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

THOM ROOKE AND HARVEY V. SPARKS

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.

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Supported by U.S. Public Health Service Grant HL 16760 and by a Fellowship from the Michigan Heart Association.

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Received April 25, 1979; accepted for publication March 28, 1980.

**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 a cuffed 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 telemtherometer (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...
vascular reactivity with time, in half of the experiments.

To control for possible changes in state measurements of each variable at the various preceding series of infusions, using identical doses of air in amounts sufficient to induce hypercapnia were made for at least two trials at each of three different catecholamine infusion rates for each dog. 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 unchanged 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 tested for statistical significance using Student’s paired t-test. When two or more successful infusions of a single dose of catecholamine were obtained, the runs were averaged so that each dog is represented by no more than one point per dose of catecholamine; n always refers to the number of dogs.
**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 MVO$_2$ and coronary blood flow, O$_2$ delivery, and coronary vascular conductance at high and low systemic Pco$_2$. These data are grouped and analyzed according to infusion rate and CO$_2$ level in Table 1. Figure 1 shows that an increased arterial Pco$_2$ produced a small increase in coronary blood flow and coronary vascular conductance relative to MVO$_2$. In addition, for any rate of isoproterenol infusion, the MVO$_2$ during high Pco$_2$ was—on the average—22% lower than during low Pco$_2$, although this difference was not statistically significant (Table 1).

Panel A of Figure 2 shows the effect of arterial Pco$_2$ on the relationship between MVO$_2$ and great cardiac vein oxygen content when MVO$_2$ was raised by infusion of isoproterenol. O$_2$ extraction is significantly ($P < 0.05$) lowered at all values of MVO$_2$ by addition of CO$_2$ from 75 ± 1.2% during low arterial Pco$_2$ to 62 ± 0.30% during high Pco$_2$. Note that at both high and low arterial Pco$_2$, venous O$_2$ is not altered by increasing MVO$_2$ but elevated arterial Pco$_2$ markedly increases venous O$_2$ for a given 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 MVO$_2$, coronary blood flow, 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 O$_2$ delivery tended to be higher for a given MVO$_2$ in the presence of elevated arterial Pco$_2$. This effect is more pronounced at low values of MVO$_2$ and seems to disappear as cardiac activity was increased. Elevated CO$_2$ produced no apparent change in the relationship between MVO$_2$ and heart rate to a given infusion rate of norepinephrine, especially at high doses of norepinephrine. In these experiments, the MVO$_2$ at high CO$_2$ averaged 36% less for a given norepinephrine infusion rate than at low CO$_2$.

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

We tested the possibility that α-receptor stimulation is responsible for the difference in the relationship between great cardiac vein O$_2$ content and MVO$_2$ when norepinephrine and isoproterenol are compared (Fig. 2, A and B) by infusing norepinephrine at both high and low CO$_2$ in the presence or absence of phentolamine. Figure 4A shows the re-
Table 1: Responses to Right Atrial Infusion of Isoproterenol

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Low CO₂</th>
<th>High CO₂</th>
<th>5 μg/min</th>
<th>Low CO₂</th>
<th>High CO₂</th>
<th>10 μg/min</th>
<th>Low CO₂</th>
<th>High CO₂</th>
<th>20 μg/min</th>
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<tbody>
<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>
<td>14.5 ± 1.8</td>
<td>10.4 ± 1.5</td>
<td>20.8 ± 3.1</td>
<td>16.2 ± 2.8</td>
<td></td>
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</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>
<td>111 ± 10</td>
<td>99 ± 8.5</td>
<td>159 ± 23</td>
<td>154 ± 18</td>
<td></td>
<td></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>
<td>19.8 ± 3.0</td>
<td>16.7 ± 1.3</td>
<td>26.3 ± 3.0</td>
<td>26.4 ± 3.0</td>
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</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>
<td>1.06 ± 0.14</td>
<td>0.97 ± 0.08</td>
<td>1.54 ± 0.18</td>
<td>1.47 ± 0.16</td>
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</tr>
<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>
<td>4.1 ± 0.51</td>
<td>7.1 ± 1.0*</td>
<td>4.5 ± 0.69*</td>
<td>7.0 ± 0.72*</td>
<td></td>
<td></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>
<td>211 ± 10.2</td>
<td>172 ± 15.8</td>
<td>220 ± 14.6</td>
<td>196 ± 21.3</td>
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</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>
<td>104 ± 1.1</td>
<td>102 ± 1.8</td>
<td>103 ± 1.8</td>
<td>105 ± 0.5</td>
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<td></td>
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<tr>
<td>Arterial PₐO₂ (mm Hg)</td>
<td>96 ± 4.5</td>
<td>104 ± 10.5</td>
<td>95 ± 4.1</td>
<td>103 ± 10.2</td>
<td>96 ± 4.3</td>
<td>105 ± 11.1</td>
<td>100 ± 4.8</td>
<td>105 ± 10.9</td>
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</tr>
<tr>
<td>Arterial PₐCO₂ (mm Hg)</td>
<td>22 ± 2.9</td>
<td>77 ± 3.8</td>
<td>22 ± 2.4</td>
<td>73 ± 4.3</td>
<td>22 ± 2.4</td>
<td>77 ± 2.1</td>
<td>21 ± 2.6</td>
<td>77 ± 2.1</td>
<td></td>
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<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>
<td>7.53 ± 0.02*</td>
<td>7.10 ± 0.02*</td>
<td>7.54 ± 0.01*</td>
<td>7.10 ± 0.03*</td>
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</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.

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 arteriolar PₐCO₂ 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...
blood PCO₂ by more than 40 mm Hg and observing the change in coronary flow and oxygen delivery over a range of myocardial O₂ consumptions. We find that when flow is allowed to vary, this increase in PCO₂ causes far less increase in flow or oxygen consumption than accompanies increased MVO₂.

A possible source of error in this experiment is our assumption that raising arterial blood PCO₂ by more than 40 mm Hg causes a similar rise in arteriolar PCO₂. Because CO₂ is conserved across the myocardium, an increase in arterial CO₂ content must result in an equivalent increase in venous CO₂ content, given a steady state production of CO₂ by the myocardium. Because the relationship between Pco₂ and CO₂ content is fairly linear, the same statement holds for Pco₂. We believe that if both arterial and venous blood Pco₂ are raised to the same extent, it is likely that arteriolar wall Pco₂ is similarly raised in the steady state. The increase of 40 mm Hg is four times the largest increases in venous Pco₂ which have been observed with increased myocardial metabolism (Parker et al., 1969). Thus it appears that we have raised arteriolar wall Pco₂ far more than is likely to occur during increased myocardial metabolism.

In spite of this, the change in arterial Pco₂ caused only a small increase in coronary blood flow (or conductance, or O₂ 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 Pco₂ are too small to be a major cause of functional hyperemia because the vasodilator potency of CO₂ is too low.

Our conclusion regarding the vasodilator potency of CO₂ 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 Pco₂, holding either flow delivery of O₂ or venous Po₂ constant. The difference may be that we allowed local regulation of flow to occur, whereas Case and his colleagues held flow constant. If CO₂ 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 CO₂ 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 CO₂. For example, circulating catecholamines as well as sympathetic neural activity increase with elevated Pco₂ (Tenney, 1956). However, we doubt that these factors caused coronary vasoconstriction counteracting the effect of increase Pco₂, because a-receptor blockade did not raise great cardiac vein O₂ content above the level found with isoproterenol during high CO₂ (Fig. 4). Of

**Figure 2** Great cardiac venous O₂ content as a function of myocardial O₂ consumption (MVO₂) at high and low arterial Pco₂. Isoproterenol (A) or norepinephrine (B) was used to raise MVO₂. Each point represents the mean of one observation in each of four (A) or five (B) animals. Bars give the standard error of the mean.
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 (80 µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low CO₂</td>
<td>High CO₂</td>
<td>Low 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>
</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>
</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>
</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>
</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>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>178 ± 4.2</td>
<td>139 ± 11.4*</td>
<td>195 ± 5.1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>100 ± 7.7</td>
<td>105 ± 6.8</td>
<td>110 ± 5.1</td>
</tr>
<tr>
<td>Arterial P O₂ (mm Hg)</td>
<td>100 ± 5.2</td>
<td>106 ± 7.7</td>
<td>89 ± 6.7</td>
</tr>
<tr>
<td>Arterial P CO₂ (mm Hg)</td>
<td>23 ± 1.2</td>
<td>70 ± 2.8</td>
<td>24 ± 1.5</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>
</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.
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In > 6

High CO₂

Low CO₂

ISO @ HIGH CO₂

NOREPI @ HIGH CO₂

BEFORE PHENTOLAMINE

NOREPI @ HIGH CO₂

AFTER PHENTOLAMINE

FIGURE 4 Panel A shows effect of phentolamine on great cardiac venous O₂ content as a function of myocardial oxygen consumption (MVO₂) at high and low arterial PCO₂. At high CO₂, arterial PCO₂ averaged 75 ± 5 before and 77 ± 4 mm Hg after phentolamine. At course, any direct or indirect effects on MVO₂ are accounted for by making all of our plots with MVO₂ as the independent variable.

Even if CO₂ is not a major metabolic vasodilator, it may well have significant effects on myocardial O₂ delivery under free-flow conditions. We evaluated the importance of small changes in the relationship between MVO₂ and coronary blood flow or O₂ delivery by plotting great cardiac vein O₂ content as a function of MVO₂. Figure 2A shows clearly that an increase in systemic Pco₂ caused an increase in great cardiac vein O₂ content at any observed O₂ consumption when isoproterenol was infused. It follows that venous and, probably, tissue Po₂ are increased by elevated Pco₂. This is especially likely because elevated Pco₂ shifts the hemoglobin dissociation curve to the right so that blood Po₂ is higher for any given O₂ content.

The results obtained from the norepinephrine series differ distinctly from the results with isoproterenol. Elevated Pco₂ at rest produced a large increase in great cardiac vein O₂ content (Fig. 2B). However, when MVO₂ was raised by infusing norepinephrine, elevated arterial Pco₂ did not increase O₂ delivery relative to MVO₂ and great cardiac vein O₂ content was not raised. Even though great cardiac vein O₂ was the same at high and low Pco₂, it is still likely that tissue Po₂ was somewhat higher with elevated arterial Pco₂, owing to the shift in the hemoglobin-dissociation curve.

How can we account for the difference between the effect of CO₂ in the presence of norepinephrine and isoproterenol? The most straightforward possibility is that norepinephrine activates coronary α-receptors causing vasoconstriction which competes with the vasodilator influence of increased systemic Pco₂. We tested that possibility by administering norepinephrine in the presence of phentolamine to block the coronary α-receptors. In this situation, at high MVO₂, elevated systemic Pco₂ caused an increase in great cardiac vein O₂ content which approached the increase observed during isoproterenol stimulation (Fig. 4). This suggests that when α-receptor activation competes with raised arterial Pco₂, it can reduce markedly the ability of Pco₂ to increase delivery of O₂ relative to consumption. This fits nicely with the results of Feigl and his colleagues who have demonstrated the ability of coronary α-receptor activation to lower coronary sinus O₂ (Feigl, 1975) by reducing O₂ delivery relative to MVO₂ (Mohrman and Feigl, 1978). The experiments with phentolamine do not rule out the possibility that another reason for the low CO₂, arterial Pco₂ 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 CO₂ from Figures 2 and 4A.
Table 3  

**Effect of Indomethacin on Response to Isoproterenol Infusion**

<table>
<thead>
<tr>
<th>Infusion rate of isoproterenol (µg/min)</th>
<th>Pre-Indomethacin</th>
<th>Post-Indomethacin</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>High CO₂</td>
<td>Low CO₂</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

| MVO₂ (ml O₂/min per 100 g)             | 5.9 ± 0.5         | 10.7 ± 0.9        | 5.8 ± 0.4         | 16.5 ± 1.9        |
| CBF (ml/min per 100 g)                 | 56 ± 4            | 101 ± 12          | 43 ± 3            | 124 ± 15          |
| DO₂ (ml O₂/min per 100 g)              | 10.9 ± 1.0        | 19.6 ± 2.5        | 8.5 ± 0.6         | 25.0 ± 3.3        |
| CVC (ml/min per mm Hg)                 | 0.57 ± 0.07       | 1.15 ± 0.20       | 0.44 ± 0.04       | 1.35 ± 0.19       |
| GVC O₂ content (vol %)                 | 8.8 ± 0.69        | 8.5 ± 0.88        | 4.5 ± 0.56        | 4.5 ± 0.69        |
| Heart rate (beats/min)                 | 139 ± 6           | 181 ± 8           | 143 ± 8           | 206 ± 7           |
| MAP (mm Hg)                            | 102 ± 7           | 95 ± 7            | 100 ± 5           | 96 ± 6            |

* Indicates that P for the paired t-statistic is <0.05, comparing same condition before and after indomethacin administration. See Table 1 for symbol definitions.

...disparity between the results with norepinephrine and isoproterenol is that the coronary β-receptor is activated better by isoproterenol than by norepinephrine. In view of the controversy on the question of the identity of the type of β-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 CO₂. 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 MVO₂ and flow when oxygen consumption was raised by infusing isoproterenol. If prostaglandins mediate the vasodilator effect of CO₂, we would expect that indomethacin would markedly reduce the effect of CO₂ on coronary O₂ delivery, and that this would be reflected by a reduction in the effect of CO₂ on great cardiac vein O₂ content. This was not observed. Indomethacin did not reduce the effect of CO₂ on coronary hemodynamics or of great cardiac vein O₂ content. However, indomethacin reduced control coronary blood flow, conductance, and O₂ delivery as well as great cardiac vein O₂ content at both high and low CO₂. (The difference was not significant at low CO₂ for coronary blood flow and coronary vascular conductance; see Table 3.) We did not bring attention to a reduction in control flow, conductance, and O₂ delivery in our earlier study done at normal arterial Pco₂ 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 Pco₂. 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 MVO₂. 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 MVO₂, but that this increase returns to control if the CO₂ 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 MVO₂ observed by us may be the result of a time dependent decay in the effect of CO₂.

Only one other group of investigators previously has studied the influence of CO₂ on the relationship between coronary blood flow and MVO₂ during increased cardiac activity. Feinberg et al. (1960) raised MVO₂ during either high or low arterial Pco₂ by clamping the aorta. For both resting (7–8 ml O₂...
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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.

Acknowledgments

We wish to thank Dr. Francis Belloni for his helpful discussion of this work. Mr. Joel Silver provided invaluable technical assistance.

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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.
Arterial CO2, myocardial O2 consumption, and coronary blood flow in the dog.
T Rooke and H V Sparks

Circ Res. 1980;47:217-225
doi: 10.1161/01.RES.47.2.217

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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