Impairment of Myocardial O$_2$ Supply due to Hyperventilation

By William A. Neill, M.D., and Mark Hattenhauer, M.D.

SUMMARY

Thirteen patients with ischemic coronary heart disease purposely hyperventilated for seven minutes in order to induce hypocapnic alkalosis. One patient experienced chest pain, and one exhibited chemical signs of myocardial hypoxia. Heart rate, blood pressure and myocardial O$_2$ consumption did not change significantly. Coronary blood flow decreased and coronary (a-v)O$_2$ difference widened. Since the alkalosis increased the blood O$_2$ affinity, the fall in Po$_2$ in coronary venous blood was proportionately even greater than the fall in O$_2$ concentration. Thus, hypocapnic alkalosis due to hyperventilation interferes with myocardial O$_2$ supply by 1) coronary vasoconstriction and 2) increased O$_2$ affinity of blood.

Hyperventilation increases arterial blood Po$_2$ and, by the Bohr effect, increases the affinity of blood for O$_2$ in proportion to the degree of hypocapnic alkalosis. The hemoglobin is more fully saturated with O$_2$ at any given Po$_2$, i.e., the O$_2$ dissociation curve is shifted to the left. Unless arterial hypoxemia was present initially, these changes only slightly augment oxygenation of arterial blood in the pulmonary capillaries, due to the configuration of the O$_2$ dissociation curve. At the same time, with the higher pH in the systemic capillaries, the hemoglobin will give up the expected amount of its O$_2$ only if the Po$_2$ falls below normal; and a decrease in capillary blood Po$_2$ might significantly impair O$_2$ diffusion into the tissue. In the coronary circulation where vasomotor regulation is influenced prominently by the needs of the myocardium for O$_2$, decreased capillary blood Po$_2$ might be expected to result in compensatory vasodilatation and increased coronary blood flow, as in anemia. Hypocapnic alkalosis, however, increases vascular resistance and decreases blood flow in some tissues, including the forearm and brain. Although the results of experiments with the coronary circulation in anesthetized animals are inconclusive, voluntary hyperventilation has been reported to increase resistance, decrease blood flow and lower venous O$_2$ concentration in the normal coronary circulation of human subjects. Thus, in those subjects, the impaired blood O$_2$ release appeared not to be compensated by augmented blood flow but instead to be compounded by coronary vasoconstriction.

If increased blood O$_2$ affinity and coronary vasoconstriction also occur in patients with ischemic coronary heart disease, voluntary hyperventilation might result in myocardial hypoxia. The present report is an investigation of voluntary hyperventilation in the resting state in patients with symptomatic chronic ischemic coronary heart disease. We determined the effect of hyperventilation on systemic hemodynamics, coronary blood flow, myocardial O$_2$ supply, and in vivo O$_2$ affinity of coronary venous blood.

Methods

We studied 13 men with stable exertional angina pectoris who were being evaluated for possible coronary bypass graft surgery. Their ages ranged from 45 to 58 years (mean 50 years). Coronary arteriography was performed in 12 of the men and demonstrated single vessel disease in one patient, double vessel disease in five patients, and triple vessel disease in six patients. Four of the 11 patients with technically satisfactory left ventriculograms had ejection fractions < .50 or decreased regional wall motion. Eight patients had a previous myocardial infarction. No patient had significant valvular heart disease or clinical evidence of cardiac failure. Written consent was obtained from the patients after we explained the investigative nature of the procedure. The patients practiced hyperventilating the day before the study. On the morning of the study, the patients fasted and received no sedation or nitrates. With the patient supine, we introduced catheters into the brachial artery percutaneously, coronary sinus via basilic vein cutdown, and into either the pulmonary artery via the same basilic vein cutdown or the left ventricle percutaneously via a femoral artery. Observations were made 1) with the patient at rest and 2) during the interval between the third and seventh minutes of vigorous, steady hyperventilation. The sequence was random. When hyperventilation was done first, we waited for 20–30 minutes before making resting observations.

ECG lead II and brachial artery and left ventricle pressures were recorded on a photographic Electronics for
MYOCARDIAL O₂ SUPPLY IN HYPERVENTILATION

Medicine recorder. Paired arterial and coronary venous blood samples were analyzed for Po2 and pH (Radiometer Co., Copenhagen), hemoglobin concentration (spectrophotometer), and lactate and pyruvate concentrations. The O₂ capacity of the blood was calculated from the hemoglobin concentration. Blood O₂ concentration or content (bound to hemoglobin and dissolved) was calculated from Po2 and O₂ capacity, after adjusting the O₂ dissociation curve for the observed pH change ("calculated" O₂ concentration values). Coronary venous blood O₂ concentration also was determined manometrically in 11 patients ("manometric" O₂ concentration values). For coronary (a-v)O₂ difference we used calculated arterial O₂ concentration and manometric coronary venous O₂ concentration, except in the two patients in whom manometric analyses were not done. Coronary blood flow was determined in ten patients by the exponential clearance rate of 133 xenon. The [133Xe] xenon was injected via the left ventricle or pulmonary artery catheter, and the clearance rate determined from timed coronary venous blood samples obtained through a manifold connected to the coronary sinus catheter. Five 15-second samples were withdrawn at a rate of 0.1 ml/sec during the early exponential clearance phase (between 30 and 105 seconds after injection, allowing for dead space in the sampling system). The clearance rate was corrected for arterial recirculation of [133Xe] xenon. Left ventricle myocardial O₂ consumption was calculated as the product of coronary blood flow and coronary (a-v)O₂ difference. A lactate extraction coefficient, (a-v)/aL, less than 0.09, or an increase in coronary venous blood lactate/pyruvate concentration ratio (L/P) of greater than 12% (without accompanying increased arterial L/P) was interpreted as evidence of myocardial hypoxia.

Results

Most patients experienced mild lightheadedness and tingling of the hands and lips, which began after 2 to 3 minutes and continued throughout the period of hyperventilation. In one patient, mild chest pain typical of his exertional angina occurred during the last two minutes of hyperventilation and subsided two minutes after normal breathing was resumed. No significant ST or T wave changes occurred in lead II of the ECG in any patient.

Hemodynamic data are summarized in table 1. There were no significant changes in heart rate, systemic arterial pressure or left ventricular end-diastolic pressure. Coronary blood flow decreased (fig. 1). Mean data for blood gases and pH are given in table 2. Hyperventilation decreased mean arterial blood Pco2 to 18.7 mm Hg and increased mean arterial blood pH to 7.56. Arterial blood Po2 and O₂ concentration increased (fig. 2). Coronary venous blood Po2 and O₂ concentration both decreased (figs. 3 and 4), but Po2 decreased by a proportionately greater amount. This discrepancy can be explained by the coronary venous blood alkalosis since mean coronary venous blood O₂ concentration calculated from the Po2 and pH values was not significantly different from O₂ concentration determined by manometric analysis (calculated value was greater by a mean of 0.3 ml/100 ml). Thus, hyperventilation exerted no significant effect on blood O₂ affinity other than that attributable to the increase in pH.

The fall in coronary blood flow was accompanied by a proportional widening of the coronary (a-v)O₂, and there was no significant change in myocardial O₂ consumption.

Lactate and pyruvate data are given in table 3. The arterial blood lactate concentration increased during hyperventilation. Extraction of pyruvate by the myocardium decreased significantly, whereas the

![Table 1](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Hemodynamic Data</th>
<th>Rest</th>
<th>Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (min⁻¹)</td>
<td>71 ± 2.2*</td>
<td>73 ± 2.7</td>
</tr>
<tr>
<td>SAP, (mm Hg)</td>
<td>140 ± 3.6</td>
<td>140 ± 3.2</td>
</tr>
<tr>
<td>SAP, (mm Hg)</td>
<td>72 ± 2.7</td>
<td>73 ± 1.9</td>
</tr>
<tr>
<td>SAP, (mm Hg)</td>
<td>100 ± 2.8</td>
<td>100 ± 2.9</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>14 ± 2.3</td>
<td>12 ± 2.2</td>
</tr>
<tr>
<td>CBF, (ml/100 g · min)</td>
<td>99 ± 6.7</td>
<td>87 ± 4.8</td>
</tr>
</tbody>
</table>

*Mean = SEM.
Specific patients.
**Statistical difference, hyperventilation vs rest (paired t-test), P < 0.05.
Abbreviations: HR = heart rate; SAP = systemic arterial blood pressure; s = systole; d = diastole; m = mean; LVEDP = left ventricular end-diastolic blood pressure; CBF = coronary blood flow.

![Figure 1](http://circ.ahajournals.org/)

Effect of four minutes of voluntary hyperventilation on coronary blood flow ([133Xe]). Each line represents one patient. Mean values for coronary blood flow at rest and during hyperventilation are indicated.
Discussion

These studies show that hyperventilation decreased coronary blood flow and coronary venous blood $O_2$ concentration in patients whose myocardial $O_2$ supply was already compromised by ischemic coronary disease. Since systemic arterial blood pressure did not change significantly during hyperventilation, the observed decrease in coronary blood flow implies increased coronary resistance. Coronary vascular resistance normally is responsive to simultaneous changes in myocardial $O_2$ needs, so that coronary (a-v)$O_2$ difference remains nearly constant. In our studies, however, no fall in myocardial $O_2$ needs occurred. Heart rate and systolic arterial blood pressure, important determinants of myocardial $O_2$ needs, did not decrease; and calculated myocardial $O_2$ consumption remained essentially constant. Moreover, the widening of the coronary (a-v)$O_2$ difference is inconsistent with decrease in $O_2$ needs as the basis of the decrease in blood flow. When arterial blood $O_2$ concentration was augmented by breathing high concentrations of $O_2$, coronary blood flow decreased. \(^{12,13}\) Under those circumstances, however, coronary venous blood $O_2$ concentration rises, \(^{12-15}\) and the decrease in coronary blood flow presumably is due to a reduction in the amount of blood flow needed to maintain myocardial $O_2$ supply. The slight increase in arterial blood $O_2$ concentration which occurred during hyperventilation in our patients, however, cannot explain their decrease in blood flow, since their coronary

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**Figure 2**

Effect of five minutes of voluntary hyperventilation on arterial blood $O_2$ concentration.

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**Figure 3**

Effect of five minutes of voluntary hyperventilation on coronary venous blood $O_2$ concentration.

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**Figure 4**

Effect of five minutes of voluntary hyperventilation on coronary venous blood $P_{O_2}$. 
venous blood $O_2$ concentration decreased. The decrease in coronary blood flow appears to be due to a direct vasomotor effect of the hypocapnic alkalosis. Our data do not distinguish between hypocapnia and alkalosis as potential causes of the coronary vasoconstriction. Other experiments, however, suggest that alkalosis is more likely responsible for the vasoconstriction.\textsuperscript{5, 10-18}

Hyperventilation raised arterial blood $O_2$ concentration by 5%, which represents a minor potential benefit to myocardial $O_2$ supply. By contrast, the simultaneous detrimental effect of increased $O_2$ affinity of the blood on its ability to release $O_2$ in the coronary capillaries was quantitatively much more powerful. In a previous investigation in humans,\textsuperscript{4} coronary venous blood $P_{O_2}$ was calculated from $O_2$ concentration, assuming that the increase in $pH$ was the only factor influencing blood $O_2$ affinity. In the present study, changes in blood $O_2$ affinity can be examined directly in the 11 patients in whom coronary venous blood $P_{O_2}$ and $O_2$ concentration were both measured. In these 11 patients, mean coronary venous blood $O_2$ concentration fell from 6.2 to 5.6 ml/100 ml. If blood $O_2$ affinity were to remain constant, that fall in $O_2$ concentration would correspond to a decrease in $P_{O_2}$ only from 19.5 to 18.5 mm Hg. Yet, coronary venous blood $P_{O_2}$ fell to 16.2 mm Hg. Conversely, with a constant $O_2$ affinity, the observed decrease in $P_{O_2}$ to 16.2 mm Hg would have permitted a fall in coronary venous blood $O_2$ concentration to as low as 4.4 ml/100 ml, widening the coronary (a-v)O$_2$ difference and augmenting myocardial $O_2$ delivery by 8%. These data constitute direct evidence for increased blood $O_2$ affinity and decreased $O_2$ release in the coronary capillaries. The increase found in $O_2$ affinity was approximately equal to that predicted by the blood pH change which occurred.

These experiments demonstrate that hypocapnic alkalosis interferes with myocardial $O_2$ supply by a combination of coronary vasoconstriction and increased $O_2$ affinity of the blood in the coronary capillaries. This effect of hyperventilation could be important in several clinical situations. 1) Pulmonary vascular congestion. The hypocapnic alkalosis that frequently results from dyspnea could potentiate myocardial hypoxia and further impair left ventricular function. 2) Angina pectoris provoked by cold or emotion. The sensitivity of certain patients with ischemic heart disease to cold exposure or emotional stress might be due to associated hyperventilation.\textsuperscript{10} 3) Psychoneurotic chest pain. Chronic hyperventilation frequently occurs in anxiety without being apparent to either the patient or the observer.\textsuperscript{19} Even when initiated voluntarily, when hyperventilation is maintained, the sensation of excessive breathing may largely recede within an hour while asymptomatic hypocapnic alkalosis remains as severe as in our patients.\textsuperscript{20} 4) Exertional chest pain and ST-segment depression despite normal coronary angiograms.\textsuperscript{21-23} Some observers have been impressed by the prevalence of anxiety in these patients. Excessive breathing during exercise is an unexplored possible basis of their manifestations of exertional myocardial hypoxia.

### Table 2

<table>
<thead>
<tr>
<th>Blood Gas Data</th>
<th>Rest</th>
<th>Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{O_2}$ (mm Hg)</td>
<td>33.1 ± 1.22*</td>
<td>18.7 ± .74***</td>
</tr>
<tr>
<td>$pH_a$ (units)</td>
<td>7.40 ± .007</td>
<td>7.56 ± .009***</td>
</tr>
<tr>
<td>$pH_v$ (units)</td>
<td>7.36 ± .008</td>
<td>7.50 ± .010***</td>
</tr>
<tr>
<td>$P_{O_2}$ (mm Hg)</td>
<td>66 ± 2.2</td>
<td>84 ± 3.7***</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mm Hg)</td>
<td>19.5 ± .67</td>
<td>16.3 ± .56 ***</td>
</tr>
<tr>
<td>$O_2$ Cap (ml/100 ml)</td>
<td>20.4 ± .62</td>
<td>20.5 ± .62</td>
</tr>
<tr>
<td>$C_{O_2}$ (ml/100 ml)</td>
<td>19.1 ± .53</td>
<td>20.2 ± .61***</td>
</tr>
<tr>
<td>$CVO_2$ (ml/100 ml)</td>
<td>6.1 ± .20</td>
<td>5.5 ± .24***</td>
</tr>
<tr>
<td>$C_{O_2}/V(O_2$) (ml/100 ml)</td>
<td>13.0 ± .50</td>
<td>14.7 ± .59***</td>
</tr>
<tr>
<td>$MV_{O_2}$ (ml/100 g · min)</td>
<td>12.7 ± .88</td>
<td>12.8 ± .76</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
***$P < 0.01$, hyperventilation vs rest, paired $t$-test.

### Table 3

<table>
<thead>
<tr>
<th>Lactate and Pyruvate Extraction Data</th>
<th>Rest</th>
<th>Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>L (mmole/L)</td>
<td>.49 ± .02*</td>
<td>.57 ± .03***</td>
</tr>
<tr>
<td>L (a-v/a)</td>
<td>.24 ± .03</td>
<td>.20 ± .03</td>
</tr>
<tr>
<td>Pa (mmole/L)</td>
<td>.100 ± .004</td>
<td>.107 ± .006</td>
</tr>
<tr>
<td>P (a-v/a)</td>
<td>.25 ± .02</td>
<td>.15 ± .03***</td>
</tr>
<tr>
<td>L/Pa</td>
<td>.49 ± .08</td>
<td>5.3 ± .19</td>
</tr>
<tr>
<td>L/Pv</td>
<td>5.0 ± .15</td>
<td>5.0 ± .18</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
***$P < 0.001$, hyperventilation vs rest, paired $t$-test.

Abbreviations: L = lactate; P = pyruvate; a = arterial; c = coronary venous.

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