THE RESPIRATORY AND CIRCULATORY RESPONSE OF NORMAL MAN TO INHALATION OF 7.6 AND 10.4 PER CENT CO₂ WITH A COMPARISON OF THE MAXIMAL VENTILATION PRODUCED BY SEVERE MUSCULAR EXERCISE, INHALATION OF CO₂ AND MAXIMAL VOLUNTARY HYPERVENTILATION

ROBERT D. DRIPPS AND JULIUS H. COMROE, JR.

From the Department of Pharmacology and the Harrison Department of Surgical Research*
School of Medicine, the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania and the Division of Anesthesia, Hospital of the University of Pennsylvania

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The effects of inhalation of low concentrations of CO₂ have been investigated widely in man (1, 2, 3, 4). The effects produced by higher concentrations (7.5–10 per cent CO₂) have been recorded incompletely and only upon small groups. To supplement our knowledge of the quantitative aspects of respiration and circulation it seemed worthwhile to measure the response of a large group of normal subjects to these higher concentrations of carbon dioxide. In addition the maximal respiratory minute volume produced by inhalation of 7.6 per cent and 10.4 per cent CO₂ was compared with that resulting from exhausting muscular exercise and maximal voluntary hyperventilation.

METHODS. Forty-four male medical students between the ages of 21 and 26 served as subjects. Eighteen of these had just completed a six weeks program of athletic training and were in excellent physical condition.

A typical experiment was conducted as follows: The subject sat either upon a chair or a stationary bicycle. No attempt was made to secure a basal state. An aviation type half-mask was strapped tightly to the face. The subject breathed through rubber valves (Japanese gas mask type) which offered minimal resistance. Expired air was conducted through tubing 1½ inches in diameter to a balanced compensating 300 liter spirometer. Measurement of the volume of expired air (not corrected to S.T.P.) respiratory rate, pulse rate and systolic and diastolic blood pressure were recorded. Some or all of the following procedures were then completed: 1, determination of maximal voluntary breathing capacity (5) over a half-minute period; 2, inhalation of “7.6 per cent CO₂” in oxygen (mixtures varied from 7.4 to 7.8 per cent CO₂); 3, inhalation of 10.4 per cent CO₂ in oxygen, and 4, exercise at a maximal rate upon a heavily loaded stationary bicycle. This exercise consisted of a “warm-up” period of several minutes on the bicycle followed by exertion at a maximal rate of pedalling for 60–75 seconds. All subjects except one considered this to be exhausting. Carbon dioxide mixtures were supplied in 6,000 liter high pressure tanks. Each tank was connected through a regulator to a 10 liter rubber bag which was attached to the

*This work was performed under contract with the Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland.
inspiratory valve of the mask when desired. The bag was kept approximately half full during periods of CO₂ inhalation. The system did not permit re-breathing. The inhalations of CO₂ were continued until the respiratory minute volume reached a plateau (not more than 10 per cent variation during four consecutive thirty second periods) or until the subject became definitely uncomfortable. After each procedure, the subject was allowed to have a 5-10 minute rest. During this period, the subject breathed room air. Twenty-three subjects performed the maximal voluntary breathing capacity test, 42 inhaled 7.6 per cent CO₂, 31 breathed 10.4 per cent CO₂ and 25 exercised on the bicycle.

RESULTS. 1. Respiration. The maximal minute volume, rate and depth of breathing attained by the subjects inhaling 7.6 and/or 10.4 per cent CO₂ are recorded in table 1. The averages of the maximal minute volumes were 51.5 liters per minute for 7.6 per cent CO₂ and 76.3 liters per minute for 10.4 per cent CO₂. Figure 1 shows graphically the average maximal minute volume of subjects breathing 7.6 and 10.4 per cent CO₂. For sake of completeness it includes the data of Shock and Soley (1, 2) and of Heller, Killiches and Drinker (4) dealing with the respiratory responses to 1, 2, 4 and 5 per cent CO₂ inhalation. The extremes encountered in our experiments were widely separated: 24 to 102 liters/min. for 7.6 per cent CO₂ and 40 to 130 liters/min. for 10.4 per cent CO₂. These marked variations could not be correlated with height, weight, surface area, age or maximal breathing capacity.

Plateaus for minute volume were reached in only 27 of 42 individuals breathing 7.6 per cent CO₂ at times varying from 2.5 to 8.5 minutes (average 5.8 min.) and in 13 of 31 subjects inhaling 10.4 per cent CO₂ at times ranging from 2.5 to 6.0 minutes (average 3.5 min.).

The increase in respiratory minute volume was achieved largely by an increase in depth of breathing. Depth of breathing increased approximately four fold while the rate was little more than doubled. The failure of rate to increase until high concentrations of CO₂ are inhaled has been noted by Haldane (3).

When the CO₂-O₂ mixtures were discontinued, respiration returned rapidly to normal. One minute after discontinuing 7.6 per cent CO₂, average respiratory minute volume was 200 per cent of normal, at 2 minutes it was 73 per cent above normal and at 3 minutes it was 29 per cent above normal. One minute after discontinuing the inhalation of 10.4 per cent CO₂, the average respiratory minute volume was 220 per cent above normal, at 2 minutes, 38 per cent and at 3 minutes respiratory minute volume had returned to normal values.

Twenty-seven subjects breathed both 7.6 and 10.4 per cent CO₂ mixtures. In 25 of these, inhalation of the higher concentration led to further increase in minute volume of respiration but in 2 the maximal minute volume of respiration was slightly lower when 10.4 per cent was breathed. In one of these steady maximal values had been reached on both occasions and it appears that 10.4 per cent CO₂ was above the optimal concentration of CO₂ required to produce maximal respiratory stimulation in this subject. In the other maximal values were not reached on either occasion and consequently a similar conclusion is not warranted.

A comparison was made in 19 subjects of the maximal ventilation produced
RESPONSE TO HIGHER CONCENTRATIONS OF CO₂

TABLE 1
The maximal effect of 7.6 and 10.4 per cent CO₂ upon rate, depth and minute volume of respiration

<table>
<thead>
<tr>
<th></th>
<th>7.6% CO₂ (42 SUBJECTS)</th>
<th>10.4% CO₂ (31 SUBJECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>28.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Range</td>
<td>16-72</td>
<td>0.86-3.12</td>
</tr>
<tr>
<td>Standard dev</td>
<td>10.8</td>
<td>0.56</td>
</tr>
</tbody>
</table>

TABLE 2
Comparison of maximal respiratory minute volumes produced by inhalation of 7.6 and 10.4 per cent CO₂, severe muscular exercise and maximal hyperventilation in 19 normal men

<table>
<thead>
<tr>
<th></th>
<th>7.6% BREATHING</th>
<th>10.4% BREATHING</th>
<th>MUSCULAR EXERCISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol.</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>M.B.C.</td>
<td>100</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>% of M.B.C.</td>
<td>100</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>Max Respiration</td>
<td>166</td>
<td>48.9</td>
<td>71.4</td>
</tr>
<tr>
<td>Range</td>
<td>132-198</td>
<td>26-86</td>
<td>40-114</td>
</tr>
<tr>
<td>Standard dev</td>
<td>20.3</td>
<td>15.4</td>
<td>21.4</td>
</tr>
<tr>
<td>% of M.B.C.</td>
<td>100</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>Range</td>
<td>80-140</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Standard dev</td>
<td>10.8</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 Respiratory response to CO₂. The data of Shock and Soley for 1, 2 and 4 per cent CO₂ in air and those of Heller et al. for 5 per cent CO₂ in air are included. The hatched line represents one standard deviation on each side of the mean. The solid bar represents the standard error of the mean on each side of the mean. The smoothest possible curve is drawn through the solid bars.
\( a \), by inhalation of 7.6 and 10.4 per cent \( \text{CO}_2 \); \( b \), by severe muscular exercise, and 
\( c \), by voluntary hyperventilation (maximal breathing capacity) (table 2). The 
averages were 48.9 liters for 7.6 per cent \( \text{CO}_2 \), 71.4 for 10.4 per cent \( \text{CO}_2 \) in-
halation, 109.6 for muscular exercise and 166 liters per minute for voluntary 
hyperventilation. Our values for maximal breathing capacity are higher than 
those reported by others (5); this is probably due to the fact that our subjects 
breathed through both mouth and nose instead of through a mouthpiece alone. 
Our figures for the maximal ventilation during severe exercise are as high or higher 
than those previously reported; three of our subjects had minute volumes in 
excess of 130 liters per minute. In only seven instances was the hyperpnea 
produced by \( \text{CO}_2 \) as much as 50 per cent of the maximal breathing capacity and 
in only two cases was it more than 60 per cent (65 and 71 per cent) of the maximal 
breathing capacity. In only two subjects did the hyperpnea produced by \( \text{CO}_2 \) 
inhalation exceed that produced by severe muscular exercise; in one of these the 
load on the bicycle was insufficient to cause exhausting work.

\[ \text{TABLE 3} \]

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects</th>
<th>Change in Pulse Rate per Min.</th>
<th>Increase in Systolic B.P. mm Hg</th>
<th>Increase in Diastolic B.P. mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Range</td>
<td>Average</td>
</tr>
<tr>
<td>7.6% ( \text{CO}_2 )</td>
<td>42</td>
<td>+16.7</td>
<td>-10 to +68</td>
<td>34</td>
</tr>
<tr>
<td>10.4% ( \text{CO}_2 )</td>
<td>29</td>
<td>+15.6</td>
<td>-4 to +36</td>
<td>29</td>
</tr>
</tbody>
</table>

2. Circulation. The average of the maximal observed increases in pulse rate, 
systolic blood pressure and diastolic blood pressure produced in each subject by 
inhalation of 7.6 and 10.4 per cent \( \text{CO}_2 \) are shown in table 3. The circulatory 
changes from subject to subject were just as variable as the respiratory responses 
though there was little correlation between the two; the several individuals who 
had the greatest increases in respiration with \( \text{CO}_2 \) inhalation did not have the 
greatest increases in circulation. The 7.6 per cent \( \text{CO}_2 \) mixture was breathed for 
an average of 7.4 minutes. In 30 of the 34 subjects blood pressure reached a 
plateau (fluctuations over a two minute period were less than 10 per cent). The 
10.4 per cent \( \text{CO}_2 \) mixture was inhaled for an average of 3.8 minutes 
and blood pressure determinations during the inhalation became stabilized in only 
13 of the 30 individuals. The data in table 3 suggest that 10.4 per cent \( \text{CO}_2 \) 
was no more potent a circulatory stimulant than the 7.6 per cent mixture. This 
interpretation may not be justified because of the relatively brief exposure to 
the higher concentration.

Immediately following the removal of the bag containing \( \text{CO}_2 \) mixtures, the 
diastolic blood pressure often fell abruptly, while the systolic pressure decreased 
only slightly. The average immediate fall in diastolic pressure in the 29 subjects
breathing 10.4 per cent CO₂ was 31.2 mm. Hg and in systolic pressure was only 7.4 mm. Hg. The fall in diastolic pressure was usually followed by an acceleration of the pulse and a prompt return toward previous figures. This phenomenon had been noted previously by Goldstein and DuBois (6).

3. Symptoms incident to inhalation of CO₂. The symptoms most frequently noted during or following inhalation of 7.6 per cent CO₂ were headache in 23 (55 per cent), dizziness in 14 (33 per cent) and dyspnea in 13 (31 per cent). The symptoms noted most often incident to inhalation of 10.4 per cent CO₂ were dizziness in 18 (58 per cent), headache in 13 (42 per cent) and dyspnea in 10 (32 per cent) (table 4). Seventy-two per cent of the headaches occurred either in the period immediately after withdrawal of the CO₂ mixture or became accentuated at that point. In three subjects inhalation of 10.4 per cent CO₂ abolished a headache which had been initiated by 7.6 per cent CO₂ and persisted after the shift to room air. Forty-one per cent of the dizziness was first noted or accentuated in the immediate post inhalation period. These symptoms appeared at the same time as the abrupt fall in diastolic blood pressure. However, the average drop in diastolic blood pressure of those subjects with post CO₂ headache or dizziness was exactly the same as for the group which failed to note these symptoms.

Other symptoms noted were: Irritation of nose, palpitation, mental clouding, dimness of vision, muscle tremor or twitching, "generally uncomfortable", tingling, cold extremities, exhaustion, mental depression, substernal pain and "sensation as though in first stage of nitrous oxide anesthesia."

It is interesting to note the levels of ventilation at which dyspnea was noted. Those who noted no dyspnea had maximal minute volumes ranging from 24 to 114 (average 60 liters per min.), those who noted slight to moderate dyspnea had maximal minute volumes ranging from 29 to 110 (average 62.7 liters per min.) and those who had marked dyspnea had minute volumes between 50 and 130 liters per minute (average 86.8).

TABLE 4

Major symptoms incident to CO₂ inhalation

<table>
<thead>
<tr>
<th></th>
<th>7.6% CO₂ (42 SUBJECTS)</th>
<th>10.4% CO₂ (31 SUBJECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During inhalation</td>
<td>Only after inhalation</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Sweating</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Faintness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fullness in head</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The symptoms noted were: Irritation of nose, palpitation, mental clouding, dimness of vision, muscle tremor or twitching, "generally uncomfortable", tingling, cold extremities, exhaustion, mental depression, substernal pain and "sensation as though in first stage of nitrous oxide anesthesia."
Discussion. Marked individual variations in respiratory and circulatory responses to CO\textsubscript{2} inhalation have been noted previously. Figure 1, which illustrates the average maximal minute volumes, with one standard deviation and a standard error of the mean on either side of the mean, shows that these individual differences are most pronounced when high concentrations of CO\textsubscript{2} are inhaled. Low concentrations of CO\textsubscript{2} act almost wholly on the medullary centers while high concentrations may act upon the chemoreceptors as well (7). Consequently this variability of response to high concentrations of CO\textsubscript{2} can be due to differences in sensitivity of either the medullary center or of the chemoreceptors. It is known that human chemoreceptors vary widely in their response to another stimulus, anoxia (8). Six of our subjects who had excellent respiratory responses to 7.6 per cent CO\textsubscript{2} inhalation were given 10 per cent O\textsubscript{2} to breathe; in each case a poor response to anoxia was observed. This is only presumptive evidence however that the chemoreceptors were not involved in the CO\textsubscript{2} response, since their sensitivity to low O\textsubscript{2} and to high CO\textsubscript{2} tension might not run parallel. Since the individual variations could not be correlated with height, weight, surface area, maximal breathing capacity or with chemoreceptor response to anoxia, it is probable that they represent differences in the sensitivity of the medullary centers to increased CO\textsubscript{2} tension.

It is not certain that the maximal responses obtained in this study represent the maximal capacity of an individual to react to CO\textsubscript{2} since we did not determine responses to concentrations of CO\textsubscript{2} higher than 10.4 per cent. Brown (9) exposed 7 subjects to 12.4 per cent CO\textsubscript{2} and found that the respiratory responses in six were less than when 10.4 per cent CO\textsubscript{2} was inhaled. Since 12.4 per cent CO\textsubscript{2} could be inhaled only two minutes, it is possible that sufficient time did not elapse for full CO\textsubscript{2} action. On the other hand, it must be remembered that the observed effect of CO\textsubscript{2} is the algebraic sum of two factors: 1, a direct stimulant effect of CO\textsubscript{2} upon the medullary centers and chemoreceptors, and 2, a narcotic action (10) which tends to depress the respiratory center. It appears probable that despite the vigorous hyperpnea in our subjects a narcotic effect was occurring simultaneously. In support of this view is the finding that 33 per cent of those breathing 7.6 per cent CO\textsubscript{2} complained of dizziness and 58 per cent of those inhaling 10.4 per cent CO\textsubscript{2} had this symptom. Seven (23 per cent) of those breathing 10.4 per cent CO\textsubscript{2} felt as though they were about to faint, 2 (6 per cent) were completely unaware of their surroundings, 2 (6 per cent) noted a similarity to the onset of nitrous oxide anesthesia, 1 (3 per cent) became unconscious and 1 (3 per cent) noted analgesia.

Two other aspects of this narcotic effect are of interest. First, it is probable that inhalation of high concentrations of CO\textsubscript{2} in the treatment of individuals with depressed medullary centers (due to anesthesia, morphine or barbiturate poisoning, carbon monoxide poisoning) may produce further narcosis, whether hyperpnea or hypertension develops or not. Consequently, if increased ventilation alone is desired, it might be preferable to produce this by mechanical means. When other effects of CO\textsubscript{2}, such as cerebral vasodilatation, shift in H\textsubscript{b}O\textsubscript{2} or H\textsubscript{b}CO dissociation curves are indicated, the narcotic effect of CO\textsubscript{2} must be borne
in mind. Second, the narcotic effect might be a partial explanation of the finding that inhalation of high concentrations of CO₂ produces only 43 per cent (average) of the maximal ventilation possible by voluntary hyperventilation. Since many physiologists believe that CO₂ is the most potent stimulant to respiration, its inhalation should produce higher minute volumes unless inhibitory factors act concurrently. One inhibitory factor may arise from the increase in blood pressure, which through pressure receptor reflexes may inhibit the medullary respiratory center. Another factor may be the narcotic action of CO₂. It is probable that, though 20–30 per cent CO₂ may be needed for the production of surgical anesthesia, concentrations in the 10.1 per cent range may produce less marked but definite cerebral and medullary depression.

Hardgrove, Roth and Brown (11) stated that 10 per cent CO₂ could be inhaled for five minutes without ill effects. Only two of our 31 subjects and none of Brown's (9) were able to tolerate 10.4 per cent CO₂ for five minutes because of dyspnea, headache, dizziness, faintness or fainting. Our and Brown's concentration of CO₂ was 0.4 per cent higher than Hardgrove et al.'s and this may be a partial explanation. The recumbent position in Hardgrove's group may also have aided in the tolerance to CO₂ inhalation.

Our experiments indicate that after high concentrations of CO₂ were breathed for short periods of time (2.5 to 10 min.), CO₂ was eliminated rapidly from the body since the respiratory minute volume returned to normal within 3 minutes (average). Such rapid elimination does not always occur, however, if the blood CO₂ has been elevated for hours instead of minutes or if the blood pressure is low instead of abnormally high (12).

An opportunity was afforded in these experiments to note the level of minute volume at which the subjects noted dyspnea. Several subjects breathing more than 100 liters per minute insisted that they had no dyspnea, though they noticed augmented respirations. This re-emphasizes that dyspnea bears no consistent relation to the minute volume of respiration. Some subjects did not even notice augmented respiration (hyperpnea) when breathing 30–40 liters per minute.

Barcroft and Margaria (13) noted upon themselves that the hyperpnea following inhalation of CO₂ was considerably less than that produced by severe exercise. Our findings upon a much larger series confirm their observations and also their conclusions that the small changes in arterial pCO₂ occurring during muscular exercise cannot be an explanation for the hyperpnea of muscular exercise. It is believed that many factors contribute to the increased ventilation of exercise, of which maintenance of arterial pCO₂ at near-normal levels is only one (14).

Attention should be called to the fact that subjects performing strenuous muscular exercise usually do not breathe more than 66 per cent of the maximal breathing capacity, even at a time when their working muscles have incurred an oxygen debt. The muscles therefore are not able (either by activation of stretch receptors or by elaboration of chemical substances locally or into the general circulation) to increase respiration to a maximum. This failure of
respiration to increase to maximal capacity may be due to fatigue of the respiratory muscles (this is not an important factor in the maximal breathing capacity test which lasts for only 30 sec.) or to the presence of inhibitory factors. The rise in blood pressure associated with strenuous exercise may be such a factor by inhibitory reflexes aroused in the carotid sinus and aortic arch pressure receptors. The failure of respiration to increase further may also be due to the fact that fatigue of the leg muscles rather than dyspnea was the factor which limited the severity and length of the exercise.

The rapidity of fall in diastolic blood pressure at the termination of the CO₂ inhalation at a time when systolic blood pressure and respiration have returned only partially toward normal indicates a sudden decrease in peripheral resistance. It is known that CO₂ has a direct vaso-dilator effect on peripheral vessels, which is masked by a stimulant effect upon the medullary vasoconstrictor center. The abruptness of fall in diastolic blood pressure suggests a sudden withdrawal of a vasoconstrictor reflex rather than a gradual decrease in stimulant amounts of CO₂ acting upon the vasomotor center. Whether such a reflex could arise in the respiratory passages in response to irritant concentrations of CO₂ or in the chemoreceptors in response to abnormally high levels of arterial pCO₂ is a matter for speculation. It has been suggested that the sudden reduction of high arterial or alveolar CO₂ tensions may play a part in the production of “cyclopropane shock”, in which systolic and diastolic blood pressure may fall abruptly at the termination of long periods of depressed respiration and CO₂ accumulation (15).

**SUMMARY AND CONCLUSIONS**

The respiratory and circulatory responses of normal young men to inhalation of 7.6 and 10.4 per cent CO₂ were measured.

When 7.6 per cent CO₂ in oxygen was inhaled (42 subjects) the average minute volume of respiration increased to a maximum of 51.5 liters per minute (range 24 to 102), pulse rate increased by 16.7 beats per minute and blood pressure rose 30.8 mm.Hg systolic and 22.2 mm.Hg diastolic.

When 10.4 per cent CO₂ in oxygen was inhaled (31 subjects) the average maximal minute volume rose to 76.3 liters per minute (range 40 to 130), pulse rate increased 15.6 beats per minute and blood pressure rose 33.4 mm.Hg systolic and 25.0 mm.Hg diastolic.

When the CO₂ inhalation was stopped, respiration and systolic blood pressure returned slowly to normal; diastolic blood pressure fell abruptly upon removal of the mask, often to lower than control figures.

A comparison was made in 19 subjects of the maximal ventilation produced by a, inhalation of 7.6 per cent CO₂; b, inhalation of 10.4 per cent CO₂; c, exhausting muscular exercise, and d, maximal voluntary hyperventilation; the average figures were 48.9, 71.4, 109.6 and 166 liters per minute, respectively. The reasons for the failure of the body to respond with greater hyperpnea to high concentrations of CO₂ and severe muscular exercise are discussed.

Data bearing upon the following are included: 1, the times for which 7.6 and 10.4 per cent CO₂ are tolerated by healthy men; 2, the symptoms produced
by these concentrations, and 3, the degree of hyperpnea at which dyspnea was noted by normal subjects.

REFERENCES

(1) SHOCK, N. W. AND M. H. SOLEY. This Journal 130: 777, 1940.
(2) SHOCK, N. W. AND M. H. SOLEY. This Journal 137: 256, 1942.
(6) GOLDSTEIN, J. D. AND E. L. DUROIS. This Journal 81: 650, 1927.
(8) DRIPTS, R. D. AND J. H. COMROE, JR. This Journal to be published.
(15) DRIPTS, R. D. Anesthesiology, 8: 15, 1947.