THE EFFECTS ON THE CIRCULATION AND RESPIRATION OF AN INCREASE IN THE CARBON DIOXIDE CONTENT OF THE BLOOD IN MAN

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The purpose of the experiments recorded here was to establish the normal curves of the circulatory and respiratory responses to a gradual increase of carbon dioxide in the inspired air and to determine whether there is an after-effect.

A gradual increase of carbon dioxide in the inspired air was secured by allowing the subject of experimentation to rebreathe 52 liters of air in a Larsen-Henderson rebreathing apparatus (23). In one series of 52 experiments, preliminary to the rebreathing, oxygen was added to the atmospheric air in sufficient amount to raise the content to about 30 per cent and then throughout the period of rebreathing a small flow of washed oxygen was allowed continually to enter the reservoir of the apparatus. In another series of 20 experiments the subject rebreathed the 52 liters of atmospheric air with the result that carbon dioxide not only accumulated but the oxygen content of the air was gradually exhausted. Preceding each experiment preliminary observations were made on each physiological condition to establish the normals for a basis of comparison; and during the experiments the respiratory changes, the pulse rate and arterial blood pressures were recorded. Determinations of the composition of the alveolar air, venous and capillary blood pressures, the hand volume and the rate of blood flow through the hand were added as the occasion permitted and included 8 to 10 studies of each.

The respiratory data were obtained by recording the movements of the spirometer drum on a kymograph and also by reading the minute volume of breathing with the Larsen automatic recorder (23). The alveolar air samples were taken from a special opening in the mouthpiece by the method of Haldane and Priestley (9). The arterial blood pressures were determined with the Tycos sphygmomanometer by the

auscultatory method; the venous blood pressure with Hooker's glass capsule; the capillary blood pressure with the Danzer-Hooker "micro-capillary tonometer;" the hand volume changes with the arm plethysmograph and the blood flow through the hand by two methods, Stewart's (26) hand calorimeter and Hewlett's (13) cuff device.

There were 16 subjects who served for a total of 72 experiments. The time of rebreathing lasted from 17 to 32 minutes with an average of 23.5 minutes; the percentage of the final content of carbon dioxide ranged from 5.7 to 9.3, mean 7.3 $\pm$ .075.

A gradual increase in carbon dioxide up to the percentages experienced in this study does not as a rule cause disagreeable sensations. There may be a considerable change in the breathing before the hyperpnea is noticed; but when the carbon dioxide has risen to 4 or 5 per cent, it is no longer unnoticed and more and more, as the carbon dioxide increases, does the air breathed fail to satisfy the intense longing for fresh air; furthermore the effort to fill and empty the lungs reminds us of the respiratory urge of strenuous physical exercise. After a while there is a feeling that the inspiratory efforts begin before expiration is completed.

Some persons develop a headache at about 5 per cent CO_2 which may be intense, but it has not been observed to last for more than 20 minutes after the experiment. An occasional person felt slightly dizzy when the breathing was greatest and a feeling of nausea has occurred. One subject, in several trials, complained of pains in the chest and expectorated some brown colored sputum streaked with blood. This subject had the highest per minute volume of ventilation obtained at 8 per cent CO_2. There has been no evidence that the man suffered any lasting ill effects from these experiences.

THE CIRCULATION. *Pulse rate.* Our data clearly give evidence that the heart rate is accelerated by carbon dioxide. In only 3 out of 72 experiments was the rate unaffected. For the group of experiments in which a high percentage of oxygen was maintained in the inspired air the mean pulse rate for each per cent of carbon dioxide up to 6 per cent has been plotted in figure 1 and tabulated in table 1. Because the number of cases at 7 per cent carbon dioxide was somewhat reduced and at 8 per cent much reduced, we have added the average increases for these percentages to the mean pulse rate of 6 per cent carbon dioxide instead of calculating the mean rate. The curve of the means indicates that the pulse rate is slightly increased even at 1 per cent, but the stimulating action is most pronounced from 5 per cent and upward.

The group of 20 experiments, in which the oxygen content of the inspired air decreased as the carbon dioxide increased, had a mean normal pulse rate of 71.3 beats. The mean pulse rate for each percentage of carbon dioxide from 1 to 7 per cent was as follows: 72.6, 73.1, 73.5, 75.6, 76.5, 78.5 and 82.9 respectively. The total increase for this group up to 7 per cent was 11.6 beats, and for the group in which the oxygen was maintained at about 30 per cent was 15.5. This is a difference that cannot be attributed to the available oxygen, but is probably explained by the fact that in the high oxygen group we were dealing with individuals who had normally a more rapid and apparently a more responsive heart; their mean normal rate was 78.5 as against 71.3 for the other

TABLE 1

Mean pulse rate and arterial pressures for 46 experiments

	PULSE RATE	ARTERIAL PRESSURE IN MM. Hg.		
		Systolic	Diastolic	Pulse
Normal	78.5	106.1	71.3	35.4
1 per cent CO_2	79.8	109.0	73.8	36.1
2 per cent CO_2	80.7	109.5	74.3	36.6
3 per cent CO_2	82.8	111.3	75.1	37.2
4 per cent CO_2	84.4	113.5	77.3	37.6
5 per cent CO_2	86.0	116.7	79.1	37.7
6 per cent CO_2	90.0	122.5	83.0	40.1
7 per cent CO_2	94.0	127.4	84.6	42.8
8 per cent CO_2	97.3	134.1	91.1	43.0
Last on	93.6	128.7	83.6	45.5
First off	90.4	115.7	71.7	46.6

group. In both groups of experiments there is evidence of a slight stimulation at 1 and 2 per cent of carbon dioxide, with a stronger action from 5 per cent and onward.

Some subjects were much more sensitive than others. One resistant man tested on six consecutive days always went to between 6 and 7 per cent carbon dioxide before there was any evidence of stimulation. Another subject in four trials always began to respond around 4 or 5 per cent, while 3 individuals always gave the first evidences of response around 3 and 4 per cent. One man tested on six consecutive days became more sensitive as the days passed, on the first two days the pulse rate first began to accelerate at 6 and 7 per cent of carbon dioxide and on the last days at 1 and 2 per cent. Several others showed a considerable variability. On the whole it can be said that the individual shows a

disposition to respond at about the same percentage of carbon dioxide in several exposures. So the pulse rate curve of figure 1 represents a generalized condition rather than an individual curve of response.

While the after-effect on the pulse rate of breathing carbon dioxide has not always been watched, yet our observations, which were often continued for 5 to 7 minutes after the subject was restored to atmospheric air, show that the effect persists for some time. In nearly every case the pulse rate had not returned to normal in the post-period of

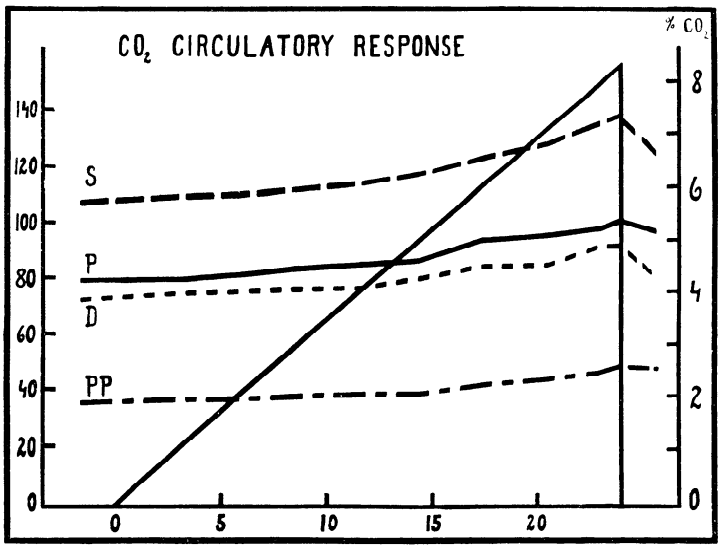

Fig. 1. The mean circulatory response of 48 cases to a gradual increase in inspired CO_2. *P*, pulse rate; *S*, systolic pressure; *D*, diastolic pressure; and *PP*, pulse pressure.

observation. The mean pulse rate for 46 experiments was 93.6 at the last count just before the subjects were restored to air, and still 90.4 one minute later.

THE ARTERIAL PRESSURE. *Systolic arterial pressure.* In table 1 and figure 1 are given the mean results of the carbon dioxide influence on the systolic pressure in experiments in which the oxygen content was greater than that of atmospheric air. The normal pressure was 106.1 mm. and the means for 1 and 2 per cent of carbon dioxide were 109 and 109.5 mm. This slight rise was not the effect of carbon dioxide, as the readings for the first 2 minutes will show, but is a psychic rise such as is

commonly present in experiments of this type. It appears, therefore, that carbon dioxide is without influence on the systolic pressure until it has increased to between 2 and 3 per cent in the inspired air. As the content of inhaled carbon dioxide continues to increase the systolic pressure rises in ever increasing degree.

The group of 20 experiments, in which the available oxygen was gradually decreased throughout the period of rebreathing, had a mean normal systolic pressure of 108.8 mm. The mean pressure for each percentage of carbon dioxide from 1 to 7 per cent was as follows: 108.6, 109.4, 112, 113.8, 115.6, 119.4 and 123.3 mm. The effect upon the systolic pressure was somewhat greater in those cases in which the available oxygen was higher than in atmospheric air. The onset of the action of carbon dioxide was, however, about the same for both groups.

While individual differences in the time of response were present there was, however, greater constancy in the percentage at which the rise began than occurred with the pulse rate acceleration. In the majority of experiments the systolic pressure began to rise at 3 or 4 per cent of carbon dioxide, in only 4 did the rise appear as late as at 6 or 7 per cent. In two of the experiments no change occurred, but these individuals reacted at other times with the ordinary type of response.

The after-effects on the systolic pressure were less persistent than on the pulse rate. There was a rapid fall in pressure during the first minute after the subject was restored to atmospheric air, this being followed by a period of more gradual decline. The mean pressure for the 46 experiments just prior to restoring the subjects to atmospheric air was 128.7 mm. and 1 minute after receiving the air was 115.7 mm. The pressure was often back to normal in 2 or 3 minutes; but sometimes the final return to normal, following the sudden drop, was delayed during the entire post-period of observation which was continued for from 5 to 7 minutes.

Diastolic pressure. The diastolic pressure increased in both types of experiments. In a considerable number of cases this pressure started to rise before the systolic but often the two pressures rose together, the systolic rising most rapidly; but in all cases the diastolic pressure continued to augment as long as the carbon dioxide increased in quantity. That the diastolic is as a rule affected earlier than the systolic pressure is shown in the curve of the means in figure 1. The total average rise when 7 per cent carbon dioxide had been reached was 13.3 mm. for the high oxygen and 7.7 mm. for the low oxygen group. So in the diastolic response, as in the systolic, the high oxygen group appeared to be most sensitive to the carbon dioxide.

The after-effects fall into two classes. In about 75 per cent of the experiments the diastolic pressure went slightly subnormal, or at least returned to normal, within the first minute after atmospheric air was given; while in the other 25 per cent this pressure remained above normal for the entire period of 5 to 7 minutes of post-observation. For the high oxygen group the mean pressure for the last reading when under the influence of carbon dioxide was 83.6 mm., and 71.7 mm. 1 minute after air was given. The mean for the preliminary normal was 71.3 mm.

Pulse pressure. Since the systolic rose more than the diastolic pressure, there occurred an increase in the pulse pressure which is first clearly defined at between 5 and 6 per cent of carbon dioxide. The mean pulse pressures at intervals up to 8 per cent carbon dioxide have been plotted in figure 1.

VENOUS BLOOD PRESSURE. The influence on venous pressure of a gradual increase of carbon dioxide in the inspired air was determined on 11 persons. A summary of the data obtained from the high oxygen group is given in table 2. In 21 experiments conducted under the two conditions the pressure, with only two exceptions, rose steadily during the period of rebreathing. The average venous pressure in the high oxygen group prior to the rebreathing was 5.4 cm. H_2O. By averaging the cases up to 5 per cent carbon dioxide and then adding to the 5 per cent result the average increase for 6 and 7 per cent carbon dioxide, because of the dropping out of cases at the higher percentages, the following curve of change in the venous pressure was obtained: 6.1, 6.7, 7.7, 7.8, 8.3, 8.8, and 9.5 cm. H_2O. So at 7 per cent of carbon dioxide the venous pressure showed an average increase of 74 per cent. The average change throughout the experiments is plotted in figure 2. The stimulating action was usually already evident at 1 per cent carbon dioxide, but in some became more effective at between 4 and 5 per cent.

The majority of observations were made on the low oxygen group, six of these with the Hooker method and the remainder with the Henderson method, in which the height of the hydrostatic column was recorded in the veins of the arm. However, in these experiments the rise in pressure was easily seen and averaged 3.9 cm. of H_2O.

The after effect on the venous pressure was about as prolonged as on the pulse rate. In 4 of the high oxygen cases the pressure was still above normal 5 to 7 minutes after the subjects were restored to atmospheric air. The other 3 cases came back to normal in 1, 2 and 4 minutes, respectively. In the low oxygen group in 9 out of 14 experiments the venous pressure was still well up 5 to 10 minutes after the rebreathing period.

CAPILLARY PRESSURE. Our capillary pressures were not corrected for hydrostatic pressure. Since only the change in pressure was of interest to us, the subject was required not to move hand and body during the experiment. We have omitted the correction because Danzer and Hooker (5) found it to be of uncertain value. The capillary pressure determinations are given in table 3. In each case they were made

TABLE 2

Venous pressure in cm. H_2O

	NORMAL	PER CENT OF CARBON DIOXIDE							LAST ON	FIRST OFF
		1	2	3	4	5	6	7		
G. C.	1.0	2.3	2.5	2.3	3.0	3.5	3.9		3.9	1.7
E. C. S.	11.3	11.4	11.8	11.4	11.8	11.9	13.0	13.6	15.2	12.2
D. T.	4.3	4.5	5.4	9.3	9.3	9.8	10.0	10.5	10.5	8.1
L. E. T.	1.6	4.1	4.6	5.9	6.3	7.2	6.8	6.7	7.0	7.4
K. O. N.	4.8	4.8	5.0	5.0	5.1	5.6	6.4		7.0	7.6
I. F. P.	14.0	14.0	14.8	16.2	15.6	16.4			18.8	17.2
C. J. B.	0.7	1.5	3.0	3.8	3.8	3.4	4.3	5.9	7.6	0.2

TABLE 3

Capillary pressure in mm. Hg

	NORMAL	PER CENT OF CARBON DIOXIDE								LAST ON	FIRST OFF
		1	2	3	4	5	6	7	8		
E. C. S. 1	38	36	52	63	67	72	73	62		60	48
E. C. S. 2	24	24	24	24	25	28	34	35	36	36	24
E. C. S. 3	29	29	32	35	37	37	39	43	49	49	34
D. T. 1	33	39	41	42	43	45	47	52		59	50
D. T. 2	40	37	38	35	42	44	46	49		49	38
D. T. 3	28	30	29	27	25	30	33	42	46	46	33
L. H. B.	41	44	46	58	54						
C. J. B.	10	14	15	15	15	15	17			17	15

on a single vessel and each record is the average of several readings which were made at regular intervals throughout the experiment. A definite rise occurred in each experiment; this appeared in 3 cases as early as 1 per cent carbon dioxide, in 2 at 2 per cent, in 2 at 4 per cent, and in 1 not until 5 per cent.

The curve of change is given in figure 2. The average capillary pressure before the exposure to carbon dioxide was 30.4 mm. Hg, this was increased as follows at the respective percentages of carbon dioxide

from 1 to 7: 31.6, 33.4, 37.4, 38.5, 40.9, 43.5 and 45.7 mm.; the last three, because cases were dropping out, are not averages but were obtained by adding the average increase for the given per cent to the preceding number. So at 7 per cent carbon dioxide the average capillary pressure was 50.3 per cent above normal.

When a subject was restored to atmospheric air the capillary pressure returned rather quickly to normal. The average pressure was 45.1 mm. for the last determination of the carbon dioxide effect and was 34.6

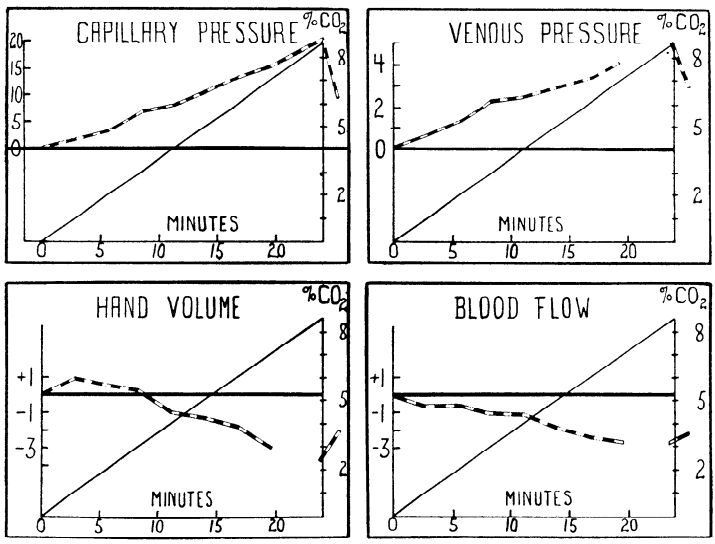

Fig. 2. Curves of the mean response to a gradual increase of CO_2. Normals have been recorded as O, the curves show the amount of change above and below normal. The scale to the left is in mm. Hg for capillary pressure, cm. H_2O for venous pressure, cc. for hand volume, and grams of blood per 100 cc. hand volume for blood flow.

mm. 1 minute after being restored to air, while the further return to normal was made within the next 3 or 4 minutes. In the rate of return to normal the capillary pressure reacted similarly to that of the arterial pressures and did not correspond to the slow return of the pulse rate and the venous pressure.

HAND VOLUME. The changes in hand volume were followed in 8 persons by using a plethysmograph in which the hand was surrounded by water heated to body temperature. The changes in volume were read directly on a graduated tube connected with the plethysmograph.

The entire apparatus was suspended by a coiled steel spring so that the movements of respiration did not cause a thrust and suction action of the hand into and out of the chamber of the plethysmograph. The subject was instructed to sit quietly. The usual changes in the hand volume are given by a curve in figure 2. Seven out of eight subjects gave the typical response in which a slight increase in volume occurred during exposure to from 1 to 3 per cent of carbon dioxide, following this the volume slowly returned to normal and went subnormal at 4 or 5 per cent carbon dioxide. The increase in volume above normal reached as much as 4 cc., while the greatest decrease below normal was 7 cc.

The exceptional case had a steady increase in hand volume throughout the entire experiment. Along with this increase in hand volume the systolic pressure, during the first half of the experiment, gradually went

TABLE 4

Blood flow in grams per 100 cc. of hand volume

	NORMAL	PER CENT OF CARBON DIOXIDE							POST PERIOD
		1	2	3	4	5	6	7	
E. C. S.	2.6	2.3	2.0	2.2	2.6	2.2	2.2	2.1	3.3
D. T.	10.5	7.6	7.4	6.8	5.6	4.6	4.0	4.0	2.4
G. C.	0.9	0.8	0.8	0.5	0.4	0.4	0.6	0.8	0.6
L. E. T.	6.5	6.5	7.9	6.8	6.8	5.9	5.0	4.2	6.3
K. O. N.	12.7	12.6	10.0	10.0	10.0	8.7	7.7	6.8	8.4
B. L. J.	4.4	4.2	5.8	5.0	4.9	4.0	3.1		4.0

subnormal by as much as 10 mm.; but beginning at 5 per cent carbon dioxide the pressure again slowly increased until at 8 per cent of carbon dioxide it was 12 mm. above normal.

After a subject was restored to fresh air the hand volume usually did not change at once but it soon increased and ordinarily was back to normal within about 5 minutes.

BLOOD FLOW. Our attempts to determine the rate of blood flow have thus far been limited to the indirect methods, namely, those of Stewart (26) and of Hewlett and Van Zwaluwenburg (13), for estimating the flow through the hand; and the recoil board method of Henderson (11) for the output of the heart per beat. The data obtained with Stewart's hand calorimeter are given in table 4 and the curve of the average change in figure 2. The general tendency brought out by this method is a retardation in the rate of the flow of blood in the hands as the carbon dioxide of the inspired air increases, this retardation averaging 44.4

per cent at 7 per cent of carbon dioxide. Up to 2 per cent of carbon dioxide a slight increase in the flow may occur, but it ordinarily begins to lessen from between 2 and 3 per cent of carbon dioxide.

Similar results were obtained in 6 experiments with the Hewlett-Van Zwaluwenburg (13) method. In 3 cases the rate of flow increased up to 2 and 3 per cent of carbon dioxide, and then slowly decreased and continued to retard until at the end it was subnormal; in another case the flow gradually decreased throughout the entire experiment; while in the other two cases there was no clearly defined change, the rate fluctuating above and below normal throughout the entire period.

The observations with the recoil board were also made on six subjects. This method depends upon the Newtonian principle that "every action has an equal and opposite reaction." During a few seconds the subject holds his breath while a record is made of the recoil curves. The distance through which the body and board recoils is believed to afford an index of the relative size of the heart beats in an individual at different times. In figure 3 one of our records has been reproduced. In this experiment the records labeled N1 to N6 are the preliminary normals and N31 to N36 are post-experiment normals. There is a marked decrease in the amplitude in records 19 to 24 and a slight increase in 26 to 29 taken just before the subject was returned to fresh air. The evidence obtained from all the recoil curves indicates that the systolic discharge from the heart is not increased and may even be somewhat decreased. At least three of the experiments indicate a decrease, one of which is given in figure 3. The remaining records show recoil curves of quite uniform amplitude.

Our circulatory results obtained on men subjected to a gradual increase in carbon dioxide in the inspired air, up to 7 and 9 per cent, should be compared with other observations on the effects of carbon dioxide. Hill and Flack (14) have found man able to breathe 15.3 per cent of carbon dioxide. They studied the circulatory effects on cats and dogs, using from 10 to 30 per cent of carbon dioxide, and found that with moderate doses the blood pressure was raised, while the effect was most marked between 10 and 25 per cent. At these percentages they believed the vagus and vasomotor centers were stimulated and that at higher concentration the blood pressure fell, owing to a depressant effect upon the heart muscle. Kaya and Starling (21) in the spinal animal observed that carbon dioxide caused a rise in the arterial pressure and that a moderate excess did not injuriously affect the heart, furthermore it was thought that possibly the functional capacity might be increased.

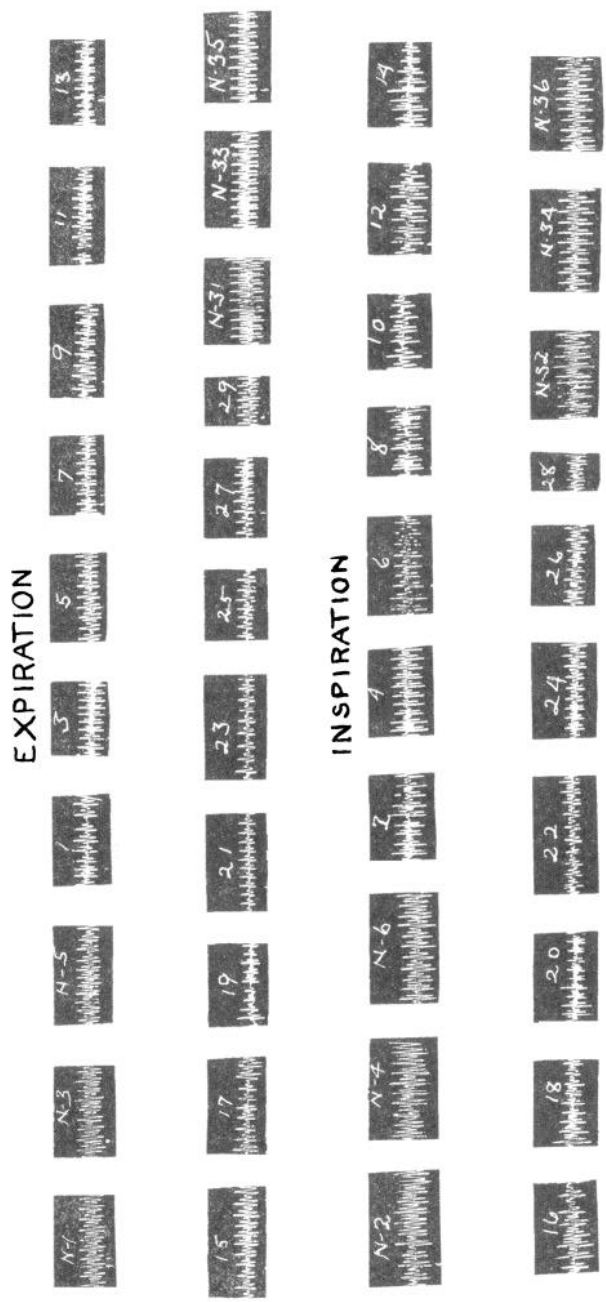

Fig. 3. Recoil board record during exposure to a gradual increase to 8 per cent in the inspired CO_2. The records were taken at regular intervals while the breath was held. *N*, normal before and after.

Jerusalem and Starling (20) with the heart-lung preparation showed that moderate percentages of carbon dioxide (2 to 8) increased the ventricular output. Itami (19) likewise found the cardiac output increased and concluded that a rise in blood pressure caused by small percentages up to 8 per cent is chiefly due to the increased action of the heart pump. Over against these observations are the experiments of Hooker (16) and Ketcham, King and Hooker (22) in which carbon dioxide was shown to relax vascular and cardiac muscle. It was pointed out that Jerusalem and Starling's results might be due indirectly to the effect upon the pulmonary vascular bed. Patterson (24) with the heart-lung preparation found that the administration of carbon dioxide caused a reduction in the amplitude of the heart, an increase of the diastolic volume and a slower rhythm, the result being a reduction of the minute volume. Campbell, Douglas, Haldane and Hobson (3), by determining the circulation rate by means of the carbon dioxide in arterial and venous blood, found that 5 or 6 per cent of inspired carbon dioxide while increasing the breathing about five times the normal did not appreciably influence the circulation rate. Our data obtained by means of the Henderson recoil board method for determining the relative size of the heart beats appear to support the Campbell, Douglas, Haldane and Hobson conclusion. We are continuing our study and hope to report on this point at another time. In the opposite condition in which carbon dioxide was quickly removed from the blood of animals by overventilation of the lungs, Dale and Evans (4) found the reduction in the heart output per minute was too small to be a serious factor in the fall of arterial pressure.

The lessened flow of blood that we found in the hand may be accounted for by the observations of Itami (19) and of Fleisch (8). In the intact animal Itami observed that constriction of the fore-limb vessels accompanied the general rise of blood pressure caused by carbon dioxide; and Fleisch in experiments on the hind legs of frogs perfused with Locke's solution found that carbon dioxide caused a dilatation with low concentrations (up to 3 per cent), while with stronger solutions a constriction became evident. He assumed that the dilator effect is due to action on a nervous component and the vasoconstriction to a direct action on the muscles of the arterioles. Dale and Evans (4) with cats and rabbits obtained an expansion of a normal limb with excessive ventilation of the lungs and a shrinkage again when respired air was inspired. They conclude that carbon dioxide has a specific stimulating action on the vasomotor centers in the brain and spinal cord.

Our data obtained with men indicate that carbon dioxide exerts a stimulating action, either directly or indirectly, on the vascular tissues in that with the rise in arterial pressure there is also a peripheral vasoconstriction indicated by the changes in hand volume and lessened flow of blood through the hand. It appears that the heart is also stimulated, since there is almost always some increase in the frequency of the heart beat. The rise in capillary and venous pressure which was also always present suggests an increased return of blood to the heart and, therefore, a well-defined increase in the minute volume of blood flow from the heart. Contrary to this indication we find the heart output per beat may sometimes be lessened and never clearly increased. The available evidence indicates that the minute volume is not appreciably altered. This then makes it difficult to explain the rise in the capillary and venous blood pressures. Henderson and Harvey (12) working with decerebrated cats observed that an accumulation of carbon dioxide in the blood caused an abnormally high venous pressure, a dilatation of the veins and an exaggeration of the volume of venous return to the heart, but that there was little or no effect upon the arterial pressure other than an increase in the amplitude of the pulse. They found, as we find for men, that the venous pressure develops gradually as the carbon dioxide accumulates in the tissues and again gradually falls as the carbon dioxide is ventilated out of the tissues. They believe that carbon dioxide acts directly on the venules, a decrease, as in acapnia, causing venule constriction and an increased venule dilatation. Dale and Evans (4) do not accept this explanation but attribute the changes to variations of the normal tone of the arterioles or of the capillaries or of both through the action of carbon dioxide on the vasomotor centers.

RESPIRATION. Haldane and Priestley (9) have well shown that the respiratory center is extraordinarily sensitive to very slight increases in the carbon dioxide percentage of the alveolar air. A study of two men by use of a body plethysmograph and a box arranged over the head so that the carbon dioxide of the inspired air was allowed to rise to around 6 per cent, showed that the depth of breathing increased as much as 320 per cent and that the frequency rose from 14 to 27. The frequency of breathing was not changed until the carbon dioxide reached 3.2 to 4.8 per cent. Douglas and Haldane (6) found that the hyperpnea of a gradual increase in the inspired carbon dioxide develops smoothly and gradually. Experiments by Hill and Flack (14) on cats and dogs revealed an increasing excitatory effect up to 35 per cent, but above 35 per cent the carbon dioxide had a depressing effect upon the respiration.

Paul Bert (2) reported that death sometimes occurred when the carbon dioxide rose to 30 per cent.

By the method of rebreathing 30 liters of air in which the carbon dioxide gradually accumulated and the oxygen gradually diminished, Hough (18) found that the respiratory response of individuals differed, one subject having recourse chiefly to increased depth, another to increased rate, while a third might make use of both expedients. The dyspnea was almost invariably ushered in by an increase in the depth, and this was found to increase while the carbon dioxide rose to as much as 4 to 6 per cent. In the later stages a decrease in depth usually occurred which was always connected with an increase in rate. It was said that "in general, then, the rate and depth of respiration tend to vary inversely."

The alveolar air. In order that we might be certain that our subjects were under conditions comparable with those used by other workers we determined the alveolar carbon dioxide on a group of eight cases and compared our data with some of those recorded by Haldane and Priestley (9). Our determinations were all made on alveolar air at the end of inspiration by the Haldane and Priestley method. In order to establish the average condition for the group we first plotted the data for each man and from the resulting curve estimated the alveolar air percentage of carbon dioxide for each per cent of the carbon dioxide in the inspired air for the respective units 1 to 7. The average for the normal carbon dioxide content of the alveolar air under normal atmospheric air of 0.03 per cent carbon dioxide was 5.4 per cent and the average at each per cent of inspired air from 1 to 7 respectively was as follows: 5.6, 5.9, 6.2, 6.63, 7.2, 7.63 and 8.4. The method of establishing the curve necessarily gives greater accuracy after the inspired carbon dioxide reaches 2 per cent than it does from normal atmospheric air to 2 per cent carbon dioxide. However, if it be approximately correct it is evident that even a slight increase in the inspired carbon dioxide does influence the alveolar carbon dioxide and thus the arterial blood content of this gas. The curve of alveolar carbon dioxide increase rises gradually but with ever increasing increments after reaching 2 per cent in the inspired carbon dioxide. Haldane and Priestley have tabulated 3 experiments on 2 subjects which taken together show even a more gradual early rise, but these are correspondingly steep after reaching 4 per cent in the inspired carbon dioxide.

Minute-volume of breathing. Our results for the two groups of experiments, high and low oxygen, are summarized in table 5 in which the mean minute-volume and the percentage of increase are given. Accord-

ing to Hough (17) the minute-volume and rate of breathing are distinctly lower when with the same content of carbon dioxide the air contains 60 to 80 per cent of oxygen, than when the initial atmosphere is ordinary air. Our two groups reacted very much alike even though the available oxygen at 7 per cent of carbon dioxide for the low oxygen group averaged only 16.3 per cent, while some were as low as 11.8 per cent; and for the high oxygen group it ranged between 25 and 35 per cent. At 7 per cent of carbon dioxide the average increase in the breathing was 516.9 per cent for the former and 511.9 per cent for the latter group. In this our results agree with Campbell, Douglas, Haldane and Hobson (3) who find that the alveolar oxygen pressure can be varied within wide limits

TABLE 5

The mean minute volume of respiration

CARBON DIOXIDE	HIGH OXYGEN GROUP		LOW OXYGEN GROUP	
	Average respiratory volume in liters	Per cent of increase	Average respiratory volume in liters	Per cent of increase
per cent				
0.03	6.30		7.53	
1.0	8.29	31.6	9.33	23.9
2.0	11.30	79.5	11.30	50.0
3.0	15.61	147.8	14.14	87.8
4.0	19.44	207.9	18.79	149.5
5.0	25.70	307.9	24.05	219.4
6.0	32.67	418.6	32.89	336.8
7.0	38.55	511.9	46.47	516.9
8.0	46.60	639.7		

without sensibly affecting the excitability of the respiratory center to carbon dioxide. In another type of experiment Benedict and Higgins (1) found that oxygen-rich gas mixtures have no influence on respiration.

The minute-volume ordinarily increased within the first minute or two of rebreathing. In the 52 experiments with a high content of oxygen there were only 5 times in which there was no evidence of increased breathing at 1 per cent of carbon dioxide; and in the 20 experiments, in which the oxygen gradually decreased as the carbon dioxide increased, there were 2 times in which the response had not begun at 2 per cent carbon dioxide and 2 more in which it was not evident at 1 per cent. At 1 per cent carbon dioxide the high oxygen group had an average increase of 31.6 per cent and the low oxygen group an increase of 23.9 per cent. Zuntz (27) found that the presence of 1 per cent of carbon dioxide in-

creased the minute volume by more than 20 per cent; while Scott (25), working with decerebrated cats, obtained an increase of 23 per cent at 1 per cent carbon dioxide.

In every one of our cases the minute-volume increased steadily to the end of the experiment. The maximum increase of 1052 per cent was found in a man who had a normal ventilation of 7.13 liters that was raised to 75.0 liters at 8 per cent of carbon dioxide. This subject's pulse rate rose from 95 to 110, the systolic arterial pressure from 102 to 152 mm. and the diastolic pressure from 68 to 90 mm. The nearest approaches to this record were from 7.8 to 560 liters, 717 per cent, and from 7.6 to 540 liters or 711 per cent increase.

The frequency of respiration. The changes in the rate of breathing have been carefully followed in 20 cases to determine the individual differences. The average normal rate of breathing ranged between 8 and 18, average 12.7 breaths per minute. As the carbon dioxide increased in the inspired air the average frequency at each increase from 1 to 8 per cent respectively was as follows: 12.8, 14.4, 15.1, 17, 17.9, 19, 21.6 and 22.6. These are individual differences, but we have not found them necessarily constant. There is a tendency for women to make the compensations for the minute-volume increase more by an increasee in the rate than in the depth of breathing. Thus in certain instances the depth of breathing was not altered until 3.5 or 4 per cent carbon dioxide had been reached, while the rate gradually increased from the very first minute. Of the 20 cases the frequency first gave an increase as follows; at 1 per cent, 3 cases; at 2 per cent, 7 cases; at 3 per cent, 2; at 4 per cent, 3; at 5 per cent, 3; at 6 per cent, 1; and at 7 per cent, 1. The frequency, therefore, was already increased in 60 per cent of cases before 4 per cent of carbon dioxide had been reached.

Not once did the rate fail to increase, the increase at 7 per cent carbon dioxide ranged from 2 to 18 breaths per minute, or from 17 to 200 per cent.

The depth of breathing. Almost all of our data were obtained from persons accustomed to serving as subjects of experimentation, hence there is little or no evidence of psychic disturbances in the rate and depth of breathing. The normal depth ranged between 410 and 780 cc., with an average of 570 cc. The ordinary response in the depth of breathing to carbon dioxide is shown in the following average depths for a group of 20 experiments determined for the respective percentages of of carbon dioxide from 1 to 8: 630, 780, 1000, 1150, 1480, 1760, 1920, 1820 cc; an average increase at 7 per cent carbon dioxide of 337 per cent.

In all but 6 experiments the depth of breathing was already somewhat increased at 1 per cent carbon dioxide, in 4 of these the response was delayed to between 2 and 3 per cent, to between 3 and 4 per cent in one and between 4 and 5 per cent in the other. In those instances in which the depth of breathing had not increased at 1 and 2 per cent of carbon dioxide the frequency of breathing had already definitely accelerated so that the minute-volume was increased. In one experiment the rate in 9 minutes, up to 3.2 per cent carbon dioxide, increased from 9 to 16 breaths per minute; the depth of breathing at the beginning was 622 cc.

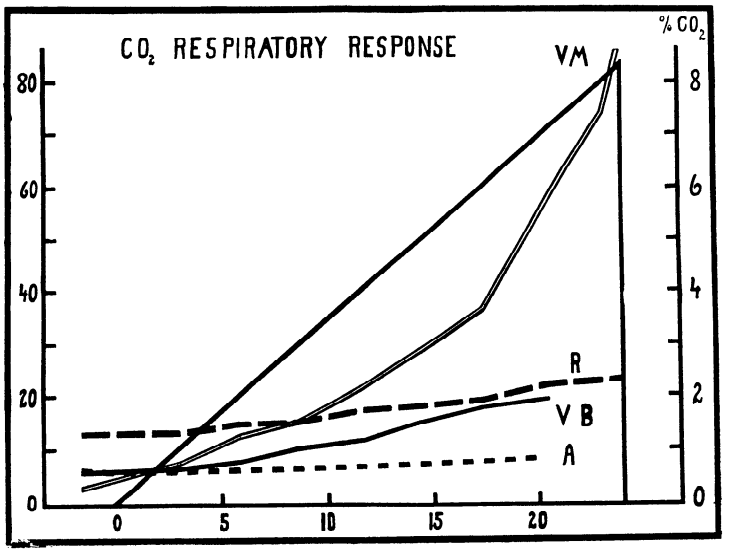

Fig. 4. Curves of means. *VM*, minute-volume; *VB*, volume per breath; *R*, frequency; *A*, per cent of alveolar CO_2.

and in the ninth minute 619 cc.; while the minute-volume during this time rose from 5.7 to 9.9 liters. From then on both the rate and depth gradually continued to increase.

There is of course a limit to the depth of breathing. When this is reached further recourse for increasing the per-minute volume is limited to a greater use of the increase in the frequency of breathing. So apparently in 7 experiments the maximum depth of breathing was reached at 6 or 7 per cent of carbon dioxide after which the further increase in per minute volume was made by hurrying the breathing, and in 4 of these toward the end of the experiment the depth decreased somewhat as the breathing became more rapid. The inverse relation-

ship between the rate and depth of respiration reported by Hough was not as a rule observed among our cases. In figure 5 are reproduced typical kymograph records of the three types of respiratory response observed. The first is from a case in which the compensation was largely made by an increase in rate, the second in which it was made in the depth of breathing, and the third in which a combination of increase in rate and depth was made. The relations of the several respiratory changes have been brought out in figure 4 by plotting the data with respect to time and the percentage of carbon dioxide.

Chest girth. It was noticed when listening to the heart sounds during the period of rebreathing that the pulmonic and aortic heart sounds grew less distinct as the breathing deepened and that the ribs appeared to be held more nearly horizontal than usual. So chest measurements were made throughout 12 experiments. The circumference determined at the end of expiration over the nipples was increased as the experiment proceeded by from one-half to one and a half inches, the increase averaging about an inch. Furthermore the return to the original size after the close of the experiment was slow, never within the first 10 to 20 minutes and apparently sometimes not for several hours. Some subjects felt that it was impossible to exhale completely, or that the succeeding inspiration began before exhalation was satisfactorily completed. The after-effect on the chest circumference suggested an increased tone of muscle, but there was no evidence of such tone in other than the chest muscles.

The time at which each of the several circulatory and respiratory factors is first affected and the amount of response are well shown by an experiment on one subject, E.C.S., which is given in detail in figure 6. The systolic, S, diastolic, D, and pulse pressures, PP, were unchanged until the fifth minute (1.5 per cent carbon dioxide) when each began a steady rise but at different rates, with the systolic rising most rapidly and in greatest degree. The pulse rate, P, did not clearly accelerate until the 19th minute (about 5.8 per cent CO_2). The minute-volume, V, of breathing increased from the beginning, while the frequency, R, of breathing did not definitely increase until the 18th minute (5.5 per cent CO_2). The depth of breathing clearly increased from the beginning and was responsible for the increase in the minute-volume. In this experiment the respiratory response to carbon dioxide is in evidence before the vasomotor system or the heart are stimulated. The order and time at which the several factors responded in this case are typical for men generally.

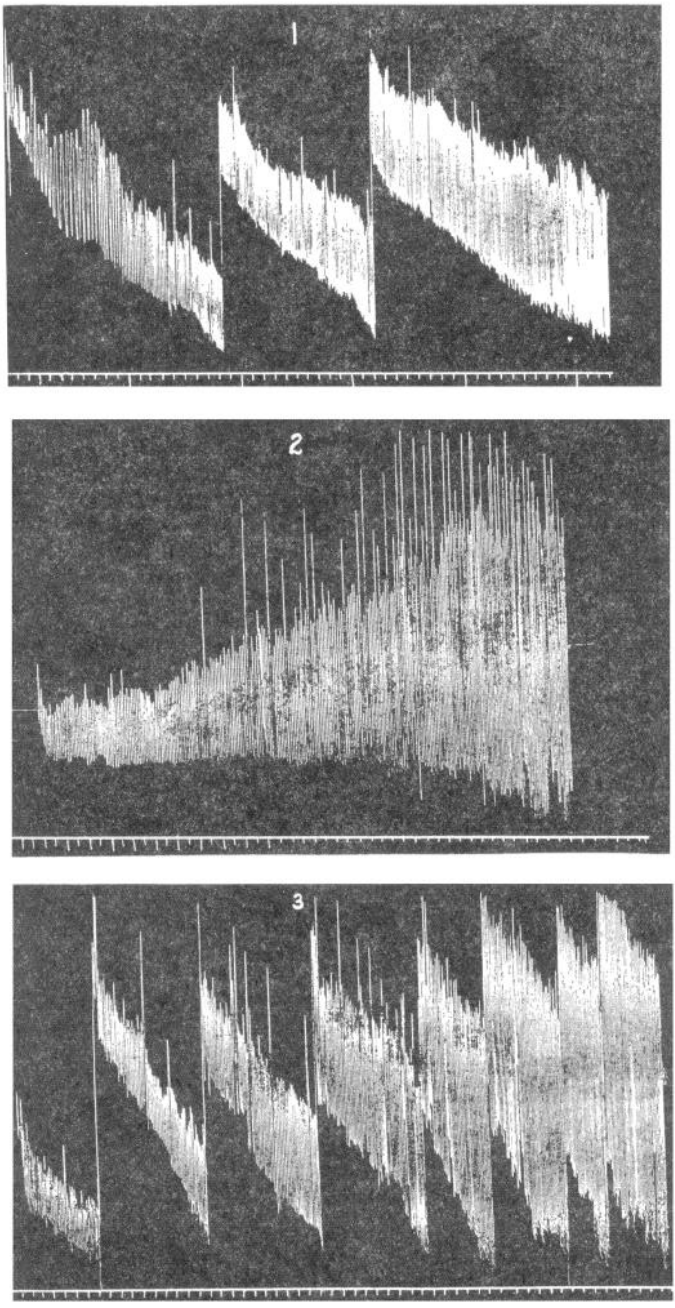

Fig. 5. Types of respiratory response

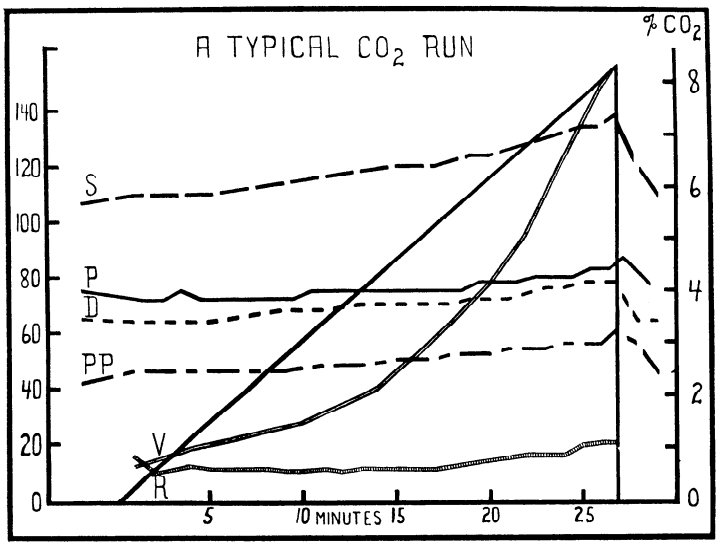

Fig. 6. Subject E. C. S. Final CO_2, 8.4 per cent. *S*, systolic pressure; *D*, diastolic pressure; *PP*, pulse pressure; *P*, pulse rate; *V*, minute-volume of breathing; *R*, frequency of breathing.

SUMMARY

1. The effects of a gradual increase in carbon dioxide have been determined in two types of experiments, in one the oxygen was maintained at about 30 per cent and in the other the oxygen decreased as the carbon dioxide accumulated in the inspired air.

2. The pulse rate usually first accelerated at about 5 per cent carbon dioxide, sometimes as early as 1 per cent. An after-effect usually was present for 5 to 7 minutes.

3. The systolic, diastolic and pulse arterial blood pressures always increased, ordinarily beginning to rise at between 2 and 4 per cent carbon dioxide. The systolic pressure rises most rapidly, but the diastolic rise is frequently seen first. The after-effect is fleeting.

4. The capillary blood pressure rises steadily as the inspired carbon dioxide increases and shows no after-effect.

5. The venous blood pressure always rises and begins to do so as early as 1 per cent of carbon dioxide. An after-effect of from 5 to 10 minutes occurs.

6. The changes in hand volume were an increase up to about 3 per cent carbon dioxide, followed by a gradual decrease to below normal.

7. The blood flow through the hand decreased as the inspired carbon dioxide increased, while the minute-volume from the heart was not materially altered.

8. The minute-volume of breathing increased gradually and smoothly from the very beginning of the accumulation of carbon dioxide in the inspired air. The volume per breath usually increased as early as the minute-volume.

9. The frequency usually increased later than the depth of breathing, but had accelerated in 60 per cent of all experiments before 4 per cent of carbon dioxide was reached.

We wish here to express our appreciation of assistance given by Major L. H. Bauer.

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