respiration*. New Haven, 1922, p. 185.
- Harrison, T. R., and Pilcher, C., *J. Clin. Invest.*, 1930, viii, 291. Studies in Congestive Heart Failure. II. The Respiratory Exchange During and After Exercise.
- Harrison, T. R., Robinson, C. S., and Syllaba, G., *J. Physiol.*, 1929, lxvii, 62. The Effect of Muscular Exercise on the Oxygen Capacity of the Blood of Man.
- Harrison, T. R., Turley, F. C., Jones, E., and Calhoun, J. A., *Arch. Int. Med.*, 1931, xlviii, 377. Studies in Congestive Heart Failure. X. The Measurement of Ventilation as a Test of Cardiac Function.
- Hasselbalch, K. A., *Biochem. Ztschr.*, 1912, xlvi, 403. Neutralitätsregulation und Reizbarkeit des atemnzentrums in ihren Wirkungen auf die Kohlensäurespannung des Blutes.
- Himwich, H. E., and Loebel, R. O., *J. Clin. Invest.*, 1927-28, v, 113. The Oxygen Saturation of Hemoglobin in the Arterial Blood of Exercising Patients.
- Hooker, D. R., Wilson, D. W., and Connett, H., *Am. J. Physiol.*, 1917, xliii, 351. The Perfusion of the Mammalian Medulla: The Effect of Carbon Dioxide and Other Substances on the Respiratory and Cardio-vascular Center.
- Lennox, W. G., *Arch. Int. Med.*, 1930, xlvi, 630. The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins.
- MacKenzie, Sir James, *Diseases of the Heart*. London, 1925, 4th ed., p. 33.
- Meakins, J. C., and Davies, H. W., *Respiratory Function in Disease*. Edinburgh, 1925, p. 328.
- Means, J. H., *Medicine*, 1924, iii, 388. Dyspnea.

- Myerson, A., Halloran, R. D., and Hirsch, H. L., *Arch. Neurol. and Psychiat.*, 1927, xvii, 807. Technique for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery.
- Myerson, A., Loman, J., Edwards, H. T., and Dill, D. B., *Am. J. Physiol.*, 1931, xcvi, 373. The Composition of Blood in the Artery, in the Internal Jugular Vein and in the Femoral Vein during Oxygen Want.
- Peters, J. P., and Barr, D. P., *J. Biol. Chem.*, 1921, xlv, 537. The Carbon Dioxide Absorption Curve and the Carbon Dioxide Tension of the Blood in Cardiac Dyspnea.
- Pilcher, C., Clark, G., and Harrison, T. R., *J. Clin. Invest.*, 1930, viii, 317. Studies in Congestive Heart Failure. III. The Buffering Power of the Blood and Tissues.
- Scott, R. W., *Am. J. Physiol.*, 1918, xlvii, 43. The Significance of Undissociated Carbon Dioxide in Respiration.
- Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, lxi, 523. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. I.
- Van Slyke, D. D., and Sendroy, J., Jr., *J. Biol. Chem.*, 1927, lxxiii, 127. Carbon Dioxide Factors for the Manometric Blood Gas Apparatus.
- Winterstein, H., *Arch. f. d. ges. Physiol.*, 1911, cxxxviii, 167. Die Regulierung der Atmung durch das Blut.