Effects of Breathing 10 Per Cent Carbon Dioxide on the Pulmonary Circulation of Human Subjects

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SUMMARY
The effects on the pulmonary circulation of breathing 10% CO₂ for 10 to 20 min were studied in five eucapnic and 11 convalescing hypercapnic patients to recreate the CO₂ tensions which they had experienced during respiratory failure. Right heart catheterization permitted measurements of pulmonary arterial and wedge pressures and obtaining samples of mixed venous blood. Breathing CO₂ increased mean pulmonary arterial pressures from 33 to 50 mm Hg (52%); pulmonary arterial wedge pressures were unchanged, and cardiac output increased only 22%. In three hypercapnic and two eucapnic subjects reduction of blood hydrogen ion levels by rapid infusion of 120 to 135 mEq NaHCO₃ during CO₂ breathing did not lower pulmonary arterial pressure significantly, nor raise cardiac output. Neither vascular pressures nor cardiac outputs changed during oxygen breathing. Larger increases in cardiac output, which were produced by exercise, raised pulmonary artery pressure only half as much as breathing 10% CO₂ did. Therefore, pulmonary vascular resistance (PVR) that was elevated to an average of 4.8 mm Hg/L/min at rest while breathing air was increased to 6.5 mm Hg/L/min during CO₂ breathing (P < 0.01). In contrast, PVR was unchanged (4.6 mm Hg/L/min) during exercise. This difference between PVR while breathing CO₂ and during exercise was statistically significant (P < 0.02). Restoration of the pH of the blood toward normal by the infusion of bicarbonate during breathing of CO₂ raised the pulmonary arterial pressure. The five eucapnic subjects showed similar changes during CO₂ breathing and exercise, although their base-line values were significantly different. The differences were due, at least in part, to lower Paco2. This evidence suggests that CO₂ acts on pulmonary arterioles and capillaries that are exposed to alveolar gases to increase the pulmonary vascular impedance.

Additional Indexing Words:
Cardiac output Pulmonary hypertension Acidosis Exercise Pulmonary function Cor pulmonale

Patients with severe hypoxia and hypercapnia due to respiratory failure have pulmonary hypertension which decreases or disappears as they recover. Severe hypoxia has been shown to raise pulmonary artery pressure in human subjects and experimental animals, probably by direct effects on small blood vessels. Mild hypercapnia and acidosis produced by breathing 5% CO₂, however, have raised pulmonary artery pressure only

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sions of sodium bicarbonate during CO₂ breathing to reduce arterial and venous blood hydrogen ion levels were studied in several patients. The effects of breathing CO₂ were compared to those of raising cardiac output to a similar degree by moderate exercise. Finally the effects on the pulmonary circulation of lowering CO₂ by hyperventilation and of breathing oxygen were assessed in certain patients. The results of this investigation suggest that alveolar CO₂ tension causes the small vessels in the lungs of human subjects to increase vascular resistance. Moreover, this effect does not depend upon increased blood flow, hypoxia, or changes in the H-ion level of arterial blood.

Methods

**Group Studied**

Sixteen hospitalized male patients were studied. Eleven had bronchitis with persistent hypercapnia (group 1), and five were eucapnic.

**Table 1**

**Clinical Features of the 11 Hypercapnic Patients with Bronchitis and 5 Eucapnic Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Dyspnea*</th>
<th>Smoking (pack-yr)</th>
<th>Cough (yr)</th>
<th>Sputum (ml/day)</th>
<th>Dyspnea (yr)</th>
<th>Asthma</th>
<th>Roentgenogram</th>
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</tr>
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</tr>
<tr>
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<td>++++</td>
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<td>7</td>
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<td>4E</td>
</tr>
<tr>
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<tr>
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</table>

* Walking; + = two flights of stairs; ++ = slightly up hill or hurrying on level; +++ = limited distance at own pace on level.
† E = emphysema, grade 1–4.
‡ Obesity.

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EFFECTS OF CO₂ ON PULMONARY CIRCULATION

and had other chronic pulmonary diseases (group 2). The 11 hypercapnic patients had chronic bronchitis, which was diagnosed by chronic coughs productive of sputum, and had been admitted to the hospital because of respiratory failure (tables 1 and 2). Seven of these bronchitic patients had, in addition, three or more of the roentgenographic signs of emphysema. These signs consisted of a lung field length equal to or greater than the width, flat diaphragms on posteroanterior chest roentgenograms, flat diaphragms on lateral chest roentgenograms, a retrosternal clear space greater than 2.5 cm, and bullae, clear areas, or evidence of vascular "pruning." All hypercapnic patients were moderately to severely disabled and had been dyspneic for 6 to 30 years, the average being 16.9 years. Four patients had paroxysmal dyspnea associated with severe wheezing (asthma). Average cigarette consumption of the group was 45.6 pack-years. (The smoking of one package of 20 cigarettes per day for 1 year equals one packyear).

The patients' average weight was 161 pounds. Nine had lost weight during hospitalization, and seven of these had been edematous at the time of admission. However, all 11 gave histories of pitting edema of the ankles. Hematocrit values were elevated in nine patients. Vital capacities were moderately to severely reduced and maximal midexpiratory flow rates (MMEF) which averaged 0.41 L/sec showed severe airway obstruction. At the time of hospitalization arterial blood carbon dioxide tensions (Paco₂) were between 54 and 96 mm Hg and averaged 70.5 mm Hg and oxygen tensions (Pao₂) were between 33 and 55 mm Hg and averaged 39.5 mm Hg. Eight patients were acidotic at the time of admission.

The five eucapnic subjects had not been in respiratory failure. Three were asthmatic and two had pulmonary bullae but no other roentgenographic signs of emphysema. They were younger, between 31 and 48 years, their pulmonary function was much less impaired (tables 1 and 2), and they had smoked less than half as many cigarettes per capita as had the hypercapnic group. Chronic coughs had been present for a shorter time, and only three patients produced sputum. Dyspnea had been present only one third

Table 2

Circulatory and Respiratory Findings in Hypercapnic and Eucapnic Patients When Admitted to the Hospital

<table>
<thead>
<tr>
<th>Patient</th>
<th>Body wt (lb)</th>
<th>Wt loss (lb)</th>
<th>Edema</th>
<th>Hematocrit (ml/100 ml)</th>
<th>Vital capacity (L)</th>
<th>MMEF* (L/sec)</th>
<th>Paco₂ (mm Hg)</th>
<th>Pao₂ (mm Hg)</th>
<th>[H⁺] (nM/L)</th>
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<td>0.36</td>
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<td>72</td>
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<td>42.7</td>
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<td>(7)</td>
<td>55</td>
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<td>0.41</td>
<td>70.5</td>
<td>39.5</td>
<td>46.6</td>
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</table>

| Eucapnic |              |              |        |                        |                   |               |              |              |             |
| 12       | 316          | 61           | 2+     | 55                     | 2.33              | 1.36          | 68.5         | 43           | 38.9        |
| 13       | 168          | 0            | 0      | 49                     | 3.27              | 0.71          | 46.5         | 76           | 41.2        |
| 14       | 274          | 49           | 3+     | 68                     | 3.68              | 0.89          | 45.2         | 52           | 43.6        |
| 15       | 169          | 0            | 0      | 40                     | 3.79              | 1.90          | 40           | 55           | 39.9        |
| 16       | 166          | 0            | 0      | 44                     | 4.84              | 1.75          | 39.5         | 69           | 39.8        |
| Mean     | 218.6        | 55.0         | 2.5    | 51.5                   | 3.58              | 1.32          | 47.8         | 66.6         | 40.5        |

* MMEF = maximal midexpiratory flow rate (the average flow rate from 25% to 75% of a forced expiration).

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as long as in the hypercapnic group. Two patients who were obese and had had hypercapnia, elevated hematocrits, and edema at the time of admission lost 49 and 61 pounds while hospitalized. These findings were consistent with the obesity-cardiopulmonary insufficiency syndrome. Both patients had become compensated and were eucapnic at the time of study. These five men had larger vital capacities and less obstruction to air flow than the hypercapnic group. They were not hypercapnic nor acidicotic and were only moderately hypoxic when studied.

Procedures

Airway obstruction and moderate hypercapnia in patients of group 1 made it feasible to expose them to exogenous CO₂ to recreate or slightly exceed their endogenous CO₂ levels when in respiratory failure. Thus, certain physiological features of the previous acute illness were simulated in the laboratory. However, the other five patients also tolerated CO₂ breathing for at least 12 min. Patients were studied after they had reached a plateau of clinical improvement measured by normal or stable arterial blood oxygen and PaCO₂ and H-ion concentrations. No patient had signs or symptoms of coronary artery disease, systemic hypertension, or myocardial failure.

The subjects were studied while resting supine in the postabsorptive state without premedication. Venous catheterization of the right heart was done in the conventional manner under fluoroscopic control percutaneously from an antecubital vein. This permitted measurement of pulmonary wedge and pulmonary arterial pressures and the obtaining of mixed venous blood samples. A catheter was inserted into a brachial artery percutaneously to measure arterial blood pressure and to obtain blood samples.

Pressures were measured with strain-gauge pressure transducers (Statham P23Db) and registered photographically with appropriate amplification by an oscilloscopic amplifier-recorder system (Electronics for Medicine PR-8). Pressure transducers were mounted at a level of 5 cm below the sternal angle. Mean pressures were obtained by electrical averaging and checked by planimetry of pressure tracings. Pressures were measured continuously during breathing of CO₂ or O₂ mixtures and during exercise or other experimental states except during sampling of blood.

Expired gas was collected in Douglas bags for 2 to 3 min and analyzed for O₂ and CO₂ content to calculate oxygen consumptions and respiratory exchange ratios. The CO₂ content was measured from the increase in O₂ concentration in the expired gas samples after absorption of CO₂, using a paramagnetic O₂ analyzer. Arterial and mixed venous blood samples obtained anaerobically during gas collections were analyzed for O₂ and CO₂ tensions in a physiological blood tension analyzer (Instrumentation Laboratories) using Severinghaus and modified Clark electrodes. Blood pH was measured in a glass electrode pH meter at 37 C. Oxygen content of arterial and mixed venous blood was measured by a spectrophotometric method except during oxygen breathing, when it was measured by the method of Van Slyke. Cardiac outputs were calculated by the Fick principle. Pulmonary vascular resistance (mm Hg/L/min) was calculated from the pulmonary artery pressure minus pulmonary wedge pressure divided by cardiac output.

After 10 or more minutes of rest following the insertion of catheters, pulmonary vascular pressure and cardiac output were measured in duplicate while patients breathed room air. Thereafter, the patient breathed 9 to 10% CO₂ in 21% O₂ and 69% nitrogen for at least 10 min. Pressures and cardiac outputs were remeasured twice in sequence for 2-min intervals after 6 min. Following the second cardiac output while breathing 10% CO₂, eight patients were given intravenous infusions of sodium bicarbonate 80 to 130 mEq in 200 to 300 ml of 5% glucose in water for 2 to 3 min. Thereafter, in five subjects expired gas and blood samples were collected and pressures were obtained to measure changes in cardiac output and vascular pressures.

Twenty minutes following the second determination of cardiac output during breathing of CO₂ or the bicarbonate infusion, cardiac output was measured again while the patient was supine and breathing room air. Thereafter patients breathed 40% or 100% O₂ for 10 to 15 min and pressures and cardiac outputs were remeasured. The oxygen consumption was measured using a 13.5 L spirometer containing a CO₂ absorber. Thereafter, patients exercised by pedaling a bicycle while lying supine and breathing room air to at least double their resting O₂ consumptions. Cardiac outputs and vascular pressures were measured during 2 min after 5 min of exercise. The purpose of exercise was to raise cardiac output to a level comparable to that achieved during breathing of CO₂ in the same subjects without changing blood gases. This was done to help distinguish that portion of the increase in pulmonary arterial pressure during CO₂ breathing attributable to increased cardiac output from that due to primary effects of CO₂ on pulmonary vessels.

In one hypercapnic and one eucapnic patient pressures and cardiac outputs were measured during continuous hyperventilation and compared...
EFFECTS OF CO₂ ON PULMONARY CIRCULATION

643
to values while at rest and breathing air. Carbon dioxide tension was reduced by 10 to 20 mm Hg by an intermittent positive pressure respirator with a ventilatory rate of 10 and a tidal volume of 900 to 1,200 ml. Finally, three patients who were studied while in respiratory failure were restudied after recovery, one at 14 days, one at 120 days, and one at 1 year to compare circulatory parameters after endogenous CO₂ tensions had been reduced to normal.

Pulmonary angiograms were obtained in seven hypercapnic and three eucapnic subjects at the completion of the measurement of pressures and cardiac outputs. While patients were supine, two anteroposterior films were exposed each second by a rapid cassette changer after the injection of 50 ml of contrast medium (Conray 400) into the main pulmonary artery or the right ventricle through the catheter.

Data for hypercapnic and eucapnic subjects are arranged in tables 3 and 4 by descending \( \text{Paco}_2 \) in the resting control samples. Pulmonary arterial and wedge pressures in the text and tables are mean pressures which reflected similar changes in systolic and diastolic pressures. The statistical significance of changes in mean differences for each parameter from control levels in each group during breathing 10% CO₂, exercise, and breathing O₂ were evaluated by the Student's \( t \)-test. The significance of the differences between responses to breathing CO₂ and exercise in each group and the differences in resting values between the eucapnic and hypercapnic patients were tested similarly.

Table 3

Comparative Effects of Breathing 10% CO₂ and of Supine Bicycle Exercise on Pulmonary Circulation, Arterial Blood CO₂ and O₂ Tensions, H-ion Levels, and Ventilation in 11 Bronchitic Patients

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<th>Patient</th>
<th>Status</th>
<th>( \text{Paco}_2 ) (mm Hg)</th>
<th>( \text{Pao}_2 ) (mm Hg)</th>
<th>H ion (nM/L)</th>
<th>( \text{Ppa} ) (mm Hg)</th>
<th>( \text{CO} ) (L/min)</th>
<th>( \text{PVR} ) (mm Hg)</th>
<th>( \text{Vd} ) (L/min)</th>
<th>( \text{Vo} ) (ml/min)</th>
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* Sequential cardiac outputs during the breathing of 10% CO₂.
### Table 4

Comparative Effects of Breathing 10% CO₂ and of Supine Bicycle Exercise on Pulmonary Circulation, Arterial Blood CO₂ and O₂ Tensions, H-ion Levels, and Ventilation in Five Eucapnic Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Status</th>
<th>PaCO₂ (mm Hg)</th>
<th>PaO₂ (mm Hg)</th>
<th>H ion (nM/L)</th>
<th>F_Pa (mm Hg)</th>
<th>CO (L/min)</th>
<th>PVR (mm Hg/L/min)</th>
<th>F_RA (mm Hg)</th>
<th>V̇E (L/min)</th>
<th>̇V̇O₂ (ml/min)</th>
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* Sequential cardiac outputs during breathing of 10% CO₂.
† Hyperventilating.

### Table 5

Responses to Breathing 10% CO₂, to Supine Exercise and to Breathing Oxygen of 11 Hypercapnic Subjects and Five Eucapnic Subjects

<table>
<thead>
<tr>
<th>Activity (inspired gas)</th>
<th>Rest</th>
<th>Room air</th>
<th>10% CO₂</th>
<th>21% O₂</th>
<th>P*</th>
<th>Exercise</th>
<th>P†</th>
<th>P‡</th>
<th>Rest (40-100% O₂)</th>
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<td>76.3</td>
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<td>&lt;0.001</td>
<td>60.1</td>
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<tr>
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<td>&lt;0.001</td>
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<td>PacO₂ (mm Hg)</td>
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<td>83.1</td>
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<td>&lt;0.001</td>
<td>52.1</td>
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<td>104.0</td>
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</table>

**Hypercapnic**

Eucapnic

| PacO₂ (mm Hg)            |      | 37.9     |         | <0.001 | 64.9|          |     |     |                  |
| 37.9                     |      | 64.9     |         | <0.001 | 43.3|          |     |     |                  |
| H⁺ (nM/L)                |      | 37.0     |         | <0.001 | 56.3|          |     |     |                  |
| 37.0                     |      | 56.3     |         | <0.001 | 40.2|          |     |     |                  |
| PacO₂ (mm Hg)            |      | 76.8     |         | <0.001 | 123.6|          |     |     |                  |
| 76.8                     |      | 123.6    |         | <0.001 | 68.8|          |     |     |                  |
| P_Fa (mm Hg)             |      | 14.6     |         | <0.01  | 30.4|          |     |     |                  |
| 14.6                     |      | 30.4     |         | <0.01  | 23.8|          |     |     |                  |
| CO (L/min)               |      | 8.7      |         | <0.05  | 11.9|          |     |     |                  |
| 8.7                      |      | 11.9     |         | <0.05  | 14.7|          |     |     |                  |
| PVR (mm Hg/L/min)        |      | 1.2      |         | <0.01  | 2.8 |          |     |     |                  |
| 1.2                      |      | 2.8      |         | <0.01  | 1.3 |          |     |     |                  |
| V̇E (L/min)              |      | 8.0      |         | <0.05  | 43.9|          |     |     |                  |
| 8.0                      |      | 43.9     |         | <0.05  | 15.1|          |     |     |                  |
| ̇V̇O₂ (ml/min)           |      | 282      |         | <0.01  | 430 |          |     |     |                  |
| 282                      |      | 430      |         | <0.01  | 600 |          |     |     |                  |
| P_Fa (mm Hg)             |      | 98       |         | <0.01  | 125|          |     |     |                  |
| 98                       |      | 125      |         | <0.01  | 106|          |     |     |                  |

* Significance of the difference between values during 10% CO₂ and control levels.
† Significance of the difference between values during exercise and control levels.
‡ Significance of the difference between values during 10% CO₂ breathing and during exercise. Abbreviations: NS = not significant; + = incomplete data.
EFFECTS OF CO₂ ON PULMONARY CIRCULATION

Figure 1

A proportional relationship was demonstrated between the increase in \( P_{Pa} \) and increase in \( Paco_2 \) produced by breathing CO₂ in both hypercapnic and eucapnic subjects. Two hypercapnic subjects with high control values probably had obliterator pulmonary vascular disease. The two subjects with steep increases had fluid retention at the time of study.

Results

Control Values

The hypercapnic subjects at rest after catheters had been inserted had arterial blood CO₂ tensions between 45 and 65 mm Hg (tables 3 and 5). Hydrogen-ion concentrations (H-ion) varied from 37.5 to 50.1 nM/L. Three subjects were persistently acidotic. Oxygen tensions were between 36 and 63 mm Hg. The mean pulmonary artery pressures (\( P_{Pa} \)) of the hypercapnic subjects averaged 32.9 mm Hg at rest while breathing room air when \( Paco_2 \) averaged 55.4 mean mm Hg (fig. 1). In contrast \( P_{Pa} \) in eucapnic subjects averaged 14.6 mm Hg when mean \( Paco_2 \) averaged 37.9 mm Hg (table 5). Mean pulmonary arterial wedge pressures were between 5 and 8 mm Hg in all patients. Cardiac outputs were higher in the eucapnic than in the hypercapnic group, but the difference in cardiac index of 0.5 L/min/m² was not significant. Average calculated pulmonary vascular resistance (PVR) was four times higher (4.8 mm Hg/L/min) in the hypercapnic group than in the eucapnic patients (1.2 mm Hg/L/min). The differences between the mean values for \( Paco_2 \), H ion, \( PaO_2 \), pulmonary artery pressure, and pulmonary vascular resistance in the two groups were statistically significant \( (P > 0.01) \) although minute ventilation and oxygen consumption were similar.

Carbon Dioxide Breathing

Breathing 10% CO₂ in 21% O₂ and 69% N₂ raised the arterial blood CO₂ tension 21 mm Hg and H-ion concentration 13.2 nM/L (table 5) in the hypercapnic patients. Oxygen tensions rose 37.1 mm Hg; this increase practically abolished the hypoxia which had been present during the control period. Ventilation increased 26%, and oxygen consumption rose 24%. While breathing CO₂ pulmonary artery pressures rose gradually so that they were above control levels after 1 min and were significantly elevated after 5 min. They averaged 17.2 mm Hg or 52% above control levels during the seventh to twelfth minute when cardiac outputs were measured. Mean pulmonary arterial wedge pressures remained normal despite the increased amplitude of intrathoracic pressure changes during breathing of CO₂. Cardiac outputs were only 1.5 L/min above control levels. Thus pulmonary vascular resistance rose to 6.5 mm Hg/L/min from the elevated resting level of 4.8 mm Hg/L/min. Duplicate measurements of cardiac output and of respiratory exchange ratio at rest while breathing air differed by an average of only 0.31 L/min and 0.07, respectively. The average of the difference between the duplicate measurements of cardiac output while breathing CO₂ was 0.02 L/min despite considerable variations. In eight instances the second cardiac output of the pair was equal to or less than the first. This suggested that the measurements were reliable and that a reasonably constant cardiac output had been achieved after 7 min, despite the continued absorption of CO₂. Systemic blood pressure rose from a control mean of 93.3 mm Hg while

Circulation, Volume XXXIX, May 1969
breathing air to 117.5 mm Hg while breathing CO₂ so that an increase in systemic vascular resistance paralleled that of pulmonary vascular resistance.

In eucapnic subjects breathing 10% CO₂ produced a larger ventilatory response so that minute ventilation rose 45.1% and oxygen consumption rose 52% (148 ml/min) above resting levels. However, Paco₂ increased 27 mm Hg; H-ion concentration increased 19.3 nM/L and Pao₂ rose 46.8 mm Hg. Pulmonary arterial pressures rose 100% above control levels (to 30.4 mm Hg), mean pulmonary arterial wedge pressures were unchanged from control levels, and cardiac outputs averaged 3.2 L/min above control levels of 8.7 L/min. The cardiac outputs of these five patients were so varied that the difference in means was not significant. Pulmonary vascular resistances more than doubled. Mean systemic blood pressures rose from an average of 98 mm Hg to 125 mm Hg. The direction and magnitude of changes in the pulmonary circulation during breathing of CO₂ were similar in the two groups despite significant differences in their control levels (table 5).

Breathing CO₂ increased the pulmonary artery pressure in all subjects, but the slope of the line relating the average of mean pulmonary arterial pressures to average Paco₂ for the group was steeper in the hypercapnic subjects. Thus PPA increased an average of 0.85 mm Hg per mm Hg rise in Paco₂ in hypercapnic subjects compared to an increase of 0.59 mm Hg in eucapnic ones (fig. 1). The correlation between simultaneous observations of PPA and Paco₂ in all patients considered together during control periods and during CO₂ breathing was high (r = 0.654, P < 0.006). Cardiac outputs and Paco₂ were less correlated (r = 0.41, P < 0.05), and PPA and cardiac output and PPA and Pao₂ were not significantly correlated.

Exercise

Exercise increased oxygen consumption (82% in hypercapnic and 113% in eucapnic patients) which was much more than breathing CO₂ did, but exercise produced only small changes in arterial blood O₂ and CO₂ tensions (tables 3 to 5). Ventilation rose an average of 69% in hypercapnic and 88% in eucapnic patients. Exercise increased cardiac outputs slightly more in both groups of patients than did breathing CO₂ (tables 3 and 5). During exercise pulmonary arterial CO₂ pressures rose significantly in hypercapnic patients, but the increases were only half as great as those which occurred during CO₂ breathing (fig. 2). Pulmonary arterial wedge pressures remained normal, and the increased driving pressures were proportional to the increased pulmonary blood flow so that calculated pulmonary vascular resistances were unchanged from control levels. Similarly, in eucapnic patients pulmonary blood flows and pulmonary arterial pressures increased proportionally so that pulmonary vascular resistance was unchanged during supine bicycling. Moreover, the PPA increased only half as much as it did during breathing CO₂.

![Figure 2](http://circ.ahajournals.org/)

The effects on PPA and cardiac output of breathing 10% CO₂ are compared with the effects of exercise on hypercapnic and eucapnic patients. Although the average increases in cardiac output were similar, PPA was increased to a significantly greater extent in both groups of patients during CO₂ breathing. This indicated that pulmonary vascular resistance had been increased by hypercapnia. Average values for Paco₂ are shown in parentheses. Numbers in circles indicate isopleths for pulmonary vascular resistance in mm Hg/L/min.
Effects of Exercise Compared to Breathing CO₂

The comparison of changes in pulmonary arterial pressure during breathing of CO₂ and during exercise that increased cardiac output similarly helped differentiate pressure increases secondary to increased cardiac outputs from increases due to primary effects on pulmonary vessels (fig. 2). Pulmonary arterial pressure increased more while breathing CO₂ than during exercise. The differences averaged 8.4 mm Hg in hypercapnic and 6.6 mm Hg in eucapnic subjects, despite similar increases in cardiac output (table 5). Both differences were statistically significant (P < 0.01 and P < 0.02). Therefore, pulmonary vascular resistances were significantly higher (6.5 compared to 4.6 mm Hg/L/min) during breathing of CO₂ at rest than with breathing of air during exercise in hypercapnic subjects (fig. 2). The same was true for eucapnic subjects.

Control pulmonary arterial pressures were half as high as in the five eucapnic subjects, as in the hypercapnic patients, but the increases while breathing CO₂ were similar to those in hypercapnic patients. The two eucapnic patients who had large increases in cardiac output during breathing of CO₂ had smaller increases in pulmonary vascular resistance. This suggested that, in lungs already receiving high blood flows, large increments in flow may block part of the pulmonary vascular effects of CO₂ or of acidosis. However, differences in intracellular buffering or the peripheral circulatory effects of hypercapnia may account for this observation. In neither hypercapnic nor eucapnic patients did augmentation of cardiac output by exercise, which exceeded the increase by breathing CO₂, raise pulmonary arterial pressure as much as had breathing CO₂. Mean pulmonary arterial wedge pressures were normal and were not elevated by breathing CO₂ or by exercise in any patient. The greater increment in P_PA during breathing CO₂ compared to exercise was clearly shown in eucapnic patients, despite considerable increases of cardiac output during both stresses.

Bicarbonate Buffering

The effects of buffering the H ion in the blood by the intravenous infusion of sodium bicarbonate which returned H-ion concentrations toward control levels were studied in seven patients (fig. 3). Bicarbonate infusion reduced H-ion levels but increased CO₂ tensions in arterial and venous blood. Pulmonary arterial pressures rose slightly in patients. Pressures in the pulmonary artery paralleled Paco₂ rather than H-ion concentration. Cardiac outputs were measured in five subjects and were increased slightly so that pulmonary vascular resistances were unchanged (table 6). Two patients in whom cardiac output was not measured after the bicarbonate infusion showed a reduction in pulmonary artery pressure which was equivalent to the decrease in H-ion concentration. However, these changes could also be explained by reduced cardiac outputs.

**Figure 3**

Sodium bicarbonate infusion during breathing of 10% CO₂ reduced H-ion concentration considerably although Paco₂ increased (note figures near points). Arrows connect control values to those during CO₂ breathing and after bicarbonate infusion. In five subjects P_PA increased as Paco₂ rose. In two patients P_PA decreased as H ion was reduced despite increased Paco₂ (see text).
Table 6
Effects of Sodium Bicarbonate Infusions (120–135 mEq) During Breathing of 10% CO₂ on PaCO₂, H-ion Levels, and Pulmonary Circulation of Five Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>PaCO₂ (mm Hg)</th>
<th>H ion (nM/L)</th>
<th>PPA (mm Hg)</th>
<th>CO (L/min)</th>
<th>PVR (mm Hg/L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>65</td>
<td>47.9</td>
<td>35</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>CO₂</td>
<td>86</td>
<td>61.5</td>
<td>45</td>
<td>9.5, 9.2*</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
<td>90</td>
<td>54.9</td>
<td>40</td>
<td>9.4</td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>60</td>
<td>50.1</td>
<td>42</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>CO₂</td>
<td>84</td>
<td>63.1</td>
<td>62</td>
<td>5.9, 7.0*</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
<td>102</td>
<td>50.1</td>
<td>66</td>
<td>8.6</td>
</tr>
<tr>
<td>10</td>
<td>Control</td>
<td>48.5</td>
<td>45.2</td>
<td>26</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>CO₂</td>
<td>81</td>
<td>68.4</td>
<td>50</td>
<td>10.5, 13.1*</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
<td>90</td>
<td>60.2</td>
<td>52</td>
<td>13.3</td>
</tr>
</tbody>
</table>

| Eucapnic                               |               |             |             |            |                   |
| 13      | Control       | 29.3         | 31.6        | 18         | 11.7             | 1.1               |
|         | CO₂           | 71           | 56.2        | 30         | 14.8, 16.8*      | 1.7, 1.5          |
|         | Bicarbonate   | 75           | 41.7        | 32         | 16.2             | 1.6               |
| 15      | Control       | 37           | 37.1        | 13         | 10.5             | 0.8               |
|         | CO₂           | 58           | 51.8        | 24         | 17.1, 18.5*      | 1.2, 1.1          |
|         | Bicarbonate   | 61.5         | 41.7        | 27         | 18.3             | 1.1               |

* Sequential cardiac outputs during breathing of CO₂.

Reduction of PaCO₂

Hyperventilation by controlled mechanical ventilation in two patients, which reduced PaCO₂ 13 and 8 mm Hg, decreased PPA 8 and 5 mm Hg, respectively. Cardiac outputs were unchanged. During initial spontaneous hyperventilation by patient 16, PPA was 18 mm Hg when PaCO₂ was 29 mm Hg and PaO₂ was 102 mm Hg. Subsequently, when PaCO₂ was 45 mm Hg during breathing of room air without hyperventilation, PPA was higher by 12 mm Hg.

Three patients were studied when they were hypercapnic and edematous and subsequently after 14, 120, and 360 days, following diuresis and recovery. In patient 7 (table 3), PaCO₂ was reduced from 53.5 to 40.5 mm Hg, and PPA decreased 23 mm Hg, and there was little change in cardiac output. Patient 2 showed a 37 mm Hg reduction in PPA despite a 50% increase in cardiac output when PaCO₂ decreased from 63 to 49 mm Hg. Initially, patient 3 had a PPA of 42 mm Hg when PaCO₂ was 62 mm Hg, but 1 year later when PaCO₂ was 36 mm Hg, PPA was 19 mm Hg. PPA rose to 45 mm Hg during CO₂ breathing which raised PaCO₂ to 69 mm Hg. Resting cardiac output decreased from 6 to 5 L/min and virtually duplicated the conditions of a year earlier.

Oxygen Breathing

While nine bronchitic subjects breathed 40 to 95% O₂ in nitrogen PaO₂ rose to an average value of 167.5 mm Hg, PaCO₂ increased 4 mm Hg and H-ion concentration increased slightly. However, the average values for PPA, cardiac output, and pulmonary vascular resistance were unchanged (table 5). A reduction in pulmonary arterial pressure was anticipated from abolishing hypoxia while breathing oxygen, but none occurred. It appeared that the slight increase in CO₂ tension or the consequent acidosis negated any such effects. Slight reductions in pulmonary arterial pressure which were observed could be attributed to reduced cardiac output while breathing O₂.

Sequential Changes

To emphasize the relationship between PaCO₂ and mean pulmonary arterial pressure,
EFFECTS OF CO₂ ON PULMONARY CIRCULATION

The temporal relationships of pulmonary circulatory changes, ventilation, and blood gas values are shown for one subject during exposure to 100% O₂, mechanical hyperventilation, breathing 10% CO₂, and infusion of bicarbonate while breathing CO₂. During breathing of oxygen there was an initial increase in Paco₂ followed by a decrease because cardiac output decreased. Therefore, the calculated vascular resistance rose during breathing of oxygen and increased further during breathing of CO₂. Changes in pulmonary artery pressure paralleled changes in Paco₂ (see text).

these parameters and minute ventilation, cardiac output, calculated pulmonary vascular resistance, and Paco₂ are shown for patient 5 during sequential changes in O₂ and CO₂ (fig. 4). Control observations were obtained while the patient was supine, at rest, and breathing air. The control pulmonary arterial pressure was 42 mm Hg when Paco₂ was 60 mm Hg and Paco₂ was 54 mm Hg. Both Paco₂ and PPA rose slightly despite a small decrease in cardiac output during O₂ breathing. When hyperventilation by respirator lowered Paco₂ was 43 mm Hg, PPA decreased to 33 mm Hg despite large fluctuations in intrathoracic pressure during the cycles of the respirator. During breathing of 10% CO₂, which also caused similar fluctuations in intrathoracic pressure, the PPA rose from the resting of 42 to 62 mm Hg and cardiac output increased to 7 L/min. The infusion of bicarbonate raised Paco₂ to 102 mm Hg, increased PPA to 68 mm Hg, and cardiac output to 8.5 L/min. Pulmonary vascular resistance rose from 5.6 at least to 8.3 mm Hg/L/min during breathing of CO₂ and decreased somewhat immediately following the bicarbonate infusion.

Anatomy of Major Pulmonary Vessels

Pulmonary angiograms on seven of the hypercapnic patients showed that major pulmonary arteries and veins were intact and appeared normal. The arterial distribution was distorted around pulmonary cysts in two of three eucapnic patients. Unfortunately what really counts, which is the number of arterioles or even the number of lobular arteries, cannot be measured by this technic. In two patients, the vascular patterns appraised by angiography during breathing of 10% CO₂ were unchanged from those during breathing of air.

Discussion

It is useful to recapitulate the observations made in this study in order to suggest a coherent interpretation. Hypercapnic subjects had significantly higher pulmonary arterial pressures and vascular resistances at rest while breathing air than did eucapnic subjects. Because factors other than hypercapnia may have produced these differences, pulmonary pressures and blood flows were remeasured after subjects were made more hypercapnic by breathing 10% CO₂ for 10 to 20 min. As Paco₂ rose, ventilation, pulmonary arterial pressures, and pulmonary vascular resistances increased despite increases in cardiac output. The increases in pulmonary arterial pressures were proportional to the increments in Paco₂.
in hypercapnic and in eucapnic subjects. Conversely, brief reductions in Paco2 during spontaneous hyperventilation or hyperventilation produced by respirators reduced pulmonary arterial pressures. Furthermore, in three subjects who were restudied at various intervals after endogenous Paco2 had fallen, pulmonary arterial pressures and vascular resistances were below initial levels. These observations could have one or more of the following explanations: (1) Carbon dioxide increased cardiac output to a greater degree than was measured so that pulmonary arterial pressures were raised in a restricted vascular bed. (2) The increased ventilation raised alveolar pressures which increased the pulmonary arterial pressure. (3) Carbon dioxide directly affected the pulmonary vasculature so that pulmonary arterial pressures rose above the levels attributable to increased cardiac output. Each of the postulates is examined below:

Cardiac outputs measured by the Fick principle during breathing of CO2 may be somewhat inaccurate because the respiratory quotient cannot be measured during the uptake of CO2 and a steady state cannot by strict definition be attained. However, the most important criterion for the Fick principle, which is a steady state for oxygen consumption, was frequently achieved in these patients after 10 min of breathing CO2. It has been suggested that after the first 5 min of breathing CO2 organs and tissues which rapidly equilibrate with CO2, such as lung, blood, liver and striated muscle, are approaching saturation. Thus, the rate of absorption of CO2 by the body may be nearing steady-state conditions. Clearly, oxygen consumption during breathing of CO2 had become sufficiently steady in these subjects so that the sequential measurements were nearly identical and the variations appeared to be random. Similarly the paired cardiac outputs which were measured sequentially during breathing CO2 showed very small mean differences in the two groups of subjects despite individual variations which were in both directions. This suggested that the means for cardiac output did reflect what was occurring; that is, the magnitudes of the increases in cardiac outputs associated with CO2 breathing were correct.

The calculated pulmonary vascular resistance is the quotient of the pressure difference across the pulmonary vessels divided by cardiac output. Thus, an independent demonstration, that the effects of increased blood flow unaccompanied by hypercapnia upon pulmonary vascular pressures were less than were the effects of a similar blood flow increment associated with hypercapnia, would be crucial. Cardiac outputs were increased to the same extent as they were during the breathing of CO2, but in contrast exercise did not increase pulmonary vascular resistances even in hypercapnic patients. Although the objection could still be raised that cardiac outputs were systematically underestimated while breathing CO2, it is unlikely that the magnitude of the error could have been great enough to raise the pulmonary arterial pressure without a change in the vascular resistance. Furthermore, this would necessitate the belief that breathing CO2 which increased O2 consumption less than did exercise, increased cardiac output more than exercise did. This appears unlikely. Even substitution of cardiac outputs during exercise for cardiac outputs during breathing CO2 in the calculation of pulmonary vascular resistance while breathing CO2 would not change the results significantly. Even if this objection were true, the reductions in pulmonary arterial pressure and vascular resistance during hyperventilation and after decrease of the endogenous CO2 levels to normal without corresponding reductions in cardiac output would still suggest that CO2 has a primary effect on the pulmonary vessels.

There has been speculation that part of the pulmonary hypertension in patients with bronchitis and emphysema reflects obliteration or destruction of small blood vessels in the lung so that cardiac output is driven through a restricted vascular bed. The rapid reduction of pulmonary hypertension by the reduction of Paco2 suggests that a dynamic and reversible process, not an anatomic one, is more
important. The correlation between PaCO₂ and mean pulmonary artery pressures in recovering patients confirms the observations of others.¹³⁻¹⁵ The data are interpreted as suggesting that the principal site of action of CO₂ is in the small pulmonary arterial vessels.

A possible alternate explanation for the increased pulmonary arterial pressure and vascular resistance is that they reflect higher mean intrathoracic pressures which developed during the two and a half to fivefold increases in minute ventilation. This possibility was examined by comparing the effects of hyperventilation produced by positive pressure respirators and voluntary hyperventilation to those of breathing CO₂. In all instances, despite the augmentation of ventilation whenever PaCO₂ was decreased, pulmonary arterial pressures and vascular resistances decreased. Perhaps localized increases in alveolar pressures during breathing of CO₂ raised the impedance to pulmonary blood flow, but there are presently no methods for making the measurements to support this speculation. Furthermore, although CO₂ breathing tripled ventilation in the hypercapnic subjects, exercise doubled it so that a proportional increase in PVR should have been observed during exercise if raised intra-alveolar pressures were responsible.

Hypoxia, which has been implicated previously as a major factor in increasing pulmonary vascular resistance in such patients,¹³,¹⁴ appeared to be of relatively little significance in this study. Furthermore, the oxygen tension increased during breathing of CO₂. This effect acting alone would have decreased pulmonary artery pressure and vascular resistance. Oxygen tensions were above the levels that have been previously associated with pulmonary hypertension, and the augmented ventilation while breathing CO₂ improved oxygenation in all subjects.

The next question to examine is the relative importance of alveolar CO₂ tension, venous blood CO₂ tension, tissue CO₂ tension, and blood H-ion concentration as the stimulus that raises pulmonary vascular resistance or produces other effects. In an attempt to select the site in the pulmonary circulation, H-ion concentrations were reduced toward control conditions by infusions of solutions of sodium bicarbonate while breathing CO₂. Such infusions usually failed to reduce pulmonary arterial pressure. In five subjects cardiac outputs were unchanged or increased so slightly after bicarbonate infusion that pulmonary vascular resistances remained elevated. These observations suggest that, in the presence of elevated CO₂ tensions, reductions of arterial blood H-ion concentrations do not affect the pulmonary circulation. Among the possible explanations are that cellular acidosis is the important factor and that it is relatively unaffected by brief acute increases in plasma bicarbonate buffering. Other studies have demonstrated that acidosis produces pulmonary hypertension without CO₂ being elevated.² The results suggest that there is a final common pathway for the effects of hypercapnic acidosis and increases in H ion without hypercapnia. Localization of the target for CO₂ effects can be only speculative at this time. The population, dimensions, or numbers of vessels cannot be specified except that they are probably distal to the lobular pulmonary arteries because the vessels that were measurable on pulmonary angiograms did not narrow during breathing of CO₂. It is also possible that the properties of the blood are changed by acidosis so that erythrocytes aggregate and impede blood flow.¹⁶ Further observations are needed to discriminate between these possibilities and others. The results and interpretations of previous studies of the effects of CO₂ breathing and acidosis are discussed to help place into perspective the tentative conclusions recommended from the present study. Studies of lungs in vitro and in experimental animals are followed by a review of observations on human subjects.

**Hypercapnia in Animals**

Animal studies have been reported which claim that hypercapnia increases or decreases or does not change pulmonary vascular resistance.³⁻⁴,¹⁷⁻²² Large differences in preparations and methods of measurement make comparisons difficult and may explain the
inconclusive results. Careful analysis of these reports reveals variations in animal species, maturity, state of health, and the type of preparation used. In addition, differences in type and depth of anesthesia, variations in minute volumes of ventilation, arterial blood oxygen tension, and alveolar or arterial CO₂ tensions make interpretation difficult. However, Bergofsky and associates suggested that since exposure of anesthetized dogs to 5% CO₂, hypoxia, and infusions of lactic and hydrochloric acid produce similar results, acidosis is the common pathway to raise the pulmonary vascular resistance. A greater effect from CO₂ than from acid infusion at equal reductions in pH has been attributed to greater intercellular H-ion elevations because CO₂ diffuses as a gas into cells; although it may also have a direct dilating effect on vessels. Another mechanism is suggested by the observation that the increase in cardiac output in intact dogs produced by breathing CO₂ is replaced by a severe depressant effect in heart-lung preparations. This suggests that catecholamine release is a humoral mediator for pressor and stimulatory effects. The results of those animal studies which are applicable to conscious human subjects suggest that breathing 5 to 10% CO₂ raises pulmonary vascular resistance.

**Hypercapnia in Human Subjects**

A role of hypercapnia in the reversible pulmonary hypertension of patients with cor pulmonale was inferred from the observed association between Paco₂ and PPa and correlations between them. However, previous attempts to demonstrate that hypercapnia increased PPa or PVR in normal human subjects or patients were inconclusive. Even when changes in PPa were shown, blood flow was not measured frequently so that interpretations are impossible. Ingenious interrelationships between hypercapnia, acidosis, hypoxemia, and fluid and electrolyte changes have been suggested to explain the reductions in PVR during infusions of bicarbonate or tris buffer (hydroxymethyl 1-amino methane) in human subjects.

The present study differs from previous ones in that sufficiently large stimuli were applied in hypercapnic and eucapnic subjects so that results were definite. Changes in Paco₂ were associated with proportional changes in the same direction of the pulmonary vascular resistance. The interpretation that CO₂ breathing increased resistance to flow in precapillary pulmonary vessels was supported by the observation that the PVR was significantly higher during acute hypercapnia than when pulmonary blood flow was increased to an equal or greater extent by exercise. Acute hyperventilation reduced PPa and PVR as Paco₂ decreased, as did the more gradual restoration of Paco₂ to normal. Therefore, it is recommended that the verdict of a recent review that, "... carbon dioxide elicits no discernible change in pulmonary vascular resistance to blood flow," be modified in the affirmative.

**References**


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EFFECTS OF CO₂ ON PULMONARY CIRCULATION

Effects of Breathing 10 Per Cent Carbon Dioxide on the Pulmonary Circulation of Human Subjects
K. H. KILBURN, T. ASMUNDSSON, R. C. BRITT and R. CARDON

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