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

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In seven healthy, conscious volunteers, hyperventilation from \( P_{\text{aco}} \) 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 \( P_{\text{aco}} \) 37 mm Hg to 26 mm Hg during anesthesia with 15–20 per cent cyclopropane decreased QI and SV. When \( P_{\text{aco}} \) 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; Hypercapnia; 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 \( CO_2 \). With halothane or balanced anesthesia, during controlled ventilation, the cardiac index response to \( CO_2 \) seems attenuated when compared with that of conscious man breathing spontaneously. 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 \( P_{\text{aco}} \) 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. In each of seven healthy, conscious, nonmedicated adult male volunteers, we controlled ventilation with a volume-limited ventilator to maintain a \( P_{\text{aco}} \) 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 \( P_{\text{aco}} \) 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 \( P_{\text{aco}} \) to a new
constant value. Several successive stepwise increases in PaCO₂ were made in each subject. Measurements were recorded six minutes after each. Two hours after induction of anesthesia with cyclopropane in oxygen, the same CO₂ 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 CO₂ response curves allowed statistical comparison of slopes of responsiveness to CO₂.

**Results**

**Effect of Hyperventilation**

*Table 1, Fig. 1*

In conscious subjects, the cardiac index changed in response to increased CO₂ only above an arterial PaCO₂ of 35 mm Hg. Increasing the rate and depth of ventilation to lower PaCO₂ did not alter cardiac index or related values. Addition of CO₂ to inspired gas at the increased rate and depth of ventilation did not change the cardiac index until PaCO₂ exceeded 35 mm Hg. All regression lines are based on the responses above PaCO₂ 35 mm Hg only.

At 15–20 per cent cyclopropane, the cardiac index was 105 per cent of control. Hyperventilation to PaCO₂ 26 ± 1.5 mm Hg reduced the cardiac index 16 per cent (P < 0.05). Furthermore, restoration of PaCO₂ 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 PaCO₂ of 26 mm Hg (fig. 1). At 25–30 per cent cyclopropane, neither hyperventilation nor addition of CO₂ to restore PaCO₂ to 34.8 mm Hg affected the cardiac index significantly.

<table>
<thead>
<tr>
<th>PaCO₂ (mm Hg)</th>
<th>Awake (n = 7)</th>
<th>15-20 Per Cent CIs (n = 5)</th>
<th>25-30 Per Cent CIs (n = 4)</th>
<th>Hyperventilation</th>
<th>Hyperventilation</th>
<th>Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Normal</td>
<td>Controlled Ventilation</td>
<td>Normal</td>
<td>Controlled</td>
<td>Ventilation</td>
<td>Controlled</td>
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<tr>
<td></td>
<td>Hyperventilation</td>
<td></td>
<td>Ventilation</td>
<td></td>
<td>Ventilation</td>
<td></td>
</tr>
<tr>
<td>P (mm Hg)</td>
<td>34.7</td>
<td>±1.5</td>
<td>34.8***</td>
<td>37.2</td>
<td>±1.7</td>
<td>26.2***</td>
</tr>
<tr>
<td>Q</td>
<td>102</td>
<td>±3.5</td>
<td>103**</td>
<td>105</td>
<td>±8.3</td>
<td>95</td>
</tr>
<tr>
<td>HR (per cent)</td>
<td>100</td>
<td>±2.3</td>
<td>103**</td>
<td>95</td>
<td>±4.6</td>
<td>90</td>
</tr>
<tr>
<td>SV (per cent)</td>
<td>100</td>
<td>±3.7</td>
<td>96</td>
<td>109</td>
<td>±6</td>
<td>99*</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>2.3</td>
<td>±1.2</td>
<td>2.5</td>
<td>4.2</td>
<td>±1.2</td>
<td>3.4</td>
</tr>
<tr>
<td>TPR (per cent)</td>
<td>100</td>
<td>±3.8</td>
<td>103**</td>
<td>115</td>
<td>±20</td>
<td>121</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.
Fig. 1. The effect on cardiac index of controlled positive-pressure hyperventilation during hypoxia or normoxia. 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 CIs</th>
<th>25–30 Per Cent CIs</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 + 53.9</td>
</tr>
<tr>
<td>Stroke index (L/m²)</td>
<td>y = 0.61x + 14.5</td>
<td>y = 0.5x + 16.1</td>
<td>y = 0.54x + 20.5</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes-sec/cm²)</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 + 7.93</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 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/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.

Fig. 2. Heart rate–PaCO₂ regression lines. Tachycardia in response to increased PaCO₂ is abolished by 25–30 per cent cyclopropane.

Fig. 3. Stroke index–PaCO₂ regression lines. Stroke index slopes in conscious subjects and during anesthesia are similar.
However, cyclopropane anesthesia modifies the compensatory response to hyperventilation. During anesthesia with 15–20 per cent cyclopropane, hypcapnic hyperventilation reduced cardiac index a small but significant amount. This was not due to hypcapnia 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 hypcapnia during 0.8 per cent alveolar halothane in human volunteers. Theye et al.12 and Prys-Roberts et al.,4 however, reported that during clinical anesthesia hyperventilation and hypcapnia 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 Hypcapnia**

In conscious man, elevation of \( \text{P}_{\text{aCO}} \) 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 Elsten's finding in older, premedicated, surgically-stimulated patients18 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.17 and Garfield et al.18 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 \( \text{P}_{\text{aCO}} \) 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.19 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
pressure (fig. 7). While the subjects were conscious, increasing CO₂ from 35 mm Hg to 55 mm Hg doubled cardiac index and concomitantly lowered mean right atrial pressure. The shift of one point in ventricular function upward and to the left could represent stimulation. During cyclopropane anesthesia, the increase in cardiac index was less and occurred while mean right atrial pressure was rising. We cannot tell whether a shift in the ventricular function curve occurred.

The effects of other anesthetics on cardiac response to CO₂ are shown in table 3. Essentially, halothane, 0.8 per cent (end-tidal) in nonmedicated volunteers⁸ and halothane (1–1.5 per cent inspired)⁷ or balanced anesthesia in premedicated patients⁹ attenuates the cardiac index response to CO₂ far more than does cyclopropane. The pharmacologic differences between cyclopropane and halothane account for the results in Martin’s study. Prys-Roberts’ older, premedicated patients, in whom induction agents were used, would have been expected to respond differently from healthy, nonmedicated, adult male volunteers.

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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 disruptable, 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.)