The Response of Canine Coronary Vascular Resistance to Local Alterations in Coronary Arterial P CO,

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SUMMARY. The effect of hypercapnia on coronary vascular resistance (CVR) was studied in seven open-chest dogs. Coronary blood flow was supplied to the cannulated left main coronary artery from the femoral artery by a precision pump. Coronary arterial P CO2 was locally controlled with a small membrane oxygenator in the coronary perfusion circuit. Each P CO2 change was made at a constant coronary flow, and CVR was calculated from the ratio of perfusion pressure to flow. Coronary sinus (CS) P CO2 and P O2 were recorded continuously from blood withdrawn through a CS catheter. Normocapnia (P CO2 = 42.3 ± 2.8 mm Hg) was obtained with a membrane oxygenator gas composition of 95% O2-5% CO2, and hypocapnia was produced with 100% O2-0% CO2. In addition to physiologically normal coronary flow (determined by a CS P O2 of 20-30 mm Hg) relatively high and low flow states were studied. At a normal control CS P O2, a decrease in coronary arterial P CO2 from 42.3 ± 2.8 to 23.8 ± 1.3 mm Hg caused CVR to increase by 84.2%, from 1.27 ± 0.06 to 2.30 ± 0.04 units. Since pH was inversely related to P CO2, the effect on CVR may have been mediated through a pH change. CS P CO2 decreased from 65.2 ± 1.9 to 39.4 ± 1.3 mm Hg. Myocardial oxygen consumption was unchanged. Increases in CVR of 74.5, 119.5, and 69.3% occurred during hypocapnia in three additional experiments in which control arterial P O2 was maintained at 52-90 mm Hg. When CS P O2 was greater than 30 mm Hg, the normocapnic CVR was high, and was only minimally increased by hypocapnia. When coronary flow was reduced to an ischemic level there was little response in CVR to hypocapnia. Thus the level of arterial P CO2 can have an important effect on CVR independent of changes in O2 consumption. Myocardial P CO2, derived from metabolically produced CO2 and contributed to by arterial CO2, may be a major factor in normal control of coronary flow.

RECENT WORK from this laboratory showed that extreme changes in myocardial O2 extraction occurred when arterial P CO2 was reduced by hyperventilation or was increased by breathing a CO2-O2 mixture. These changes in myocardial O2 extraction (which varied from a low of 13% to a high of 87%) were interpreted as representing equivalent changes in coronary flow, indicating that the level of arterial P CO2 (or the concomitant pH change) had a major effect on coronary flow. The hypothesis was presented that myocardial P CO2 is a primary agent controlling coronary flow.

The experimental technique presented here was developed to obtain more definite information about the extent of any relationship between P CO2 and coronary flow dynamics. In a canine preparation with controlled, constant coronary flow, changes in coronary arterial P CO2 were introduced through a small membrane oxygenator and were restricted to the coronary circulation. This experimental design eliminated the problems introduced by mechanical hyperventilation and by variation in systemic arterial P CO2 and allowed direct measurement of the relationship between coronary vascular resistance (CVR), coronary arterial P CO2, and coronary sinus (CS) P CO2.

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Methods

Dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv) and maintained on positive-pressure respiration. The left main coronary artery was cannulated and perfused from the femoral artery as described previously. The left chest was opened, the left main coronary artery was dissected free at its origin, and a ligature was placed about it. Both femoral arteries were cannulated, and blood was withdrawn from them into a coronary perfusion circuit (Fig. 1). This circuit ended in a modified Gregg coronary cannula which was inserted through the left subclavian artery into the left main coronary artery. Its tip was tied by the previously placed ligature. Thus all left main coronary flow passed through this circuit; the flow was delivered by a finger pump (Harvard, model 2316) modified so that flow could be controlled precisely. The pump output was independent of input and output pressure. Temperature measured just proximal to the coronary cannula was maintained at 37-38°C by a heat exchanger.

Mean coronary arterial pressure was continuously recorded just proximal to the cannula by a strain gauge (Statham P23d). The measured coronary arterial pressure was corrected for the pressure gradient due to the coronary cannula, as previously described. This gradient varied from 2 to 5 mm Hg and was subtracted from the measured coronary arterial pressure.

While coronary flow was kept constant, the P CO2 of coronary arterial blood was varied locally in the coronary perfusion circuit by means of a small membrane oxygenator (Travenol, SM0321). During control states the oxygenator diffusion gas was 5% CO2-95% O2 at a flow of 1 liter/min.
Hypocapnia was induced by switching the gas to 100% O₂ for 15 minutes, followed by a return to the control state with 5% CO₂-95% O₂. Individual blood samples for measurement of pH, PO₂, PCO₂, and hematocrit (Hct) were taken by a syringe just distal to the oxygenator and analyzed by an Instrumentation Laboratories electrode system (IL-113).

At a constant coronary flow, any change in coronary arterial pressure represents a change in CVR. CVR was calculated as the ratio of corrected coronary arterial pressure to coronary flow. There was no change in right or left atrial pressure during these experiments, and they were not included in this calculation.

The CS blood was continuously withdrawn through a catheter previously placed in the midportion of the CS under fluoroscopic guidance; the position was verified at autopsy. The CS blood was withdrawn at a rate of 5 ml/min with a roller pump (Technicon) and returned to the femoral vein. A continuous measurement of CS PCO₂ and CS PO₂ was obtained by passing this blood sequentially over the surface of PCO₂ and PO₂ electrodes (Instrumentation Laboratories), which were immersed in a water bath at 37°C. The PO₂ and PCO₂ signals were amplified separately (Instrumentation Laboratories, model 113), and the output was recorded simultaneously. The CS blood was continuously withdrawn through a catheter previously placed in the midportion of the CS under fluoroscopic guidance; the position was verified at autopsy. The CS blood was withdrawn at a rate of 5 ml/min with a roller pump (Technicon) and returned to the femoral vein. A continuous measurement of CS PCO₂ and CS PO₂ was obtained by passing this blood sequentially over the surface of PCO₂ and PO₂ electrodes (Instrumentation Laboratories), which were immersed in a water bath at 37°C. The PO₂ and PCO₂ signals were amplified separately (Instrumentation Laboratories, model 113), and the output was recorded simultaneously. The CS blood was continuously withdrawn through a catheter previously placed in the midportion of the CS under fluoroscopic guidance; the position was verified at autopsy. The CS blood was withdrawn at a rate of 5 ml/min with a roller pump (Technicon) and returned to the femoral vein. A continuous measurement of CS PCO₂ and CS PO₂ was obtained by passing this blood sequentially over the surface of PCO₂ and PO₂ electrodes (Instrumentation Laboratories), which were immersed in a water bath at 37°C. The PO₂ and PCO₂ signals were amplified separately (Instrumentation Laboratories, model 113), and the output was recorded simultaneously.

Individual CS samples were taken for measurement of pH, PCO₂, PO₂, and Hct and analyzed in the manner described for the arterial samples.

Arterial and CS O₂ content were calculated by using PO₂ and pH and the O₂ dissociation curve for dog blood⁴ to estimate O₂ saturation; O₂ content then was estimated from the Hct by the formula: O₂ content (ml/100 ml) = Hct x 0.34 x 1.36 x percent O₂ saturation (Hct x 0.34 - Hb; Hb x 1.36 = O₂ capacity) + PO₂ x 0.0031 (100 - Hct)/100.

Myocardial O₂ consumption was determined from the product (arterial – CS) O₂ content and coronary flow, and expressed in mmol/min per 100 g of left ventricle (LV).

Coronary flow and CVR were expressed per 100 g of LV weight. Continuous recordings (Beckman Dynograph) were made of phasic aortic pressure, mean coronary arterial pressure, CS PO₂, CS PCO₂, heart rate, and the electrocar-diagram (lead II). For some experiments, left atrial and right atrial pressures also were measured.

Experiments were performed on 14 dogs; data from seven of them were selected for analysis. All seven had steady arterial systolic pressures and heart rates during the series of interventions. The effect of hypocapnia on CVR was studied in two additional dogs in which coronary arterial PO₂ was maintained at a control level of 50–90 mm Hg. For these studies, a modified Kay-Cross 13-inch disk oxygenator was used, and an appropriate mixture of N₂, CO₂, and O₂ was supplied to the oxygenator to achieve the desired gas concentrations.

Results

Initial findings showed that CVR was responsive to an alteration in arterial and CS PCO₂. This response was most sensitive when the rate of coronary flow was set so that the resultant CS PO₂ was 20–30 mm Hg. At this flow rate, mean coronary arterial pressure was close to that of aortic diastolic pressure (Table 1). At an excessive coronary flow rate, resulting in an elevated CS PO₂ and elevated coronary arterial pressure, the CVR response was diminished greatly. The data consequently are presented in two sections; the first documents the existence and sensitivity of a CVR-PCO₂ relationship as observed at a normal CS PO₂, and the second shows the effect of coronary flow on this relationship.

RESPONSE IN CVR TO CHANGES IN ARTERIAL PCO₂
WHEN CONTROL CS PO₂ IS 20–30 mm Hg

Ten separate episodes were observed, at least one from each of the seven dogs, in which control CS PO₂ was in the range of 20–30 mm Hg. For these control points a near-normocapnic state was intended, obtained by using 5% CO₂-95% O₂ as the diffusing gas in the membrane oxygenator. The resultant mean control arterial PCO₂ for the group was 42.3 ± 2.8 mm Hg (Table 1).

The sequence of events following the induction of hypocapnia is best followed in a single experiment (Fig. 2). For this experiment, coronary flow was maintained at a constant rate of 61.9 ml/min per 100 g LV, and control CS PO₂ was 27.5 mm Hg. After the oxygenator gas was switched from 5% CO₂-95% O₂ to 0% CO₂-100% O₂, coronary arterial pressure rose from 76 to 153 mm Hg, with an increase in calculated CVR from 1.23 to 2.47. This increase in CVR was slow, reaching a plateau in approximately 7 minutes. However, the rate of change seems to correlate well with the simultaneously recorded CS PCO₂, which fell to a plateau at approximately the same rate. The sequence of events was reversed when 5% CO₂-95% O₂ was readministered. Results of individual syringe samples of blood gases at equilibrium points are recorded at the bottom of Figure 2. During this intervention, CS PCO₂ fell by 20 mm Hg, and CS pH rose by 0.14 units; arterial PCO₂ fell from 36.5 to 23.4 mm Hg, and arterial pH increased by 0.15 unit. Other factors which might cause a change in CVR (myocardial O₂ consumption, heart rate, aortic pressure, arterial O₂ content, and left main coronary flow) were essentially unchanged throughout the experiment. A possible source of error might have been a
TABLE 1  Summary of Changes in Coronary Vascular Resistance (CVR) and Blood Gas Composition during Hypocapnia when Coronary Sinus (CS) Po2 Falls between 20 and 30 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypocapnia</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Po2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>26.1 ± 0.94</td>
<td>21.8 ± 0.78</td>
<td>10</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>501.2 ± 72.8</td>
<td>601.4 ± 5.3</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>65.2 ± 1.9</td>
<td>39.4 ± 1.3</td>
<td>10</td>
<td>†</td>
</tr>
<tr>
<td>A</td>
<td>42.3 ± 2.8</td>
<td>23.8 ± 1.3</td>
<td>5</td>
<td>†</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>7.24 ± 0.02</td>
<td>7.39 ± 0.01</td>
<td>5</td>
<td>†</td>
</tr>
<tr>
<td>A</td>
<td>7.32 ± 0.02</td>
<td>7.46 ± 0.02</td>
<td>5</td>
<td>*</td>
</tr>
<tr>
<td>nO2 (mmol/min per 100 g LV)</td>
<td>0.443 ± 0.017</td>
<td>0.428 ± 0.009</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>CF</td>
<td>59.2 ± 3.0</td>
<td>59.2 ± 3.0</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure aorta (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>110.6 ± 2.6</td>
<td>109.6 ± 3.0</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87.0 ± 3.7</td>
<td>82.5 ± 2.8</td>
<td>10</td>
<td>*</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>147.9 ± 8.7</td>
<td>150.4 ± 8.1</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure, coronary artery (mm Hg)</td>
<td>75.6 ± 4.5</td>
<td>132.2 ± 5.5</td>
<td>10</td>
<td>†</td>
</tr>
<tr>
<td>CAP/ADP</td>
<td>0.87 ± 0.03</td>
<td>1.61 ± 0.05</td>
<td>10</td>
<td>†</td>
</tr>
<tr>
<td>CVR</td>
<td>1.27 ± 0.06</td>
<td>2.30 ± 0.04</td>
<td>10</td>
<td>†</td>
</tr>
<tr>
<td>% ΔCVR</td>
<td>84.2 ± 8.34</td>
<td>94.2 ± 8.34</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>% ΔCVR/mm Hg ΔCS Pco2</td>
<td>-3.57 ± 0.54</td>
<td>-3.57 ± 0.54</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>O2 content (ml/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>6.83 ± 0.78</td>
<td>7.54 ± 0.77</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>A</td>
<td>22.61 ± 0.78</td>
<td>22.79 ± 0.79</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>O2 extraction</td>
<td>69.76 ± 3.18</td>
<td>67.00 ± 2.9</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± sE.
A = coronary artery; nO2 = myocardial O2 consumption; LV = left ventricle; CF = coronary flow. n = number of dogs; CAP/ADP = ratio of coronary arterial pressure to aortic diastolic pressure. % ΔCVR/mm Hg ΔCS Pco2 = the percent change in CVR per mm Hg change in CS Pco2.

Significance
* P < 0.05.
† P < 0.001.
‡ P < 0.001.
NS = P > 0.05

change in contractility as a result of the alterations in Pco2, but such an effect was essentially excluded since myocardial O2 consumption was unchanged. This remarkable increase in CVR during hypocapnia therefore can be interpreted as being due only to the reduced coronary arterial Pco2, which presumably exerted an action on the coronary vasculature. Whether CO2 acts directly, or through a pH change, or through another unknown mechanism cannot be determined from these studies. However, the sensitivity of CVR to a change in arterial Pco2 seems clear.

A closer examination of the relationship between Pco2 and CVR is shown in Figure 3, the data being from the same experiment as shown in Figure 2. The continuously recorded value of CS Pco2 is plotted against the simultaneous CVR during induction of hypoxacnia and the return to control. This shows a continuous inverse linear relationship between Pco2 and CVR. The rapidity with which CVR adjusts to a change in Pco2 is difficult to determine from these experiments, because an alteration in coronary arterial Pco2 caused by the membrane oxygenator cannot be an instantaneous process. However, there is no obvious time lag apparent in these recordings between changes in CS Pco2 and CVR; therefore it is possible for the response to be rapid.

Table 1 includes a summary of data taken at the control point and the equilibrium hypocapnic point for this group of 10 interventions. The average reduction in CS Pco2 was 25.8 mm Hg (range = 17.5–39.4), and in each instance there resulted a rise in CVR; this averaged 84.2% (range = 39.5–127.6). Comparison of CVR during control conditions and hypocapnia showed these changes to be highly significant (paired t-test), and no significant change was present in the factors which might otherwise affect CVR (heart rate, systolic pressure, arterial O2 content, or myocardial O2 consumption). There also was a good correlation between CS Pco2 and changes in CVR (r = 0.90) (Fig. 4). As mentioned previously, the change in pH cannot be eliminated in this type of experiment, therefore CS pH also bore a good correlation with the change in CVR (r = 0.83). Also of note is moderate (16.5%) but significant decrease in CS Po2 during hypocapnia; this is an expected change in view of the increase in pH of the CS blood. Myocardial O2 extraction of 69.8% for the group is close to the normal range of 70–75% and was unchanged by hypocapnia.

EFFECT OF CORONARY FLOW ON THE SENSITIVITY OF THE CVR-Pco2 RELATIONSHIP

CVR was insensitive to alterations in Pco2 when there was marked coronary overperfusion or when the rate of perfusion was so low that the myocardium was ischemic. These relationships are illustrated in Figure 5, in which the response of CVR to hypocapnia was studied at four different
constant coronary flow (16.9 ml/min/100 g LV)
FIGURE 5 Four separate interventions on the same dog are displayed. For each intervention heart rate was constant at 120/min and systemic arterial pressure was constant at 110/75 mm Hg. In panel I, left, there is minimal response in coronary vascular resistance (CVR) associated with a high coronary sinus (CS) Po2 of 41.5 mm Hg. In panels 2 and 3, with CS Po2 values of 31.0 mm Hg and 29.5 mm Hg, respectively, there is a progressively increasing CVR response to hypocapnia. In panel 4, right, the simultaneously recorded electrocardiogram revealed S-T depression consistent with ischemia and the CVR response is flat. LV - left ventricle, CAP - mean coronary artery pressure.

Since the increase in CVR that resulted from hypocapnia apparently was dependent on the adequacy of coronary flow, the data were examined further in relation to the control CS Po2. In the first section under Results, only points with a control CS Po2 of 20-30 mm Hg were considered. Inclusion of all flows studied in these seven dogs yielded 16 non-ischemic points with CS Po2 values of 31.0 mm Hg and 29.5 mm Hg, respectively, there is a progressively increasing CVR response to hypocapnia. In panel 4, right, the simultaneously recorded electrocardiogram revealed S-T depression consistent with ischemia and the CVR response is flat. LV - left ventricle, CAP - mean coronary artery pressure.

Since the increase in CVR that resulted from hypocapnia apparently was dependent on the adequacy of coronary flow, the data were examined further in relation to the control CS Po2. In the first section under Results, only points with a control CS Po2 of 20-30 mm Hg were considered. Inclusion of all flows studied in these seven dogs yielded 16 non-ischemic points with CS Po2 varying from 21.0 to 41.5 mm Hg. In Table 2 these are arranged in order of descending CS Po2, and placed in three groups: (1) above 30 mm Hg, (2) 25-30 mm Hg, and (3) 20-25 mm Hg. Two facts are apparent. First, the percent rise in coronary flow increased as the Po2 decreased, and reached a maximum in group 3, for which the control CS Po2 averaged 22.1 mm Hg. There was little rise in CVR in group 1. The second point of interest is that the maximum CVR reached in all three groups was almost the same (2.19, 2.25, and 2.40), and these values were not significantly different. These findings suggest that in each instance the response to hypocapnia is a maximal rise in resistance. Viewed from the point of percent rise in resistance, and corrected to a standard change of 25 mm Hg in CS PCO2, there is a clear relationship between CS Po2 and the percent rise in resistance, with little effect occurring above 35 mm Hg (Fig. 6).

EFFECT OF A LOWER ARTERIAL PO2 ON THE SENSITIVITY OF THE CVR-PCO2 RELATIONSHIP

During these experiments arterial Po2 always was very high, in the range of 500-600 mm Hg (Table 1), because of the gas mixture supplied to the oxygenator. To ensure that the effects on CVR we noted were not in some way attributable to this high arterial Po2, three experiments were performed on two additional dogs, during which the control arterial Po2 was established at 52, 60, and 90 mm Hg (Table 3). With CS Po2 set in the region of 20 mm Hg by appropriate adjustment of coronary flow, the induction of hypocapnia resulted in increases in CVR of 74.5, 119.5, and 69.3%. The magnitude of the CVR increase is similar to that observed in the main group (Table 1), which averaged 84.2%, and also is similar to data for groups 2 and 3 of Table 2, in which CS Po2 ranged from 20 mm Hg to 30 mm Hg.

The time course of one of the three experiments (1A) is shown in Figure 7, and the values from syringe samples at the control and equilibrium points are shown. The results are similar to those in Figure 2. The slower rate of fall in PCO2 (and slower rate of rise in CVR) is apparently a result of using a disk oxygenator for these experiments, rather than a membrane oxygenator.

Thus it seems evident that the PCO2-CVR relationship shown in this paper is not an artifact resulting from a very high Po2. Presumably, then, the effect of hypocapnia on CVR is similar over a range of values of arterial Po2 from 530 to 52 mm Hg, and possibly lower. This finding gives added emphasis to the concept that vasomotor control of the coronary bed is determined by factors existing at the myocardial level, rather than at the arterial level. In this connection, it may be noted that even at an arterial Po2 level of 500 mm Hg, CS Po2 was 26 mm Hg (Table 1), and that in the normally functioning coronary circulation an increase of arterial Po2 from 435 mm Hg has little effect on CS Po2.4

Discussion

At present little importance is attached to any action of arterial or myocardial CO2 on coronary flow.5-7 Nevertheless, it is evident from the results of experiments reported here that CVR is inversely related to the level of arterial PO2. Moreover, the relationship is a sensitive one; a reduction in arterial PCO2 of less than 20 mm Hg will almost double CVR.

Coronary flow was held constant during each variation in PCO2 to study CVR under controlled conditions; in the intact circulation this CVR response would be translated into an equivalent change in coronary flow. We previously have examined the effect of altering arterial PCO2 in the intact dog, and obtained indirect evidence that coronary flow is
dramatically altered in the same direction as the change in Pco₂. The changes in O₂ extraction (from 13% to 87%), as arterial Pco₂ was varied from 10 to 90 mm Hg, are consistent with a 4-fold change in coronary flow which may be the maximum adjustment available. The data also suggested that a severe reduction in coronary flow, perhaps to the point of ischemia, could occur during hypocapnia. However, neither coronary flow nor CVR was measured, and potential complicating factors were present because of the mechanical effects of hyperventilation and the systemic effects of Pco₂ and pH. The data reported here provide direct evidence of a powerful effect of variations in coronary arterial Pco₂ on CVR, and suggest that a general relationship exists between Pco₂ and coronary flow such that coronary flow will vary continuously in the same direction as Pco₂.

The effect of arterial Pco₂ could be due to a direct action of CO₂ on arteriolar tone, or could be mediated through other undetermined substances. We are unable to separate the effect of pH, therefore control of CVR by an altered hydrogen ion concentration also must be considered as a possible mechanism. However, Kittle et al. observed that a coronary flow change due to a variation in arterial Pco₂ persisted when pH was restored to its original value by appropriate infusions. Nevertheless, whether pH is involved or not, it remains clear that changes in CVR may be induced by directly affecting arterial Pco₂.

There are reports by others that the level of arterial CO₂ may influence coronary flow. Coronary flow has been found to increase during CO₂ inspiration, although conflicting results also are reported. Data regarding hypocapnia are much less extensive, but show a fall in coronary flow with hyperventilation. Rowe et al. observed a 30% fall in coronary flow in man with a reduction of arterial Pco₂ to 20 mm Hg, but was unable to confirm this for the dog. With rare exceptions, however, the studies listed above provide little or no data on CO₂ in either arterial or CS blood, or on O₂ in CS blood. Daugherty et al. employed a donor lung to vary CO₂ directly in the blood perfusing the

**TABLE 2 Changes in Coronary Vascular Resistance (CVR) Listed According to Control Coronary Sinus (CS) Po₂**

<table>
<thead>
<tr>
<th>Group 1 (control CS Po₂ &gt; 30 mm Hg) (n=6)</th>
<th>Group 2 (control CS Po₂ 25-30 mm Hg) (n=7)</th>
<th>Group 3 (control CS Po₂ 20-25 mm Hg) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>33.8 ± 1.6</td>
<td>60.8 ± 1.4</td>
<td>1.88 ± 0.10</td>
</tr>
<tr>
<td>31.3 ± 2.1</td>
<td>37.7 ± 0.7*</td>
<td>2.26 ± 0.05*</td>
</tr>
<tr>
<td>27.8 ± 0.5</td>
<td>64.5 ± 2.6</td>
<td>1.31 ± 0.06</td>
</tr>
<tr>
<td>21.6 ± 1.1†</td>
<td>37.4 ± 0.7*</td>
<td>2.26 ± 0.05*</td>
</tr>
<tr>
<td>22.1 ± 0.6</td>
<td>66.7 ± 2.6</td>
<td>1.17 ± 0.12</td>
</tr>
<tr>
<td>22.3 ± 0.8</td>
<td>44.2 ± 2.1†</td>
<td>2.40 ± 0.08*</td>
</tr>
</tbody>
</table>

C = control, H = hypocapnia; values are mean ± se.
Significance of changes from control to hypocapnia are indicated by footnote symbols. Where no symbol is present, the change is statistically not significant.
* P < 0.001
† P < 0.01.

Intergroups significance was also evaluated, with the following major findings: (1) control CS Po₂ significantly different in all three groups; (2) no significant difference in CVR achieved during hypocapnia in all three groups; (3) control CVR significantly different, except between groups 2 and 3.
of coronary flow, based only on myocardial Pco₂, which
is known to be regulated in accordance with changes
in myocardial Pco₂ rather than to arterial Pco₂, and that CS Pco₂ reflects
myocardial Pco₂. While the issue of arterial Pco₂ vs.
myocardial Pco₂ in control of coronary flow cannot be
resolved from the data available, we have chosen to relate
CVR to myocardial Pco₂, and for this purpose have
presented most of the material in this study in relation to CS
Pco₂. CO₂ is delivered to the myocardium from two sources:
(1) metabolic CO₂ produced as the end product of cellular
respiration, produced in molar equivalency (at a respiratory
quotient of 1.0) to the rate of myocardial O₂ consumption;
(2) CO₂ in arterial blood. The metabolic CO₂ is diluted
according to the rate of coronary flow, so that the final
myocardial Pco₂ (and CS Pco₂) represents an interrelationship
of three factors: arterial CO₂, rate of metabolic CO₂
production, and the rate of coronary flow.

Since the heart is a site of high O₂ consumption, and
large quantities of CO₂ are continuously presented to the
myocardium, an important question arises as to whether the
resultant myocardial Pco₂ has any role in the normal
regulation of coronary flow. Normal coronary flow is
known to be regulated in accordance with changes
in myocardial O₂ consumption with such precision that CS Pₐ or O₂ content remains at a constant
crude relationship between coronary flow and myocardial O₂ consumption. A variety of factors have
been implicated in the control of the coronary circulation
but the exact mechanism is unknown and there is
no consensus as to the mediators involved.

The data reported here suggest a mechanism for control of coronary flow, based only on myocardial Pco₂, which
would preserve the known close relationship between coronary flow and myocardial O₂ consumption. The necessary
assumptions would be that (1) myocardial Pco₂ maintains a continuous control over coronary flow through its effect on
coronary arteries, (2) an altered myocardial Pco₂ occurs
and regulates the coronary vasculature and preferred to
relate the dominant control of CVR to O₂.

One might conclude from the present studies that the level of arterial Pco₂ directly affects the coronary arteriole in a
manner analogous to the cerebral circulation, since variations in CVR were achieved by altering arterial Pco₂.
However, it seems more probable that resistance in the
coronary vascular bed is related to the level of myocardial
Pco₂ rather than to arterial Pco₂, and that CS Pco₂ reflects
myocardial Pco₂. While the issue of arterial Pco₂ vs.
myocardial Pco₂ in control of coronary flow cannot be
resolved from the data available, we have chosen to relate
CVR to myocardial Pco₂, and for this purpose have
presented most of the material in this study in relation to CS
Pco₂. CO₂ is delivered to the myocardium from two sources:
(1) metabolic CO₂ produced as the end product of cellular
respiration, produced in molar equivalency (at a respiratory
quotient of 1.0) to the rate of myocardial O₂ consumption;
(2) CO₂ in arterial blood. The metabolic CO₂ is diluted
according to the rate of coronary flow, so that the final
myocardial Pco₂ (and CS Pco₂) represents an interrelationship
of three factors: arterial CO₂, rate of metabolic CO₂
production, and the rate of coronary flow.

Since the heart is a site of high O₂ consumption, and
large quantities of CO₂ are continuously presented to the
myocardium, an important question arises as to whether the
resultant myocardial Pco₂ has any role in the normal
regulation of coronary flow. Normal coronary flow is
known to be regulated in accordance with changes
in myocardial O₂ consumption with such precision that CS Pₐ or O₂ content remains at a constant
crude relationship between coronary flow and myocardial O₂ consumption. A variety of factors have
been implicated in the control of the coronary circulation
but the exact mechanism is unknown and there is
no consensus as to the mediators involved.

The data reported here suggest a mechanism for control of coronary flow, based only on myocardial Pco₂, which
would preserve the known close relationship between coronary flow and myocardial O₂ consumption. The necessary
assumptions would be that (1) myocardial Pco₂ maintains a continuous control over coronary flow through its effect on
coronary arteries, (2) an altered myocardial Pco₂ occurs
promptly as a result of any change in myocardial O₂ consumption, and thus in CO₂ production, and (3) a homeo-
static myocardial Pco₂ exists as the set-point for normal coronary flow. For example, a reduction in heart rate would result in a decreased myocardial O₂ consumption and decreased myocardial CO₂ production, a decreased myocardial Pco₂, and subsequently a coronary flow reduction through an increased CVR. Reduction in coronary flow would continue until the homeostatic Pco₂ was restored. An opposite set of reactions culminating in an increased coronary flow would result when O₂ consumption was increased. A variation in arterial Pco₂ would upset this mechanism, resulting in a coronary flow which was inappropriate for the current rate of O₂ consumption.

For this model to function properly a rapid rise in
myocardial Pco₂ is necessary, because coronary autoregulation
is known to be complete within 15 seconds after a
sudden intervention. No data are available on the rate
of myocardial Pco₂ change, but in studies on isolated mitochondria an almost immediate release of CO₂ occurs
without retention in pools of intermediates. CS Pco₂ has
not been measured frequently, but it is essentially unchanged
in man as a result of exercise or pacing, however,
so is CS Pₐ. Further evidence regarding this Pco₂-CVR
hypothesis must await experiments evaluating myocardial
Pco₂ and Pₐ independently of arterial values.

Although myocardial Pco₂ could function by itself as an
autoregulating agent, it is well known that hypoxemia is a
strong stimulus to an increased coronary flow. Also, an
increase in arterial O₂ content is associated with a decreased
 coronary flow. Although severe hypoxemia is associated
with myocardial ischemia and a release of metabolites,
there appears to be no doubt that the arterial O₂ content,
and more probably myocardial Pₐ, affects CVR in the
absence of ischemia. Thus coronary flow regulation may
well be controlled by an interplay between myocardial Pco₂
and myocardial Pₐ acting in opposite directions on the
resistance vessels.

The effect of coronary flow on the relationship between
Pco₂ and CVR was of particular interest, since it defined the
range over which this relationship can occur and the zone in
which a maximum effect might be expected. Overperfusion
of the heart is associated with a high CVR, as noted

---

**Table 3** Effect of Hypocapnia at Lower Arterial Pₐ Levels

<table>
<thead>
<tr>
<th>Expt</th>
<th>Arterial Pₐ (mm Hg)</th>
<th>CS Pₐ (mm Hg)</th>
<th>Coronary flow (ml/min per 100 g LV)</th>
<th>CVR (100 g LV)</th>
<th>Pressure, Aorta (mm Hg)</th>
<th>Rate/min</th>
<th>CVR (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>90.8</td>
<td>20.4</td>
<td>57.0</td>
<td>40.5</td>
<td>41</td>
<td>1.41</td>
<td>96/52</td>
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<td>H</td>
<td>71.9</td>
<td>14.3</td>
<td>28.6</td>
<td>14.9</td>
<td>41</td>
<td>2.46</td>
<td>100/65</td>
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<td></td>
<td></td>
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<tr>
<td>C</td>
<td>52.0</td>
<td>19.3</td>
<td>55.0</td>
<td>42.0</td>
<td>71</td>
<td>0.77</td>
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<tr>
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<td>51.0</td>
<td>16.8</td>
<td>22.7</td>
<td>16.2</td>
<td>71</td>
<td>1.69</td>
<td>100/65</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C</td>
<td>60.0</td>
<td>22.7</td>
<td>68.0</td>
<td>41</td>
<td>63</td>
<td>1.14</td>
<td>108/86</td>
</tr>
<tr>
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<td>21.5</td>
<td>33.1</td>
<td>71</td>
<td>63</td>
<td>1.93</td>
<td>110/87</td>
</tr>
</tbody>
</table>

CVR = coronary vascular resistance; CS = coronary sinus; LV = left ventricle; C = control; H = hypocapnia
previously, presumably presumably because of the excessive supply of O₃ and the elevated myocardial Po₂. An inappropriately elevated coronary flow will also result in a reduced myocardial PCO₂, which would also act to increase CVR.

Hypocapnia was without significant effect on CVR during overperfusion and had little effect at a CS Po₂ above 30 mm Hg, suggesting that a maximal increase in arteriolar tone already had been achieved as a result of the high myocardial Po₂ (and reduced PCO₂) of overperfusion. It is also probable that this represents the maximum CVR attainable by any physiological means. The finding that CVR is most responsive to the induction of hypocapnia when CS Po₂ is in the range of 20–25 mm Hg may only represent the greater potential increase in CVR available at this lower CS Po₂ and low CVR. The complete absence of any effect of hypocapnia to increase CVR in the ischemic situation is undoubtedly a special situation, since at this time the myocardium releases a great variety of metabolic substances such as lactate, potassium, phosphate, and adenosine. Also, myocardial PCO₂ as directly measured reaches extremely high levels in the ischemic heart.

By affixing control of coronary flow to myocardial PCO₂, this model permits respiratory alterations in arterial PCO₂ to disrupt autoregulation, since there can be changes in the regulator that are unaccompanied by changes in O₂ consumption (and CO₂ production). In a compromised coronary circulation, hypocapnia could thus result in myocardial ischemia. Previously we have observed that CS Po₂ can fall below 9 mm Hg during overventilation, a level that has been associated with myocardial lactate production. There are several clinical situations for which this model offers explanations when none currently satisfies. Refractory cardiac arrhythmias may occur in patients on a ventilator in association with severe hypocapnia and alkalosis. Recently, there have been several reports of "false positive" electrocardiographic S-T and T wave changes due to hyperventilation in patients who subsequently were shown to have normal coronary arteriograms.

Addendum
Since the preparation of this manuscript, an article has appeared showing that hypocapnia in man with coronary disease can result in reduction of coronary flow and evidence of myocardial ischemia (Neill, W.A., and Hattinam, M.: Impairment of myocardial O₂ supply due to hyperventilation. Circulation 52: 854–858, 1975).

Acknowledgments
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References
Inhibition of Adrenergic Neurotransmission in Canine Vascular Smooth Muscle by Histamine
Mediation by H₂-Receptors

MICHAEL A. McGrath, M.D., F.R.A.C.P., AND JOHN T. SHEPHERD, M.D., M.Ch., D.Sc.

SUMMARY Histamine depressed the contractions of dog saphenous vein strips caused by stimulation of their sympathetic nerves. This was due to a decrease in the release of norepinephrine which appears to be mediated by histamine H₂-receptors. The evidence for this is as follows: (1) Contractions of the strips caused by activating the nerve endings electrically or by depolarization with potassium ions were depressed by histamine, whereas contractions caused by tyramine and norepinephrine were either unchanged or augmented. (2) Strips were incubated with norepinephrine[7-¹H] and mounted for superfusion and isometric tension recording. The perfusate was collected for estimation of total radioactivity and for column chromatographic separation of norepinephrine and its metabolites.

Histamine (0.9 µM) depressed the release of norepinephrine[7-¹H] during contractions caused by electric stimulation, whereas the release of radioactive compounds caused by tyramine was unaffected. (3) The depression by histamine of the contractions and the efflux of radioactive compounds caused by electric stimulation were inhibited by an H₂-receptor antagonist (metiamide), but were unaffected by an H₁-receptor antagonist (pyrilamine). (4) Contractions caused by electric stimulation were depressed by an H₂-receptor agonist (4-methylhistamine) and augmented by an H₁-receptor agonist (2-methylhistamine). These findings suggest the possibility that histamine, which is abundant in sympathetic nerves, might have a regulatory role in the release of the neurotransmitter.

IN CERTAIN species, for example cat, dog, and man, the infusion of histamine causes a dose-dependent relaxation of the resistance blood vessels of the limbs.¹¹ By contrast the characteristic response of isolated blood vessels to histamine is a contraction.¹¹ Analysis of the results of recent experiments with specific histamine receptor antagonists suggests that these different responses might be a result of the activation of different histamine receptors. For example, histamine H₁-receptors, acting singly or in combination with H₂-receptors, appear to be involved in the vasodepressor

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P CO2.

R B Case and H Greenberg

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