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 Paco₂, 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 Paco₂, 37 mm Hg to 26 mm Hg during anesthesia with 15–20 per cent cyclopropane decreased QI and SV. When Paco₂ was restored to 37 mm Hg by elevating inspired CO₂ (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 CO₂. However, the QI response to CO₂ 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.)

Carbon dioxide has a dual effect on the cardiovascular system. A direct action depresses myocardial contractility and dilates vascular smooth muscle. 1, 2, 3 Indirectly, it increases myocardial and vasomotor activity via sympathoadrenal stimulation. 1, 2, 4

Results of previous studies in awake man breathing spontaneously suggested that cardiac output is increased with elevated inspired CO₂. 5–6 With halothane 7, 8 or balanced anesthesia, 9 during controlled ventilation, the cardiac index response to CO₂ seems attenuated when compared with that of conscious man breathing spontaneously. 5, 6 However, no data comparing the cardiovascular responses to CO₂ in the same individual conscious and during anesthesia are available. Furthermore, the cardiovascular response to CO₂ during cyclopropane anesthesia has not been investigated. Therefore, we determined the cardiovascular responses to alterations in Paco₂ 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 Paco₂ 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 Paco₂ to 33.8 ± 0.7 mm Hg. All measurements were repeated. With ventilator rate and depth constant at the increased level, CO₂ was added to the inspired gas to increase alveolar Pco₂ to a new
constant value. Several successive stepwise increases in \( P_{aCO_2} \) 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 \( P_{aCO_2} \) 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 \( P_{aCO_2} \) of 35 mm Hg. Increasing the rate and depth of ventilation to lower \( P_{aCO_2} \) 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 \( P_{aCO_2} \) exceeded 35 mm Hg. All regression lines are based on the responses above \( P_{aCO_2} \) 35 mm Hg only.

At 15–20 per cent cyclopropane, the cardiac index was 105 per cent of control. Hyperventilation to \( P_{aCO_2} \) 26 ± 1.5 mm Hg reduced the cardiac index 16 per cent (*P < 0.05*). Furthermore, restoration of \( P_{aCO_2} \) 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 \( P_{aCO_2} \) of 26 mm Hg (fig. 1). At 25–30 per cent cyclopropane, neither hyperventilation nor addition of CO\(_2\) to restore \( P_{aCO_2} \) to 34.8 mm Hg affected the cardiac index significantly.

**Table 1. The Cardiovascular Effects of Hyperventilation with Hypocapnia or Normocapnia, Conscious and during Cyclopropane Anesthesia*$

<table>
<thead>
<tr>
<th></th>
<th>Awake (n = 7)</th>
<th>15–20 Per Cent CtlHs (n = 5)</th>
<th>25–30 Per Cent CtlHs (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Controlled Ventilation</td>
<td>Hyperventilation</td>
<td>Normal Controlled Ventilation</td>
</tr>
<tr>
<td>( P_{aCO_2} ) (mm Hg)</td>
<td>34.7 ± 1.5</td>
<td>34.8***</td>
<td>37.2 ± 1.7</td>
</tr>
<tr>
<td>( Q ) (per cent)</td>
<td>101 ± 3.5</td>
<td>99 ± 3.2</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>96 ± 3.3</td>
<td>109 ± 6</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>2.3 ± 1.2</td>
<td>2.8 ± 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. MAP 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 hypo-
capnia or normocapnia. Decreasing PaCO₂ with hyperventilation had no effect on cardiac index (QI) in
conscious subjects, whereas during cyclopropane anesthesia, QI decreased significantly. Raising PaCO₂
during constant hyperventilation had no effect on QI in conscious subjects until PaCO₂ 40 mm Hg was
achieved, whereupon QI increased markedly (solid regression line).

During cyclopropane anesthesia, raising PaCO₂ increased QI slightly until PaCO₂ 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 PaCO₂ 25 mm Hg, since measured QI at PaCO₂
25 mm Hg, was far higher than expected from extrapolated values.

Table 2. Linear Regression Equations in Response to Increasing
Carbon Dioxide (mm Hg PaCO₂)*

<table>
<thead>
<tr>
<th></th>
<th>Conscious</th>
<th>15–20 Per Cent C āH₄</th>
<th>25–30 Per Cent C āH₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (L/min/m²) (A)</td>
<td>y = 0.1015x - 1.56</td>
<td>y = 0.0763x - 0.79</td>
<td>y = 0.0507x + 0.64</td>
</tr>
<tr>
<td>Heart rate (beats/min) (B)</td>
<td>y = 1.44x + 9</td>
<td>y = 1.07x + 13.6</td>
<td>y = 0.23x + 33.9</td>
</tr>
<tr>
<td>Stroke index (L/m²)</td>
<td>y = 0.61x + 14.5</td>
<td>y = 0.6x + 16.1</td>
<td>y = 0.54x + 20.5</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes-sec/cm⁻²)</td>
<td>y = -36.5x + 3,059</td>
<td>y = 53.6x + 4,016</td>
<td>y = -24.8x + 3,148</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg) (C)</td>
<td>y = 0.73x + 64.2</td>
<td>y = 0.08x + 102.1</td>
<td>y = 0.22 + 100.6</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg) (D)</td>
<td>y = -0.046x + 4.7</td>
<td>y = 0.09x + 1.75</td>
<td>y = 0.02x + 7.03</td>
</tr>
</tbody>
</table>

* y is the calculated dependent variable, x is PaCO₂, 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 cyclo-
propane, P < 0.025. D, mean right atrial pressure—awake vs. 15–20 per cent cyclopropane, P < 0.025.
CULLEN, ECER, AND GREGORY

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/mm Hg/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 and cutaneous 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 hypocapnia. 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 $P_aCO_2$ above 35 mm Hg increased cardiac index by increas-

![Fig. 4. MRAP–$P_aCO_2$ regression lines. Mean right atrial pressure is significantly higher during 15–20 per cent cyclopropane anesthesia than in conscious subjects, and rises with increased $P_aCO_2$ significantly differently from the conscious response ($P < 0.025$).](Image)

![Fig. 5. AEP–$P_aCO_2$ regression lines. Mean arterial pressure response to increased $P_aCO_2$ is not significantly different in conscious subjects and during anesthesia.](Image)

ing 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 Eilsten's finding in older, premedicated, surgically-stimulated patients but did inhibit the heart rate response.

Tachycardia, which occurred in response to rising CO$_2$ 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 Carfield 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 $P_aCO_2$ 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 CO$_2$ to be nonspecifically depressed by any general anesthetic.

Cyclopropane modified the relationship between cardiac index and mean right atrial
TABLE 3. Changes in Cardiac Index in
ml/mm Hg Increase in PaCO₂

<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></td>
<td></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&lt;sup&gt;4&lt;/sup&gt;</td>
<td>+7</td>
<td>+34</td>
</tr>
<tr>
<td>0.5–1 per cent inspired halothane in (O&lt;sub&gt;2&lt;/sub&gt; or NO) per cent N&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;15&lt;/sup&gt;</td>
<td>+31</td>
<td>—</td>
</tr>
<tr>
<td>1 per cent inspired halothane&lt;sup&gt;5&lt;/sup&gt;</td>
<td>+14.5</td>
<td>+23</td>
</tr>
<tr>
<td>Balanced anesthesia&lt;sup&gt;3&lt;/sup&gt;</td>
<td>+22</td>
<td>+22</td>
</tr>
</tbody>
</table>

* The cardiovascular response to CO₂ during hypocapnia is reduced or absent when compared with the cardiovascular response to CO₂ during hypercapnia. Note that general anesthetics attenuate the cardiac index response to rising PaCO₂, halothane more so than cyclopropane.

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References


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 dispicable, 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: 141 (Jan.) 1969.)