The Cardiovascular Effects of Carbon Dioxide in Man, Conscious and during Cyclopropane Anesthesia

David J. Cullen, M.D.,* Edmond I. Eger, II, M.D.,† George A. Gregory, M.D.‡

In seven healthy, conscious volunteers, hyperventilation from $P_{aco_2}$ 35 mm Hg to 23 mm Hg did not change cardiac index (QI), heart rate (HR), stroke volume (SV), total peripheral resistance (TPR), or mean right atrial pressure (MRAP). Hyperventilation from $P_{aco_2}$ 37 mm Hg to 26 mm Hg during anesthesia with 15–20 per cent cyclopropane decreased QI and SV. When $P_{aco_2}$ was restored to 37 mm Hg by elevating inspired CO$_2$ (tidal volume and respiratory rate constant), cardiovascular function was unchanged while the subjects were conscious, and rose only slightly during anesthesia. When the subjects were conscious, hypercapnia induced marked increases in QI, SV, and HR, while TPR and MRAP fell. Cyclopropane, 25–30 per cent, abolished the tachycardia of hypercapnia, and thereby halved the QI response to CO$_2$. However, the QI response to CO$_2$ still was better preserved during cyclopropane anesthesia than during halothane anesthesia or anesthesia with thiopental, narcotic, and curare. (Key words: Cyclopropane; Carbon dioxide; Hypocapnia; Hypercapnia; Controlled ventilation; Cardiovascular effects of carbon dioxide.)

Results of previous studies in awake man breathing spontaneously suggested that cardiac output is increased with elevated inspired CO$_2$.$^{5,6}$ With halothane$^{7,8}$ or balanced anesthesia,$^9$ during controlled ventilation, the cardiac index response to CO$_2$ seems attenuated when compared with that of conscious man breathing spontaneously.$^5,6$ However, no data comparing the cardiovascular responses to CO$_2$ in the same individual conscious and during anesthesia are available. Furthermore, the cardiovascular response to CO$_2$ during cyclopropane anesthesia has not been investigated. Therefore, we determined the cardiovascular responses to alterations in $P_{aco_2}$ in awake man during constant ventilation and demonstrated in the same subjects that cyclopropane interfered with these responses. The ability to respond to the stress of hyperventilation or hypercarbia may serve as a functional index for comparison of anesthetics.

Methods

The experimental methods used are described in the preceding paper.$^{10}$ In each of seven healthy, conscious, nonmedicated adult male volunteers, we controlled ventilation with a volume-limited ventilator to maintain a $P_{aco_2}$ of 34.7 ± 1.5 mm Hg (SE). Following control measurements of cardiac output, heart rate, mean arterial pressure, mean right atrial pressure, forearm venous pressure, forearm and finger blood flow, and arterial and right atrial blood gases, we increased tidal volume and respiratory rate to reduce $P_{aco_2}$ to 23.8 ± 0.7 mm Hg. All measurements were repeated. With ventilator rate and depth constant at the increased level, CO$_2$ was added to the inspired gas to increase alveolar $P_{co_2}$ to a new

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constant value. Several successive stepwise increases in Pa_CO_2 were made in each subject. Measurements were recorded six minutes after each. Two hours after induction of anesthesia with cyclopropane in oxygen, the same CO_2 challenge was tested at 15–20 per cent and then at 25–30 per cent end-tidal cyclopropane. Analysis of the data by linear regression of CO_2 response curves allowed statistical comparison of slopes of responsiveness to CO_2.

Results

Effect of Hyperventilation

(Table 1, Fig. 1)

In conscious subjects, the cardiac index changed in response to increased CO_2 only above an arterial Pa_CO_2 of 35 mm Hg. Increasing the rate and depth of ventilation to lower Pa_CO_2 did not alter cardiac index or related values. Addition of CO_2 to inspired gas at the increased rate and depth of ventilation did not change the cardiac index until Pa_CO_2 exceeded 35 mm Hg. All regression lines are based on the responses above Pa_CO_2 35 mm Hg only.

At 15–20 per cent cyclopropane, the cardiac index was 105 per cent of control. Hyperventilation to Pa_CO_2 26 ± 1.5 mm Hg reduced the cardiac index 16 per cent (P < 0.05). Furthermore, restoration of Pa_CO_2 to 36.8 ± 1.9 mm Hg during increased tidal volume and respiratory rate did not restore the cardiac index to the prehyperventilation value. However, a dogleg still existed in the curve when it was compared with an extrapolation of the cardiac index regression line to a Pa_CO_2 of 26 mm Hg (fig. 1). At 25–30 per cent cyclopropane, neither hyperventilation nor addition of CO_2 to restore Pa_CO_2 to 34.8 mm Hg affected the cardiac index significantly.

<table>
<thead>
<tr>
<th>Pa_CO_2 (mm Hg)</th>
<th>Awake (n = 7)</th>
<th>15–20 Per Cent CCl_4 (n = 5)</th>
<th>25–30 Per Cent CCl_4 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Controlled Ventilation</td>
<td>Normal Controlled Ventilation</td>
<td>Normal Controlled Ventilation</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation</td>
<td>Hyperventilation</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Pa_CO_2 (mm Hg)</td>
<td>34.7 ± 1.5</td>
<td>23.5***</td>
<td>34.8***</td>
</tr>
<tr>
<td>Q (per cent)</td>
<td>101 ± 3.5</td>
<td>99 ± 2.8</td>
<td>105 ± 8.3</td>
</tr>
<tr>
<td>HR (per cent)</td>
<td>102 ± 2.3</td>
<td>103 ± 2.8</td>
<td>95 ± 4.6</td>
</tr>
<tr>
<td>SV (per cent)</td>
<td>100 ± 3.7</td>
<td>99 ± 3.3</td>
<td>109 ± 6</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>2.3 ± 1.2</td>
<td>2.5 ± 0.9</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>TPR (per cent)</td>
<td>101 ± 3.8</td>
<td>103 ± 3.4</td>
<td>115 ± 20</td>
</tr>
</tbody>
</table>

† The upper number in each row is the mean. The lower number is one standard error. Cardiac output (Q), heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR) are expressed as percentages of the conscious control values. MRAP is mean right atrial pressure.

* P < 0.05 compared with previous value.

** P < 0.05 compared with normal controlled ventilation normocapnia at 15–20 per cent cyclopropane.

*** P < 0.001 compared with previous value.
CARDIOVASCULAR EFFECTS OF CARBON DIOXIDE IN MAN

Fig. 1. The effect on cardiac index of controlled positive-pressure hyperventilation during hypoxia or normoxia. Decreasing $P_{aCO_2}$ with hyperventilation had no effect on cardiac index ($QI$) in conscious subjects, whereas during cyclopropane anesthesia, $QI$ decreased significantly. Raising $P_{aCO_2}$ during constant hyperventilation had no effect on $QI$ in conscious subjects until $P_{aCO_2}$ 40 mm Hg was achieved, whereupon $QI$ increased markedly (solid regression line).

During cyclopropane anesthesia, raising $P_{aCO_2}$ increased $QI$ slightly until $P_{aCO_2}$ 35-40 mm Hg was achieved, whereupon $QI$ increased (dashed and dotted regression lines). The slope of the cardiac index regression line at 25–30 per cent cyclopropane is 50 per cent less than the awake value ($P < 0.05$). The slope for 15-20 cyclopropane is between the other two slopes.

The three regression lines cannot be extrapolated to $P_{aCO_2}$ 25 mm Hg, since measured $QI$ at $P_{aCO_2}$ 25 mm Hg, was far higher than expected from extrapolated values.

| Table 2. Linear Regression Equations in Response to Increasing Carbon Dioxide (/mm Hg $P_{aCO_2}$) |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Cardiac index (L/min/m²) (A)                   | $y = 0.1015x - 1.56$ | $y = 0.0763x - 0.79$ | $y = 0.0507x + 0.64$ |
| Heart rate (beats/min) (B)                     | $y = 1.44x + 9$ | $y = 1.07x + 13.6$ | $y = 0.23x + 53.9$ |
| Stroke index (L/m²)                            | $y = 0.6ix + 14.5$ | $y = 0.6ix + 16.1$ | $y = 0.54x + 20.5$ |
| Total peripheral resistance (dynes-cm⁻²)       | $y = -36.5x + 3,059$ | $y = 53.6x + 4,016$ | $y = -24.5x + 3,148$ |
| Mean arterial pressure (mm Hg) (C)             | $y = 0.73x + 64.2$ | $y = 0.08x + 102.1$ | $y = 0.22 + 100.6$ |
| Mean right atrial pressure (mm Hg) (D)         | $y = -0.046x + 4.7$ | $y = 0.09x + 1.75$ | $y = 0.02x + 7.93$ |

* $y$ is the calculated dependent variable, $x$ is $P_{aCO_2}$, the independent variable. The value given for $x$ in each block is the slope of the regression line. Significant differences for the slope of the regression line occurred only at: A, cardiac index—awake vs. 25-30 per cent cyclopropane, $P < 0.05$. B, heart rate—awake vs. 25-30 per cent cyclopropane, $P < 0.01$. C, mean arterial pressure—awake vs. 15-20 per cent cyclopropane, $P < 0.025$. D, mean right atrial pressure—awake vs. 15-20 per cent cyclopropane, $P < 0.025$. 
Effect of Hypercapnia (Table 2)

The cardiac index response to CO₂ in conscious subjects was 0.1015 l/min/mm Hg/m² (fig. 1); that is, each mm Hg increase in PaCO₂ increased cardiac index by 101 ml. Both heart rate (1.44 beats/min/mm Hg) and stroke index (61 ml/min/m²) increased. The cardiac index slope for 15 to 20 per cent cyclopropane was not significantly different from either the conscious value or the 25-30 per cent value, but lay midway between the two. Cyclopropane, 25-30 per cent, reduced the cardiac index slope to 50 per cent (0.0507 l/min/mm Hg/m²) of the conscious value (P < 0.05). This was due to a decreased heart rate response (0.23 beats/min/mm Hg) (fig. 2). Stroke index rose to similar values with the subjects conscious and at both levels of anesthesia (fig. 3). Mean right atrial pressure (MRAP) decreased slightly while the subjects were conscious (−0.046 mm Hg/mm Hg). However, during anesthesia, MRAP started from a much higher baseline and rose with increased CO₂. This rise differed significantly from the conscious response (P < 0.025) (fig. 4). Mean arterial pressure rose slightly while the subjects were conscious but remained constant during anesthesia (fig. 5). Total peripheral resistance fell to similar levels while the subjects were conscious and during anesthesia (fig. 6). Changes in forearm eu-

taneous blood flow and forearm venous compliance were small while the subjects were conscious and inconsistent during anesthesia.

Discussion

Effect of Hyperventilation

While the subjects were conscious, hyperventilation to PaCO₂ 23.8 ± 0.7 mm Hg had no effect on cardiac output, heart rate, stroke volume, total peripheral resistance, or mean right atrial pressure. Our results obtained during positive-pressure ventilation of conscious subjects agree with McGregor’s data. He found no reduction in cardiac output during spontaneous hyperventilation with hypcapnia. Normocapnia during hyperventilation did not affect cardiac output in McGregor’s study or ours. It was only with the onset of hypercapnia that cardiac output and related values increased.

The finding of an unchanged cardiac index in the conscious subject during hyperventilation and/or hypocapnia should not be surprising. Hypocapnia and alkalosis are not myocardial depressants, and in fact, Ng et al. have shown in dogs that cardiac contractility is increased during alkalosis. If increased mean intrathoracic pressure impedes venous return, the conscious subject probably compensates by α-adrenergic vasoconstriction.
However, cyclopropane anesthesia modifies the compensatory response to hyperventilation. During anesthesia with 15–20 per cent cyclopropane, hypocapnic hyperventilation reduced cardiac index a small but significant amount. This was not due to hypocapnia alone, because the cardiac index remained significantly decreased during normocapnic hyperventilation. Cyclopropane may interfere with the compensatory response to increased mean intrathoracic pressure. Too few data were obtained during 25–30 per cent cyclopropane anesthesia for statistical differences to be manifest.

Various results have been obtained with other anesthetics. Martin reported no change in cardiac index with hypocapnia during 0.8 per cent alveolar halothane in human volunteers. Theye et al. and Prys-Roberts et al. however, reported that during clinical anesthesia hyperventilation and hypocapnia reduced cardiac index to low levels. Results obtained in volunteers will differ from those in premedicated patients in whom induction agents are used.

**Effect of Hypercapnia**

In conscious man, elevation of PaCO₂ above 35 mm Hg increased cardiac index by increasing both heart rate and stroke volume. The cardiac index probably was also influenced by the decreasing total peripheral resistance. Cyclopropane did not alter the response of stroke volume or total peripheral resistance (in contrast to Elston's finding in older, premedicated, surgically-stimulated patients but did inhibit the heart rate response.

Tachycardia, which occurred in response to rising CO₂ in conscious subjects, was almost abolished by 25–30 per cent cyclopropane. This may have been due to several effects of cyclopropane. Price et al. and Garfield et al. have shown that cyclopropane has ganglionic blocking properties. Hence, increased preganglionic sympathetic activity might not induce a heart rate response. Second, cyclopropane is a sympathetic stimulant, and the additional stimulation resulting from a rise in PaCO₂ might be masked in the presence of a large background of sympathetic tone. That is, the same absolute increase in activity would represent a smaller fraction of the total activity. The relative importance of these two effects in man are unknown. In addition, the increased parasympathetic tone with cyclopropane would tend to block chronotropic stimuli. Last, one might expect the central stimulatory response of CO₂ to be nonspecifically depressed by any general anesthetic.

Cyclopropane modified the relationship between cardiac index and mean right atrial
压力（图7）。虽然受试者清醒，增加CO₂的含量从35 mm Hg到55 mm Hg，双相性升高速度和平均右心房压均下降。突然降低平均右心房压。压力的上升和心肌重量的增加使得期间心脏指数降低，这使得心室功能曲线向上移动，左心房可能处于静息状态。因而在正常情况下，增加CO₂的流量从35 mm Hg到55 mm Hg，心室压会下降，这可能意味着心脏功能压力的增加。

图6. TPR-Paco₂回归线。减少总外周阻力对CO₂的反应在清醒和麻醉患者中相似。

图7. 20 mm Hg Paco₂变化对心率和心室电位的影响。图中显示了心率和心室电位的变化。

表3. Paco₂变化对心室指数的影响

<table>
<thead>
<tr>
<th>Range of Paco₂</th>
<th>20-40 mm Hg</th>
<th>40-60 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious</td>
<td>-5</td>
<td>+101.5</td>
</tr>
<tr>
<td>15-20 per cent alveolar cyclopropane</td>
<td>+12</td>
<td>+76.3</td>
</tr>
<tr>
<td>25-30 per cent alveolar cyclopropane</td>
<td>+36</td>
<td>+50.7</td>
</tr>
<tr>
<td>0.8 per cent alveolar halothane</td>
<td>+7</td>
<td>+34</td>
</tr>
<tr>
<td>0.5-1 per cent inspired halothane in O₂ or N₂O</td>
<td>+31</td>
<td></td>
</tr>
<tr>
<td>1 per cent inspired halothane</td>
<td>+14.5</td>
<td>+23</td>
</tr>
<tr>
<td>Balanced anesthesia</td>
<td>+22</td>
<td>+22</td>
</tr>
</tbody>
</table>

*心血管对CO₂的反应在低血氧中存在或消失，这与心血管对CO₂的反应在高血氧中不同。注意：一般麻醉剂常降低心脏对CO₂的反应，这可能是因为剪切力的因素。

压力的增加。我们无法判断是否心室功能曲线发生了变化。

进一步的麻醉剂对心室反应的影响取决于CO₂的含量。必要的，星状二醛（35-150 mm Hg）或高血氧（1-1.5 mm Hg）或平衡麻醉在预配患者中降低心室反应。心室反应与CO₂的增加远大于剪切力。

参考文献


Obstetrical Anesthesia

FIBRIN-STABILIZING FACTOR IN PREGNANCY

Fibrin-stabilizing factor (Factor XIII) is an enzyme precursor of plasma. In the presence of thrombin and calcium ions, Factor XIII is converted to a transamidase which promotes formation of cross-linkages between fibrin chains. The resultant effect is the conversion of Fibrin I, which is easily disruptible, to Fibrin II, which is mechanically stronger and biochemically more resistant. During pregnancy Factor XIII concentrations diminish steadily and are approximately 50 per cent of normal at term. (Coopland, A., and others: Reduction in Plasma Factor XIII (Fibrin-stabilizing Factor) Concentration during Pregnancy, J. Lab. Clin. Med. 73: 144 (Jan.) 1969.)