Arterial CO₂, Myocardial O₂ Consumption, and Coronary Blood Flow in the Dog

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SUMMARY We determined the effect of changes in arterial Pco₂ on the relationship between O₂ delivery (DO₂) and consumption (MVO₂) by the myocardium of anesthetized dogs. Left anterior descending coronary blood flow (CBF), arterial and great cardiac vein O₂ content (GCVO₂), and arterial pressure were measured. MVO₂ was raised by infusing various doses of isoproterenol (ISO) or norepinephrine (NE) into the right atrium. CBF, DO₂, coronary conductance (CVC), and GCVO₂ were plotted as a function of MVO₂ using data obtained at high (=70 mm Hg) and low (=24 mm Hg) Pco₂. When ISO was used to raise MVO₂, we found that CBF, DO₂, and CVC were slightly higher for a given MVO₂. In addition, GCVO₂ was ~7 vol % at high CO₂, ~4 vol % at low CO₂. When NE was used to raise MVO₂, this difference was not observed at high MVO₂’s. Alpha-receptor blockade caused the results with NE to look more like the results with ISO. Indomethacin lowered GCVO₂ relative to MVO₂ under resting conditions at both high and low Pco₂, but not during infusion of ISO. These results indicate that (1) elevation of systemic arterial PCO₂ causes only a small increase in DO₂ relative to MVO₂ but that this results in a relatively large increase in tissue oxygenation, (2) NE causes a receptor-mediated vasoconstriction which competes with CO₂ vasodilation, and (3) prostaglandin release contributes a vasodilator influence at resting but not elevated MVO₂.

CASE and his colleagues (1975) showed that elevating arterial Pco₂ raised coronary sinus O₂, suggesting that the relationship between myocardial O₂ consumption (MVO₂) and flow delivery of O₂ had been altered. In other studies, this group has shown that, under conditions of constant flow, alterations in coronary arterial Pco₂ can cause relatively large changes in coronary vascular resistance (Case and Greenberg, 1976, Case et al., 1978). However, previous workers have not evaluated the vasoactivity of changes in systemic Pco₂ over a wide range of MVO₂’s, with coronary perfusion pressure held constant. Therefore we do not know if alterations in the relationship between MVO₂ and O₂ delivery occur over the whole range of values of MVO₂. In addition, there have been no previous studies which have evaluated the interactions between the effects of CO₂ on coronary vessels and catecholamines. The purpose of this study was to evaluate further the importance of changes in CO₂ and/or pH in the local control of coronary blood flow by determining the ability of changes in arterial PCO₂ to alter the relationship between MVO₂ and O₂ delivery over a wide range of values of MVO₂.

METHODS

Dogs weighing 28–35 kg were anesthetized by intravenous administration of α-chloralose (100 mg/kg) in borate solution. The procedure used for preparing this anesthetic has been described previously (Harlan, 1978). Following intubation with auffed endotracheal tube, the dogs were ventilated with a respirator (Harvard Apparatus Co.) at a tidal volume of 400–500 ml and a rate of 12–20 breaths/min. Arterial blood oxygen and carbon dioxide levels were adjusted, when necessary, by supplementing inspired air with O₂ or CO₂. Sodium bicarbonate occasionally was infused intravenously to adjust arterial pH. A femoral vein and artery were cannulated for the administration of fluids and continuous monitoring of heart rate and mean arterial pressure via a Statham pressure transducer. A catheter was positioned in the right atrium via the jugular vein for infusion of catecholamines. Periodic supplemental doses of α-chloralose were given throughout the experiment to maintain surgical anesthesia. Temperature was measured with a telemetherometer (Yellow Springs Instruments Co.) placed in the deep esophagus, and heating pads were employed to maintain a temperature of 37–39°C.

A left thoracotomy was performed and the heart was suspended in a pericardial cradle. Using the method of Herd and Barger (1965), we placed a small polyvinyl catheter (~1.1 mm o.d.) in the great cardiac vein (GCV). After heparin administration (750 U/kg, supplemented by 75 U/kg per hr), GCV blood was withdrawn continually and passed through a cuvette densitometer (Waters Instruments) which gives a signal proportional to the O₂.
saturation of hemoglobin. A segment of the anterior descending branch of the left coronary artery (LAD) was dissected free and an electromagnetic flow probe (Zepeda Instruments) was placed around it. A snare was positioned around the artery distal to the flow probe, and 10- to 15-second occlusions were performed before and after each experimental maneuver to determine zero flow. Zero did not drift by more than 10% of the reactive hyperemic response to a 15-second occlusion during the course of any experimental maneuver presented here. At the end of each experiment, the flow probe was calibrated in situ by cannulating the artery and perfusing it at several known flow rates from a peristaltic pump.

To produce systemic hypocapnia (arterial PCO₂ 20-25 mm Hg), the rate of ventilation was increased from 12-20/min to 40-45/min, after which an interval of 15-30 minutes was allowed for conditions to stabilize. When a steady state had been reached, arterial blood was passed through the densitometer. For purposes of densitometer calibration, a sample of this blood was taken and the O₂ content determined, using a catalytic O₂ content analyzer (Lex-O₂-Con). The calibration procedure has been described previously (Belloni and Sparks, 1977). Additional measurements of arterial blood PO₂, PCO₂, and pH were made with a Corning Blood Gas Analyzer. Great cardiac vein blood then was diverted through the densitometer, and oxygen content and blood gas measurements were repeated periodically (5-7 times/dog) for densitometer calibration. Heart rate, coronary blood flow, mean arterial pressure (MAP), and great cardiac vein densitometer readings were recorded continuously on a Grass polygraph. Once steady baseline values of all necessary variables had been obtained, cardiac activity was stimulated by intravenous infusion of either isoproterenol or norepinephrine dissolved in isotonic sodium chloride. The infusion was continued until a new steady state with respect to flow, MAP, heart rate, and great cardiac vein O₂ content was reached. Following this, the infusion was stopped and the cardiac activity was allowed to return to its resting level. Baseline determinations of flow, pressure, heart rate, and arterial and venous O₂ contents were repeated and followed by a different infusion rate of catecholamine. This procedure was repeated several times over a period of up to 1.5 hours, and observations on steady state values were made for at least two trials at each of three different catecholamine infusion rates for each dog.

Next, CO₂ gas was introduced into the inspired air in amounts sufficient to induce hypercapnia (arterial PCO₂ 70-75 mm Hg). Tidal volume and respiratory rate were not changed. We repeated the preceding series of infusions, using identical doses of catecholamines, and made subsequent steady state measurements of each variable at the various activity levels. To control for possible changes in vascular reactivity with time, in half of the experiments the order of exposure to high and low CO₂ was reversed. At the end of the experiment, after calibration of the flow probe, the vascular bed supplied by the left anterior descending artery was stained by intraarterial administration of carbon black or crystal violet. The stained area was cut out and weighed.

The dogs were divided into four groups. In the first group (n = 4), varying doses of isoproterenol were infused (5, 10, and 20 μg/min) to raise cardiac activity. This increased O₂ consumption, but it reduced MAP. An umbilical tape snare was placed around the thoracic aorta. By partially occluding the aorta during isoproterenol infusions, we were able to maintain the MAP above the snare near control level. In the second group (n = 5), norepinephrine was administered (20, 40, and 80 μg/min). Norepinephrine caused a rise in MAP that was minimized by removing arterial blood via a femoral arterial cannula so that MAP was unaltered from baseline in the steady state. The blood was returned to the animal via a roller pump (Cole-Palmer) when the norepinephrine administration had been stopped. In the third group, norepinephrine infusion (80 μg/min) and arterial bleeding again were used to increase myocardial metabolism while maintaining MAP constant. Following these control infusions, phentolamine was administered intravenously (loading dose, 0.25 mg/kg, followed by an infusion of 0.025 mg/kg per min). After 10-15 minutes, norepinephrine again was infused during periods of both high and low arterial PCO₂. In the presence of phentolamine, norepinephrine caused a decrease in MAP. As in the isoproterenol series, MAP was maintained with an aortic snare. In the fourth group, isoproterenol was infused at a rate of 10 μg/min to raise MVO₂. After control infusion, indomethacin (5 mg/kg) was administered intravenously. One hour later, the isoproterenol infusions were repeated at high and low PCO₂.

As mentioned previously, coronary blood flow, MAP, arterial O₂ content, and great cardiac vein O₂ content were measured before and during each infusion of catecholamine. Since the great cardiac vein drains effluent only from the tissue perfused by the left anterior descending artery (Roberts et al., 1976), MVO₂ could be calculated by multiplying left anterior descending coronary blood flow times the arterial venous O₂ difference. Oxygen delivery and coronary vascular conductance also were calculated as described previously (Harlan et al., 1978).

Statistical analyses were made using the Michigan Interactive Data Analysis System. Mean values are followed by ± 1 SE of the mean. Comparisons were made using the Michi-
Results

Isoproterenol

In four dogs, three different doses of isoproterenol were administered intravenously to produce increases in cardiac activity. Figure 1 shows the observed steady state relationships between $\text{MVO}_2$ and coronary blood flow, $\text{O}_2$ delivery, and coronary vascular conductance at high and low systemic $\text{PCO}_2$. These data are grouped and analyzed according to infusion rate and $\text{CO}_2$ level in Table 1. Figure 1 shows that an increased arterial $\text{PCO}_2$ produced a small increase in coronary blood flow and coronary vascular conductance relative to $\text{MVO}_2$. In addition, for any rate of isoproterenol infusion, the $\text{MVO}_2$ during high $\text{PCO}_2$ was—on the average—22% lower than during low $\text{PCO}_2$, although this difference was not statistically significant (Table 1).

Panel A of Figure 2 shows the effect of arterial $\text{PCO}_2$ on the relationship between $\text{MVO}_2$ and great cardiac vein oxygen content when $\text{MVO}_2$ was raised by infusion of isoproterenol. $\text{O}_2$ extraction is significantly ($P < 0.05$) lowered at all values of $\text{MVO}_2$ by addition of $\text{CO}_2$ from 75 ± 1.2% during low arterial $\text{PCO}_2$ to 62 ± 0.30% during high $\text{PCO}_2$. Note that at both high and low arterial $\text{PCO}_2$, venous $\text{O}_2$ is not altered by increasing $\text{MVO}_2$ but elevated arterial $\text{PCO}_2$ markedly increases venous $\text{O}_2$ for a given $\text{MVO}_2$.

Norepinephrine

In five dogs norepinephrine was administered to increase cardiac metabolism. Arterial bleeding was used during each infusion to minimize norepinephrine-induced increases in MAP. Steady state values of $\text{MVO}_2$, coronary blood flow, $\text{O}_2$ delivery, and conductance are shown in Figure 3. These data are grouped for each dose of norepinephrine in Table 2. Figure 3 shows that $\text{O}_2$ delivery tended to be higher for a given $\text{MVO}_2$ in the presence of elevated arterial $\text{PCO}_2$. This effect is more pronounced at low values of $\text{MVO}_2$ and seems to disappear as cardiac activity was increased. Elevated $\text{CO}_2$ produced no apparent change in the relationship between $\text{MVO}_2$ and heart rate to a given infusion rate of norepinephrine, especially at high doses of norepinephrine. In these experiments, the $\text{MVO}_2$ at high $\text{CO}_2$ averaged 36% less for a given norepinephrine infusion rate than at low $\text{CO}_2$.

Figure 2B shows the effect of arterial $\text{PCO}_2$ on the relationship between $\text{MVO}_2$ and venous $\text{O}_2$ during norepinephrine infusion. Elevated arterial $\text{PCO}_2$ raised great cardiac vein $\text{O}_2$ content in the absence of norepinephrine infusion, but as $\text{MVO}_2$ was increased by successively greater rates of norepinephrine infusion, great cardiac vein $\text{O}_2$ content dropped. At any $\text{MVO}_2$ greater than 8 ml $\text{O}_2$ / min per 100 g, increased arterial $\text{PCO}_2$ did not appear to increase great cardiac vein $\text{O}_2$ content in contrast to the results seen with isoproterenol (Fig. 2A).

We tested the possibility that $\alpha$-receptor stimulation is responsible for the difference in the relationship between great cardiac vein $\text{O}_2$ content and $\text{MVO}_2$ when norepinephrine and isoproterenol are compared (Fig. 2, A and B) by infusing norepinephrine at both high and low $\text{CO}_2$ in the presence or absence of phentolamine. Figure 4A shows the re-

Figure 1 Left anterior descending coronary blood flow (A), $\text{O}_2$ delivery (B), and conductance (C) as a function of myocardial $\text{O}_2$ consumption ($\text{MVO}_2$) at high and low arterial $\text{PCO}_2$. Isoproterenol was infused into the right atrium to raise $\text{MVO}_2$. Each point represents the response to one dose of isoproterenol in one of four dogs. In some cases, a point represents the mean of more than one trial. The same data are grouped according to dose of isoproterenol in Table 1.
Table 1 Responses to Right Atrial Infusion of Isoproterenol

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5 µg/min</th>
<th>10 µg/min</th>
<th>20 µg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low CO₂</td>
<td>High CO₂</td>
<td>Low CO₂</td>
<td>High CO₂</td>
</tr>
<tr>
<td>MVO₂ (ml O₂/min per 100 g)</td>
<td>6.1 ± 0.95</td>
<td>5.3 ± 1.7</td>
<td>10.3 ± 1.5</td>
<td>7.6 ± 0.89</td>
</tr>
<tr>
<td>CBF (ml O₂/min per 100 g)</td>
<td>45 ± 8.9</td>
<td>51 ± 6.3</td>
<td>80 ± 15</td>
<td>73 ± 6.2</td>
</tr>
<tr>
<td>DO₂ (ml O₂/min per 100 g)</td>
<td>7.9 ± 1.6</td>
<td>8.6 ± 1.8</td>
<td>13.7 ± 2.5</td>
<td>12.3 ± 1.8</td>
</tr>
<tr>
<td>CVC (ml/min per 100 g per mm Hg)</td>
<td>0.44 ± 0.07</td>
<td>0.55 ± 0.06</td>
<td>0.77 ± 0.13</td>
<td>0.70 ± 0.07</td>
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<tr>
<td>GCV O₂ content (vol %)</td>
<td>3.7 ± 0.81</td>
<td>6.6 ± 0.88*</td>
<td>4.3 ± 0.86</td>
<td>7.6 ± 0.56*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>170 ± 6.5</td>
<td>142 ± 9.2</td>
<td>177 ± 4.5</td>
<td>168 ± 14.4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>102 ± 8.6</td>
<td>93 ± 4.4</td>
<td>104 ± 2.0</td>
<td>104 ± 3.6</td>
</tr>
<tr>
<td>Arterial Po₂ (mm Hg)</td>
<td>96 ± 4.5</td>
<td>104 ± 10.5</td>
<td>95 ± 4.1</td>
<td>103 ± 10.2</td>
</tr>
<tr>
<td>Arterial Pco₂ (mm Hg)</td>
<td>22 ± 2.9</td>
<td>77 ± 3.8</td>
<td>22 ± 2.4</td>
<td>73 ± 4.3</td>
</tr>
<tr>
<td>Arterial pH (mm Hg)</td>
<td>7.52 ± 0.02</td>
<td>7.08 ± 0.02*</td>
<td>7.51 ± 0.02</td>
<td>7.08 ± 0.01*</td>
</tr>
</tbody>
</table>

* Indicates that P for the paired t-statistic is <0.05 when low and high CO₂ values are compared at the same dose; MVO₂ = myocardial oxygen consumption, CBF = left anterior descending coronary artery flow, DO₂ = left anterior descending coronary artery flow delivery of oxygen, CVC = left anterior descending coronary artery flow conductance, MAP = mean aortic pressure.

Table 1 shows the responses to right atrial infusion of isoproterenol. The table includes data on MVO₂, CBF, DO₂, CVC, GCV O₂ content, heart rate, MAP, arterial Po₂, arterial Pco₂, and arterial pH at different doses of isoproterenol under low and high CO₂ conditions. The data indicate that isoproterenol increased myocardial oxygen consumption and coronary flow at both low and high CO₂ levels.

Discussion

These experiments constitute a test of the hypothesis that CO₂ (and/or pH) mediates a significant fraction of the steady state change in coronary blood flow (or O₂ delivery) associated with increased myocardial metabolism. If this hypothesis is true, the following criterion should be met: increasing arterial PCO₂ during control activity to values similar to those occurring during increased MVO₂ should elevate flow (and O₂ delivery) to levels normally observed during increased activity. We have evaluated this criterion by raising arterial PCO₂ and measuring coronary blood flow and oxygen delivery.
blood PCO\textsubscript{2} by more than 40 mm Hg and observing the change in coronary flow and oxygen delivery over a range of myocardial O\textsubscript{2} consumptions. We find that when flow is allowed to vary, this increase in PCO\textsubscript{2} causes far less increase in flow or oxygen consumption than accompanies increased MVO\textsubscript{2}.

A possible source of error in this experiment is our assumption that raising arterial blood PCO\textsubscript{2} by more than 40 mm Hg causes a similar rise in arteriolar PCO\textsubscript{2}. Because CO\textsubscript{2} is conserved across the myocardium, an increase in arterial CO\textsubscript{2} content must result in an equivalent increase in venous CO\textsubscript{2} content, given a steady state production of CO\textsubscript{2} by the myocardium. Because the relationship between PCO\textsubscript{2} and CO\textsubscript{2} content is fairly linear, the same statement holds for PCO\textsubscript{2}. We believe that if both arterial and venous blood PCO\textsubscript{2} are raised to the same extent, it is likely that arteriolar wall PCO\textsubscript{2} is similarly raised in the steady state. The increase of 40 mm Hg is four times the largest increases in venous PCO\textsubscript{2} which have been observed with increased myocardial metabolism (Parker et al., 1969). Thus it appears that we have raised arteriolar wall PCO\textsubscript{2} far more than is likely to occur during increased myocardial metabolism.

In spite of this, the change in arterial PCO\textsubscript{2} caused only a small increase in coronary blood flow (or conductance, or O\textsubscript{2} delivery; see Fig. 1). This suggests to us that the above criterion for a metabolic vasodilator is not met; that is, the likely changes in arteriolar wall PCO\textsubscript{2} are too small to be a major cause of functional hyperemia because the vasodilator potency of CO\textsubscript{2} is too low.

Our conclusion regarding the vasodilator potency of CO\textsubscript{2} appears to conflict with that of Case and his colleagues (1976, 1978). They found very large changes in coronary vascular conductance when they varied arterial PCO\textsubscript{2}, holding either flow delivery of O\textsubscript{2} or venous Po\textsubscript{2} constant. The difference may be that we allowed local regulation of flow to occur, whereas Case and his colleagues held flow constant. If CO\textsubscript{2} is a relatively weak vasodilator, it is possible that its vasodilator effect is offset by autoregulatory adjustment of flow resulting from a change in the release of an endogenous metabolic vasodilator (e.g., adenosine). In Case's experiments, flow is held constant, and so no error signal resulting in an autoregulatory vasoconstriction would occur.

Another difference between the two sets of experiments is that Case et al. raised CO\textsubscript{2} locally, whereas we raised it systemically. It is possible that we observed less vasodilation because of a competing vasoconstrictor effect resulting from the systemic changes in CO\textsubscript{2}. For example, circulating catecholamines as well as sympathetic neural activity increase with elevated PCO\textsubscript{2} (Tenney, 1956). However, we doubt that these factors caused coronary vasoconstriction counteracting the effect of increase PCO\textsubscript{2}, because \(\alpha\)-receptor blockade did not raise great cardiac vein O\textsubscript{2} content above the level found with isoproterenol during high CO\textsubscript{2} (Fig. 4). Of
FIGURE 3 Left anterior descending coronary blood flow (A), O₂ delivery (B), and conductance (C) as a function of myocardial O₂ consumption (MVO₂) at high and low arterial Pco₂. Norepinephrine was infused into the right atrium to raise MVO₂. Each panel represents the response to one dose of norepinephrine in one of five animals. In some cases, a point represents the mean of more than one trial. The same data are grouped according to dose of norepinephrine in Table 2.

**TABLE 2 Responses to Right Atrial Norepinephrine Infusions**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Norepinephrine (20 µg/min)</th>
<th>Norepinephrine (20 µg/min)</th>
<th>Norepinephrine (80 µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low CO₂</td>
<td>High CO₂</td>
<td>Low CO₂</td>
<td>High CO₂</td>
</tr>
<tr>
<td>MVO (ml O₂/min per 100 g)</td>
<td>8.2 ± 0.82</td>
<td>5.6 ± 0.50*</td>
<td>11.2 ± 2.1</td>
<td>7.2 ± 0.96*</td>
</tr>
<tr>
<td>CBF (ml O₂/min per 100 g)</td>
<td>56 ± 5.5</td>
<td>56 ± 6.3</td>
<td>73 ± 14</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>DO₂ (ml O₂/min per 100 g)</td>
<td>10.6 ± 1.0</td>
<td>10.1 ± 1.1</td>
<td>13.9 ± 2.6</td>
<td>10.7 ± 1.8</td>
</tr>
<tr>
<td>CVC (ml/min per 100 g per mm Hg)</td>
<td>0.58 ± 0.08</td>
<td>0.56 ± 0.09</td>
<td>0.66 ± 0.11</td>
<td>0.51 ± 0.09</td>
</tr>
<tr>
<td>GVC O₂ content (vol %)</td>
<td>4.4 ± 0.35</td>
<td>7.9 ± 0.73*</td>
<td>3.6 ± 0.50</td>
<td>6.8 ± 1.00*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>178 ± 4.2</td>
<td>139 ± 11.4*</td>
<td>195 ± 5.1</td>
<td>144 ± 15.3*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>100 ± 7.7</td>
<td>105 ± 6.8</td>
<td>110 ± 5.1</td>
<td>117 ± 3.1</td>
</tr>
<tr>
<td>Arterial PO₂ (mm Hg)</td>
<td>100 ± 5.2</td>
<td>106 ± 7.7</td>
<td>89 ± 6.7</td>
<td>106 ± 6.5*</td>
</tr>
<tr>
<td>Arterial Pco₂ (mm Hg)</td>
<td>23 ± 1.2</td>
<td>70 ± 2.8</td>
<td>24 ± 1.5</td>
<td>68 ± 4.0</td>
</tr>
<tr>
<td>Arterial pH (mm Hg)</td>
<td>7.46 ± 0.03</td>
<td>7.08 ± 0.03*</td>
<td>7.47 ± 0.04</td>
<td>7.11 ± 0.03*</td>
</tr>
</tbody>
</table>

* Indicates that P for the paired t-statistic is <0.05 when low and high CO₂ values are compared at the same dose. See Table 1 for symbol definitions.
CO\textsubscript{2} AND CORONARY BLOOD FLOW/Rooke and Sparks

In > 6

\begin{itemize}
\item High CO\textsubscript{2}
\item Low CO\textsubscript{2}
\item Phentolamine
\item NOREPI
\item ISO
\end{itemize}

\begin{itemize}
\item NoREPI
\item High CO\textsubscript{2}
\item Low CO\textsubscript{2}
\item Before Phentolamine
\item After Phentolamine
\end{itemize}

\textbf{FIGURE 4} Panel A shows effect of phentolamine on great cardiac venous O\textsubscript{2} content as a function of myocardial oxygen consumption (MVO\textsubscript{2}) at high and low arterial PCO\textsubscript{2}. At high CO\textsubscript{2}, arterial PCO\textsubscript{2} averaged 75 ± 5 before and 77 ± 4 mm Hg after phentolamine. At course, any direct or indirect effects on MVO\textsubscript{2} are accounted for by making all of our plots with MVO\textsubscript{2} as the independent variable.

Even if CO\textsubscript{2} is not a major metabolic vasodilator, it may well have significant effects on myocardial O\textsubscript{2} delivery under free-flow conditions. We evaluated the importance of small changes in the relationship between MVO\textsubscript{2} and coronary blood flow or O\textsubscript{2} delivery by plotting great cardiac vein O\textsubscript{2} content as a function of MVO\textsubscript{2}. Figure 2A shows clearly that an increase in systemic PCO\textsubscript{2} caused an increase in great cardiac vein O\textsubscript{2} content at any observed O\textsubscript{2} consumption when isoproterenol was infused. It follows that venous and, probably, tissue PO\textsubscript{2} are increased by elevated PCO\textsubscript{2}. This is especially likely because elevated PCO\textsubscript{2} shifts the hemoglobin dissociation curve to the right so that blood PO\textsubscript{2} is higher for any given O\textsubscript{2} content.

The results obtained from the norepinephrine series differ distinctly from the results with isoproterenol. Elevated PCO\textsubscript{2} at rest produced a large increase in great cardiac vein O\textsubscript{2} content (Fig. 2B). However, when MVO\textsubscript{2} was raised by infusing norepinephrine, elevated arterial PCO\textsubscript{2} did not increase O\textsubscript{2} delivery relative to MVO\textsubscript{2} and great cardiac vein O\textsubscript{2} content was not raised. Even though great cardiac vein O\textsubscript{2} was the same at high and low PCO\textsubscript{2}, it is still likely that tissue PO\textsubscript{2} was somewhat higher with elevated arterial PCO\textsubscript{2}, owing to the shift in the hemoglobin-dissociation curve.

How can we account for the difference between the effect of CO\textsubscript{2} in the presence of norepinephrine and isoproterenol? The most straightforward possibility is that norepinephrine activates coronary \alpha-receptors causing vasoconstriction which competes with the vasodilator influence of increased systemic PCO\textsubscript{2}. We tested that possibility by administering norepinephrine in the presence of phentolamine to block the coronary \alpha-receptors. In this situation, at high MVO\textsubscript{2}, elevated systemic PCO\textsubscript{2} caused an increase in great cardiac vein O\textsubscript{2} content which approached the increase observed during isoproterenol stimulation (Fig. 4). This suggests that when \alpha-receptor activation competes with raised arterial PCO\textsubscript{2}, it can reduce markedly the ability of PCO\textsubscript{2} to increase delivery of O\textsubscript{2} relative to consumption. This fits nicely with the results of Feigl and his colleagues who have demonstrated the ability of coronary \alpha-receptor activation to lower coronary sinus O\textsubscript{2} (Feigl, 1975) by reducing O\textsubscript{2} delivery relative to MVO\textsubscript{2} (Mohrman and Feigl, 1978). The experiments with phentolamine do not rule out the possibility than another reason for the low CO\textsubscript{2}, arterial PCO\textsubscript{2} averaged 26 ± 1 before, and 28 ± 2 after phentolamine. Only one dose (80 µg/min) of norepinephrine was used; the points to the left represent values without and the points to the right with norepinephrine. Panel B compares the high CO\textsubscript{2} from Figures 2 and 4A.
disparity between the results with norepinephrine and isoproterenol is that the coronary \( \beta \)-receptor is activated better by isoproterenol than by norepinephrine. In view of the controversy on the question of the identity of the type of \( \beta \)-receptor which predominates in coronary smooth muscle (Baron et al., 1972; Hamilton and Feigl, 1976), we have not approached this problem experimentally.

We wished to determine whether prostaglandins mediate the vasodilator influence of CO\(_2\). To do this we used a dose of indomethacin which we previously have shown to block the coronary vasodilator effect of injected arachidonic acid almost completely (Harlan et al., 1978). We found that this dose of indomethacin did not alter the relationship between myocardial M\( V\O_2 \) and flow when oxygen consumption was raised by infusing isoproterenol. If prostaglandins mediate the vasodilator effect of CO\(_2\), we would expect that indomethacin would markedly reduce the effect of CO\(_2\) on coronary O\(_2\) delivery, and that this would be reflected by a reduction in the effect of CO\(_2\) on great cardiac vein O\(_2\) content. This was not observed. Indomethacin did not reduce the effect of CO\(_2\) on coronary hemodynamics or of great cardiac vein O\(_2\) content. However, indomethacin reduced control coronary blood flow, conductance, and O\(_2\) delivery as well as great cardiac vein O\(_2\) content at both high and low CO\(_2\). (The difference was not significant at low CO\(_2\) for coronary blood flow and coronary vascular conductance; see Table 3.) We did not bring attention to a reduction in control flow, conductance, and O\(_2\) delivery in our earlier study done at normal arterial P\( CO_2 \) but, upon reexamination of those data, we find that the same trend occurred in that study also (Harlan et al., 1978). Thus, it does not appear that prostaglandins mediate either the coronary vasodilation associated with increased metabolism (Harlan et al., 1978) or with increased systemic P\( CO_2 \). On the other hand, prostaglandin release may provide a basal vasodilator tone in the resting heart which is not apparent at high levels of activity. This was suggested previously by Hintze and Kaley (1977).

Our results differ from those of Ledingham et al. (1970), who observed a much larger change in coronary blood flow relative to M\( V\O_2 \). This difference may be explained by their observation that an 8- to 15-minute period of systemic hypercapnia produces a significant increase in coronary blood flow relative to resting M\( V\O_2 \) but that this increase returns to control if the CO\(_2\) is kept elevated for 1 hour. Our measurements were made 30 minutes to 2 hours after changing the blood gases, and so the smaller changes in coronary blood flow relative to M\( V\O_2 \) observed by us may be the result of a time dependent decay in the effect of CO\(_2\).

Only one other group of investigators previously has studied the influence of CO\(_2\) on the relationship between coronary blood flow and M\( V\O_2 \) during increased cardiac activity. Feinberg et al. (1960) raised M\( V\O_2 \) during either high or low arterial P\( CO_2 \) by clamping the aorta. For both resting (7–8 ml O\(_2\)...
have been the result of a higher arterial pressure and a more powerful myogenic response. Presence of low CO₂ than high CO₂, it is possible blood flow is decreased by metabolic acidosis and increased by metabolic alkalosis. However, their higher vascular resistance at low CO₂ could increased by metabolic alkalosis. However, their

- min/100 g and augmented (10–13 ml O₂/min per 100 g) cardiac activity, the flow was 31–44% greater for a given MVO₂ during high CO₂ than during low. This finding appears to be qualitatively the same as our result with isoproterenol (Fig. 1; Table 1). Unfortunately, the large increase in coronary perfusion pressure produced by aortic occlusion (72 mm Hg → 141 mm Hg at low CO₂; 68 mm Hg → 120 mm Hg at high CO₂) makes the results obtained at elevated MVO₂ more difficult to interpret. The pressure increase could have caused myogenic vasoconstriction and a rise in coronary vascular resistance. Since the pressure increased more in the presence of low CO₂ than high CO₂, it is possible that the higher vascular resistance at low CO₂ could have been the result of a higher arterial pressure and a more powerful myogenic response.

Our results appear to disagree with findings of Goodyear et al. (1961), who report that coronary blood flow is decreased by metabolic acidosis and increased by metabolic alkalosis. However, their data also show (as do ours) that MVO₂ is decreased by acidosis and increased by alkalosis. In fact, further analysis of their data reveals that acidosis decreased MVO₂ more than coronary blood flow and, therefore; slightly raised coronary blood flow relative to MVO₂. This illustrates the importance of considering MVO₂ when evaluating a potentially vasoactive agent because changes in MVO₂ caused by CO₂ can produce changes in resistance independent of a direct effect on the vascular wall.

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Figure 5 Effect of indomethacin on great cardiac venous O₂ content as a function of myocardial oxygen consumption (MVO₂) at high and low arterial Pco₂. One dose of isoproterenol (10 μg/min) was infused; the points at the left represent values without, and points to the right with isoproterenol. At high CO₂, arterial Pco₂ averaged 75 ± 3 before and 75 ± 2 after indomethacin. At low CO₂, arterial Pco₂ averaged 23 ± 2 before and 23 ± 2 after indomethacin.

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