Systemic circulatory responses to hypocapnia in man

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SEVERAL STUDIES have reported increases in cardiac output, increases in heart rate, and decreases in mean arterial blood pressure and in systemic vascular resistance due to vasodilation during hypocapnic alkalosis induced by voluntary hyperventilation in man (2, 3, 13, 22). Other studies, however, showed either little change in these variables or alterations suggesting a net vasoconstrictor effect (7, 12, 16, 20). Similarly, there is disagreement concerning the circulatory effects of hypocapnic alkalosis induced by hyperventilation in experimental animals (1, 6, 8, 9, 11, 14, 16, 18). In another study (10) we found that the vasodilation observed in the human forearm during voluntary hyperventilation is time dependent and generally subsides several minutes after the onset of hyperventilation and is followed by a vasoconstrictor effect if hyperventilation and hypocapnic alkalosis are continued for a sufficiently long period of time. This led us to investigate the possibility that the disagreement found in the literature concerning the systemic circulatory effects of hypocapnic alkalosis might be related to differences in the timing of the observations made by various investigators.

In our investigation of the mechanism of the vasodilation in the human forearm during hypocapnic alkalosis induced by hyperventilation, we obtained evidence suggesting strongly that this response is mediated by release of histamine, and that, in contrast to the results of others, it is not mediated by stimulation of beta-adrenergic receptors (10). In view of these findings we investigated the effects of beta-adrenergic receptor blockade and the effect of antihistamines on the systemic circulatory response to hypocapnia.

METHODS

Experiments were carried out in 30 male young volunteers. Each subject had previously participated in experiments involving voluntary hyperventilation in our laboratory and was therefore experienced with the techniques used. Subjects were studied while supine on a table. Arterial blood was obtained from a Teflon catheter placed into the brachial artery at the elbow under local anesthesia. Arterial blood pressure was measured with a Statham P23Db strain gauge connected to the arterial catheter. Cardiac output was determined by an indicator-dilution technique using indocyanine green. Dye concentration in arterial blood was determined with a Gilford densitometer which was calibrated at the end of each experiment with known dye concentrations prepared in the subject's own blood. Dye was injected rapidly through a catheter placed into the axillary vein or superior vena cava and followed quickly with a flush of 10 ml of 0.9% NaCl solution. Ventilation was monitored with pneumographs placed around the chest and abdomen. The pneumographs were connected to a low-pressure Statham strain gauge and were calibrated by simultaneous recording of pneumographic deflection and expired air volume with a wedge spirometer. The subjects breathed through a mouthpiece and low-resistance valve while their noses were occluded with a clip. The concentration of carbon dioxide in the expired air was monitored continuously with an infrared CO₂ analyzer. Arterial blood oxygen and CO₂ tensions and pH were measured with appropriate electrodes at 37 C (17).

The experimental procedure was as follows: following insertion of the arterial and venous catheters, 15 min were allowed to elapse. Control measurements of cardiac output, arterial blood pressure, heart rate, ventilation, arterial blood gas tensions, and pH were made while the subjects breathed through the mouthpiece. The subjects were then instructed to hyperventilate vigorously so that their end-tidal Pco₂ was reduced to about 20 mm Hg. When this was achieved, the subjects were instructed to adjust their breathing so that a constant low level of end-tidal Pco₂ was maintained throughout the period of hyperventilation. Repeat measurements of
the variables of interest were made during hyperventilation at appropriate intervals.

Several types of experiments were carried out: 1) in 11 subjects the time course of the circulatory changes during hyperventilation were followed for 4 min. In another series of six subjects, the period of hyperventilation was extended to 7 min. Measurements of the appropriate circulatory variables were made 1, 4, and 7 min after the onset of hyperventilation. 2) In seven subjects the effects of hypocapnic hyperventilation were compared with the effects of hyperventilation without change in arterial blood CO₂ tension. This was accomplished by introducing into the inspired air CO₂ in a concentration which was just sufficient to maintain the end-tidal CO₂ tension at the control value. A 15-min period elapsed between the two periods of hyperventilation and the order in which isocapnic and hypocapnic hyperventilation were carried out was randomized. 3) In seven subjects the effect of beta-adrenergic receptor blockade on the circulatory response to hyperventilation was studied. Beta-adrenergic receptor blockade was accomplished by intravenous administration of 5 mg of propranolol over a period of 5 min. In each subject following the administration of propranolol, intravenous infusion of 10 µg/min of epinephrine produced hypertension and bradycardia. In contrast, prior to the administration of propranolol, the infusion of epinephrine in the same dose produced tachycardia with an initial decrease in blood pressure followed by return to the control value. The second period of hyperventilation, following beta-adrenergic receptor blockade, followed the first by a period of about 20 min. 4) In eight subjects the circulatory effect of hyperventilation was studied before and after intravenous administration of the antihistamine promethazine in a dose of 25 mg given over a period of 5 min. The effectiveness of blockade was verified by the intravenous injection of 12.5 µg of histamine intravenously. Prior to administration of promethazine, histamine produced transient fall in arterial blood pressure accompanied by tachycardia. Following the administration of promethazine, there was no change in either arterial blood pressure or in heart rate.

RESULTS

Tables 1 and 2 show the time course of the circulatory changes produced by hyperventilation for 4 and 7 min, respectively, in two separate groups of subjects. During the early part of hyperventilation, there was a transient decrease in mean arterial blood pressure accompanied by an increase in cardiac index and in heart rate and by a reduction in systemic vascular resistance. The change in arterial blood pressure subsided very rapidly, whereas the increases in cardiac index and heart rate persisted, but were less pronounced 4 min after hyperventilation and subsided completely by 7 min.

McGregor and his colleagues (13) found that during isocapnic hyperventilation there was a less pronounced, but significant, increase in cardiac output than during hypocapnic hyperventilation. In contrast, earlier work in our laboratory (15) showed no significant change in cardiac output during isocapnic hyperventilation. McGregor et al. (13) made their measurements 45 sec following the onset of hyperventilation, whereas in the earlier study from our laboratory the determinations were made several minutes following the onset of hyperventilation. To determine whether or not this difference was responsible for the divergence in the results, we compared the effects of hypocapnic and isocapnic hyperventilation on the circulatory changes which occurred 1 min following the onset of hyperventilation. Table 3 shows that hypocapnic hyperventilation produced the usual changes in the circulatory variables, whereas isocapnic hyperventilation produced no significant change except a slight increase in heart rate which was significantly less pronounced than that produced by hypocapnic hyperventilation.

Table 4 summarizes the effects of hypocapnic hyperventilation on the systemic circulation before and following beta-adrenergic receptor blockade. The responses were not significantly altered by propranolol.

Table 5 compares the response to voluntary hyperventilation before and following administration of the antihistamine promethazine. Promethazine reduced significantly, but did not abolish, the increase in cardiac output and heart rate.
The largest increases in cardiac output and heart rate and the decreases in arterial blood pressure and systemic vascular resistance seen during hypocapnic hyperventilation are time dependent. This observation provides an explanation for the divergence in results obtained by previous investigators who studied the circulatory effects of hyperventilation in man and animals. Those investigators who measured these variables later on, after a steady state had been established, found no significant changes. The subsidence of the early changes associated with hypocapnic hyperventilation suggests that the mechanisms responsible for them rapidly become exhausted or that they are effectively counteracted by other mechanisms which develop more slowly. In the accompanying paper (10) we obtained evidence supporting the view that the release of histamine is primarily responsible for the increase in skeletal muscle blood flow which occurs in the early part of hypocapnic hyperventilation and suggested that the lack of persistence of this hyperemia, despite continuing hypocapnia, is due to the more slowly developing direct vasomotor effects of hypocapnia. It is possible that the return of cardiac output and heart rate to the resting level is related to similar mechanisms, perhaps with participation of additional mechanisms, such as central nervous system and the decrease in systemic vascular resistance seen during hyperventilation. It also abolished the decrease in mean arterial blood pressure.

**DISCUSSION**

Our findings show that the systemic circulatory effects of hypocapnic hyperventilation in man are time dependent. The largest increases in cardiac output and in heart rate and the most pronounced decreases in arterial blood pressure and in systemic vascular resistance occur during the 1st min of hyperventilation; they subsequently return toward the corresponding control values and generally subside within 4–7 min. This observation provides an explanation for the divergence in results obtained by previous investigators who studied the circulatory effects of hyperventilation in man and in animals. Those investigators who measured these variables later on, after a steady state had been established, found no significant changes. The subsidence of the early changes associated with hypocapnic hyperventilation suggests that the mechanisms responsible for them rapidly become exhausted or that they are effectively counteracted by other mechanisms which develop more slowly. In the accompanying paper (10) we obtained evidence supporting the view that the release of histamine is primarily responsible for the increase in skeletal muscle blood flow which occurs in the early part of hypocapnic hyperventilation and suggested that the lack of persistence of this hyperemia, despite continuing hypocapnia, is due to the more slowly developing direct vasomotor effects of hypocapnia. It is possible that the return of cardiac output and heart rate to the resting level is related to similar mechanisms, perhaps with participation of additional mechanisms, such as central nervous system and the decrease in systemic vascular resistance seen during hyperventilation. It also abolished the decrease in mean arterial blood pressure.

**TABLE 3. Comparison of circulatory effects of hypocapnic and isocapnic hyperventilation**

<table>
<thead>
<tr>
<th></th>
<th>Hypocapnic Hyperventilation</th>
<th>Isocapnic Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>D1</td>
</tr>
<tr>
<td><strong>Cardiac index, liters/min per m²</strong></td>
<td>3.0 ±0.2</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>69 ±3</td>
<td>92</td>
</tr>
<tr>
<td><strong>Mean arterial pressure, mm Hg</strong></td>
<td>94 ±3</td>
<td>85</td>
</tr>
<tr>
<td><strong>Vascular resistance, mm Hg per liter per min per m²</strong></td>
<td>33 ±3</td>
<td>22</td>
</tr>
<tr>
<td><strong>Paco₂, mm Hg</strong></td>
<td>37 ±0.7</td>
<td>24</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.4</td>
<td>7.36</td>
</tr>
</tbody>
</table>

Values are means ± se from eight experiments. *Values significantly (P < 0.05) different from zero (t test). †Values whose difference from corresponding D1 values is significantly different from zero (t test).

**TABLE 4. Effect of beta-adrenergic blockade on circulatory response to hyperventilation**

<table>
<thead>
<tr>
<th></th>
<th>Before Propranolol</th>
<th>After Propranolol</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Change from control during hyperventilation</td>
<td>Change from control during hyperventilation</td>
</tr>
<tr>
<td></td>
<td>1 min</td>
<td>4 min</td>
</tr>
<tr>
<td><strong>Cardiac index, liters/min per m²</strong></td>
<td>2.8 ±0.1</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>72 ±4</td>
<td>30</td>
</tr>
<tr>
<td><strong>Mean arterial pressure, mm Hg</strong></td>
<td>92 ±2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Vascular resistance, mm Hg per liter per min per m²</strong></td>
<td>33 ±2</td>
<td>-10</td>
</tr>
<tr>
<td><strong>Paco₂, mm Hg</strong></td>
<td>36 ±1</td>
<td>-14</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.44</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Values are means ± se from eight experiments. *Values significantly (P < 0.05) different from zero (t test).
in cardiac output and heart rate. The present findings add additional credence to the view that release of histamine plays a significant role in the vasodilation of hypocapnic hyperventilation. This is based on the observation that antihistamines reduce the changes in blood pressure, heart rate, and cardiac output accompanying hypocapnic hyperventilation. In the accompanying paper (10) we found that during hypocapnic hyperventilation there is an increase in arterial blood concentration of histamine. A variety of mechanisms may be involved in the mediation of the increase in cardiac output and in heart rate by release of histamine. It has been shown (5) that histamine exerts positive inotropic and chronotropic effects on the heart. In addition, by producing systemic vasodilation histamine might secondarily induce increases in heart rate and in cardiac output through the baroreceptor reflexes. In this respect, it is of interest that beta-adrenergic receptor blockade with propranolol did not alter the circulatory responses to hypocapnic hyperventilation. This is consistent with the findings of Feisal and his colleagues (6) in the dog. This observation was unexpected, since it has been reported that blood concentration of epinephrine increases during hypocapnic alkalosis induced by hyperventilation (91). Also, it has been shown (19) that the increased heart rate resulting from decreased baroreceptor stimulation as a result of arterial hypotension is at least in part mediated by increased cardiac sympathetic efferent activity. The possibility that the reflex mediation of tachycardia during hyperventilation is accomplished via decreased parasympathetic efferent cardiac activity is suggested by the finding of Thompson, Berry, and McIntosh (22) that the administration of atropine reduced the tachycardia and increase in cardiac output observed in the early phases of hypocapnic hyperventilation in man.

It must be noted that although the circulatory effects of hyperventilation were significantly reduced following promethazine administration, they were not abolished. As shown in Table 5, following promethazine the increase in cardiac output produced by hyperventilation was reduced by only 50%, the decrease in heart rate by only 39%, and the decrease in systemic vascular resistance by 46%. The persistence of significant vasodilation following the administration of promethazine might have been due to incomplete blockade of the effects of endogenousy released histamine or it might have been due to the participation of additional unidentified mechanisms in this response.

Our findings show that the circulatory responses to hyperventilation depend mainly on the production of hypocapnic alkalosis and that the mechanical and reflex effects of hyperventilation were not sufficient by themselves to produce the observed circulatory responses. The only significant effect of isocapnic hyperventilation was a small increase in heart rate. These results are similar to those obtained earlier in our laboratory (15). They differ slightly from the results of McGregor et al. (13) in that they found that isocapnic hyperventilation produced a small increase in cardiac output in addition to a small increase in heart rate. It is possible that the mechanical and reflex effects of hyperventilation may aid in the production of increased cardiac output during hypocapnia. For example, it has been shown that hyperventilation with or without hypocapnia causes reflex vasoconstriction (4). This is likely to result in increased venous return and aid in the increase in cardiac output during hyperventilation.

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REFERENCES


