Relative Effect of CO₂ on Canine Coronary Vascular Resistance

Robert B. Case, Alexis Felix, Maria Wachter, George Kyriakidis, and Frank Castellana

SUMMARY We determined the effect of alterations in coronary arterial PCO₂ on coronary vascular resistance (CVR) at a constant coronary sinus (CS) PO₂ and the effect of coronary arterial PO₂ variation on CVR at a constant CS PCO₂. A linear but opposing effect on CVR was found for both gases. The sensitivity of CVR to O₂ change, represented as CVR/CS PO₂, was approximately twice that of the ratio CVR/CS PCO₂ (0.0852 ± 0.006 vs. -0.0362 ± 0.005). The entire range of CVR variation obtainable through CO₂ variation was as great as that resulting from O₂ variation. During randomized variation of O₂ and CO₂, CVR can be mathematically related in a multiple linear expression to CS PO₂ and CS PCO₂.

THERE IS extensive evidence showing that coronary flow is closely linked to the rate of myocardial O₂ consumption. The most persuasive demonstration of this correlation is in the constant value of O₂ content or PO₂ in coronary venous blood during wide variations in myocardial O₂ consumption and coronary flow resulting from exercise, pacing, and volume overload. This finding also suggests that coronary flow is in some manner regulated about a constant myocardial PO₂. However, coronary sinus (CS) PCO₂ is also unchanged during these physiological stresses, although myocardial CO₂ production varies as widely as O₂ consumption. Thus it seems reasonable to hypothesize that coronary flow might also be regulated about a constant myocardial PCO₂. It was postulated that these CVR changes were primarily an expression of myocardial PCO₂ variation, although they were initiated through alterations in arterial PCO₂.

The present study was undertaken to define more specifically and extensively the effect of CO₂ on CVR and to contrast this with the effect of O₂ on CVR. Since both O₂ and CO₂ appear to possess strong vasoactivity on the coronary circulation, it was essential to examine the effect of one gas on CVR while maintaining the other at a constant value. We have proceeded on the assumption that (1) the effect of either gas on CVR is determined by its myocardial concentration; evidence supporting this is available for O₂ but not for CO₂; (2) CS blood gas values reflect their myocardial values; evidence supporting this exists for both O₂ and CO₂. We have thus examined the effect of CO₂ on CVR by varying coronary arterial PCO₂ while maintaining CS PO₂ constant, and have related the resultant CVR changes to CS PCO₂. The effect of O₂ on CVR was evaluated in an analogous fashion. In these studies, coronary arterial blood gases were locally controlled in coronary arterial blood, thus avoiding the systemic effects of hypercapnia and the mechanical effects of hyperventilation.

Experimental Design

The technique used (Fig. 1) was modified from that previously described; all interventions were made at a constant coronary flow, and resultant changes in coronary arterial perfusion pressure were used to calculate changes in CVR. A small oxygenator in the coronary arterial flow circuit permitted local control of blood PCO₂ and PO₂. CS blood gases were continuously monitored.

Mongrel dogs (16–24 kg) were anesthetized with pentobarbital and maintained on positive pressure ventilation. Under fluoroscopic guidance, a size 10F Goodale-Lubin catheter was inserted into the mid-portion of the CS. The left chest was opened, the left main coronary artery dissected free at its origin, and a tie placed about it. Both femoral arteries were cannulated, and blood from these
CO₂ and O₂ on Coronary Vascular Resistance/Case et al.

To A pO₂ Electrode

FIGURE 1 Diagram of preparation. Coronary arterial P O₂ and P CO₂ are locally controlled by the oxygenator. Coronary sinus and coronary arterial blood are continuously sampled; arterial P O₂ and coronary sinus P O₂ and P CO₂ are continuously recorded.

passed into polyvinyl tubing comprising the coronary perfusion circuit. This terminated in a modified Gregg coronary cannula, which was inserted through the left subclavian artery into the coronary artery and its tip tied by the previously placed ligature. Flow in this circuit from femoral artery to coronary artery was controlled by a finger pump (Harvard Instrument Co., model 2036) modified for precise control of flow. Pump flow was independent of input and output pressure up to 200 mm Hg. Temperature was measured just proximal to the coronary cannula; its value was kept at 37–38°C by a heat exchanger in the coronary circuit.

For maintenance of a constant arterial pressure, an overflow-type reservoir in the coronary perfusion circuit just distal to the femoral arteries (fig. 1), was set at an appropriate height to result in an aortic systolic pressure of approximately 120 mm Hg. Inflow to this reservoir from the femoral arteries was not restricted; overflow passed into the oxygenator and from there was pumped into the left main coronary artery.

Control of Coronary Arterial P O₂ and P CO₂

The coronary flow circuit contained an 11-inch Kay-Cross disk oxygenator, modified to reduce its functional blood capacity to 300 ml. Gas was supplied to the oxygenator as a mixture from three separate tanks: 100% O₂, 100% N₂, and 12% CO₂ in N₂. Each tank was equipped with a precision flowmeter, and an appropriate gas mixture was chosen to provide a desired blood gas value, assuming complete equilibrium between blood and diffusing gas.

Blood Gas Analysis

Blood gases were determined from individual syringe samples and also from a continuous recording using flow-through electrodes. CS blood was continuously withdrawn through the CS catheter (fig. 1) at a rate of 5 ml/min, using a roller pump (Technicon), and returned to a femoral vein. The CS blood was passed across the face of a P O₂ electrode with a polypropylene membrane and a P CO₂ electrode with an ILastic membrane which were contained within a water bath at 37°C. The signals were separately amplified (Instrumentation Laboratories IL 113) and the output continuously recorded. Arterial P O₂ was continuously recorded in a similar manner by continuous withdrawal of blood from a site just proximal to the coronary arterial cannula at 5 ml/min with subsequent passage through a separate P O₂ electrode and water bath and return to a femoral vein. Signals recorded from the CS P O₂, CS P CO₂, and arterial P O₂ electrodes were corrected for the delay due to transmission time and electrode response. Transmission time from coronary sinus to each electrode was 45 seconds. For the P O₂ electrode, the response time (for liquid) following a sudden P O₂ change was 32 seconds for 67% of the full response. For the P CO₂ electrode, the response time was 42 seconds for 67% of the full response. A time correction of 1 minute was used for all electrodes.

Syringe samples for P CO₂, P O₂, and pH and hematocrit were taken, when indicated, at a site in the coronary venous and coronary arterial sampling lines distal to the electrodes (fig. 1). This proved to be a convenient technique, since the sampling pumps filled the syringes
without disturbance of the coronary pressure and flow relationships. Syringe samples were analyzed by separate equipment (IL 113).

Measurement of CVR

CVR was calculated from the ratio of perfusion pressure to coronary flow. After an appropriate coronary flow had been established for each particular experiment, coronary flow was not changed further and remained constant throughout the experiment. Mean coronary arterial pressure was measured from a site just proximal to the coronary cannula by means of a Statham P23D transducer. This measurement was corrected for the pressure gradient due to flow through the cannula, to determine the actual pressure existing in the left main coronary artery. The magnitude of this pressure gradient had been determined previously at varying flow rates and hematocrits and varied from 2 to 5 mm Hg. This gradient was constant for each experiment and was subtracted from the measured pressure. CVR was calculated as the ratio of corrected coronary arterial pressure (mm Hg) to left main coronary flow (ml/min per 100 g LV) and expressed as units of CVR/100 g of LV (left ventricle). Each coronary flow value was corrected for the 5 ml/min continuously removed by sampling coronary arterial blood. Right atrial pressure was not included in these calculations since, in previous studies, it did not change during wide variations in arterial PCO\textsubscript{2}. Left atrial pressure was monitored throughout these experiments and was unchanged unless coronary arterial PO\textsubscript{2} was deliberately reduced to ischemic levels or arterial PCO\textsubscript{2} made excessively high. While a constant coronary flow is unphysiological, resistance vessels behave appropriately to situations that could alter CVR, such as administration of coronary dilators, variation in myocardial O\textsubscript{2} consumption, and variation in arterial O\textsubscript{2} supply.

Conduct of the Experiment

Experiments were conducted so as to maintain myocardial O\textsubscript{2} consumption constant, as well as mechanical factors which might affect CVR. Arterial pressure was controlled through the reservoir described above; heart rate was uncontrolled, but remained steady throughout the study. Pentobarbital was given continuously intravenously at a rate of 60 mg (1 ml) per hour. Continuous recordings of CS PO\textsubscript{2}, PCO\textsubscript{2}, coronary arterial PO\textsubscript{2}, mean coronary arterial pressure, central aortic pressure, left atrial pressure, heart rate, and the electrocardiogram (lead II) were made on a Beckman Dynograph. The experiments were conducted so as to achieve an appropriate range of values in the CS concentration of one gas, so that CVR, such as administration of coronary dilators, variation in myocardial O\textsubscript{2} consumption, and variation in arterial O\textsubscript{2} supply.

PO\textsubscript{2} vs. CVR

In examining the relationship between CS PCO\textsubscript{2} and CVR, arterial PCO\textsubscript{2} was varied over wide ranges from hypercapnia to hypocapnia, using an appropriate oxygenator gas mixture, while maintaining CS PO\textsubscript{2} close to its physiological value of 20 mm Hg and within a range of ±2 mm Hg. Since variation in arterial (and CS) PCO\textsubscript{2} is accompanied by a considerable PO\textsubscript{2} change in a similar direction in accordance with the new O\textsubscript{2} dissociation relationship, O\textsubscript{2} supply to the oxygenator was altered in a direction opposite to the CO\textsubscript{2} change at each step. This initial adjustment was an estimate, often requiring further fine adjustments to restore CS PO\textsubscript{2} to its control range. Care was exercised so that CS PO\textsubscript{2} did not at any time fall below 15 mm Hg, and such a fall was always transient so as to prevent entry into an ischemic zone at approximately 10 mm Hg which would result in a loss of normal coronary vascular reactivity. It was not possible, however, to compensate for the effect of CO\textsubscript{2} changes on CS PO\textsubscript{2} by altering coronary arterial PO\textsubscript{2} within the normal or high PO\textsubscript{2} range. During hypocapnia, for example, elevation of arterial PO\textsubscript{2} from a normal value of 90 mm Hg to 500 mm Hg could not prevent the CS PO\textsubscript{2} from falling, presumably because the arterial O\textsubscript{2} content could not be elevated significantly. It was found necessary to begin the experiment at a lower arterial PO\textsubscript{2} in the range of 45-55 mm Hg (O\textsubscript{2} saturation of 80-88% at a pH of 7.4) with coronary flow set so that CS PO\textsubscript{2} was 20 mm Hg. Thus arterial PO\textsubscript{2} was varied from 38 to 150 mm Hg during the CO\textsubscript{2} variations, while the CS PO\textsubscript{2} remained at a constant value close to 20 mm Hg.

It was felt that these unphysiological arterial PO\textsubscript{2} values were without importance in an assessment of CVR, since the continued presence of a CS PO\textsubscript{2} of 20 mm Hg assured adequate myocardial oxygenation at all times. CVR also appears to be a function of myocardial rather than arterial O\textsubscript{2} concentration. Our previous study showed that the ability of hypocapnia to increase CVR was unchanged over arterial PO\textsubscript{2} ranges from 52 to 600 mm Hg. Finally, these low arterial PO\textsubscript{2} values were restricted to the coronary circulation, and thus prevented the systemic effects associated with arterial hypoxemia.

PCO\textsubscript{2} vs. CVR

The effect of O\textsubscript{2} on CVR was examined by wide variations in O\textsubscript{2} supply to the oxygenator, with a constant percentage of CO\textsubscript{2} in the diffusing gas; this resulted in wide variations of CS PO\textsubscript{2} in the presence of an unchanged CS PCO\textsubscript{2}. The experiments were conducted so that CS PCO\textsubscript{2} remained within ±4 mm Hg of its established control value. Care was exercised so that CS PO\textsubscript{2} did not fall below 15 mm Hg, to prevent loss of normal coronary vascular reactivity due to ischemia. The combined action of O\textsubscript{2} and CO\textsubscript{2} on CVR was determined by individual variation of O\textsubscript{2} and CO\textsubscript{2} in the same dog, as described above; in two dogs, CO\textsubscript{2} and O\textsubscript{2} were allowed to vary freely, and the subsequent effect on CVR was analyzed. The effect of propranolol on the interrelationship between PO\textsubscript{2}, PCO\textsubscript{2}, and CVR was examined in two dogs (no. 3 and parts B and C of no. 7). Propranolol was given intravenously prior to the blood gas variation in 1-mg injections until there was no further decrease in heart rate with subsequent injections. In dog no. 3, both O\textsubscript{2} and CO\textsubscript{2} variations were studied individually, as outlined above. In dog 7, propranolol was given after part A and before parts B and C. O\textsubscript{2} alone was varied in parts A and B, and O\textsubscript{2} and CO\textsubscript{2} were randomly varied in part C.
Calculations

The rate of myocardial \( O_2 \) consumption was calculated from coronary flow, coronary arterial and coronary sinus \( P_{O_2} \), \( pH \), and hematocrit as described earlier. and expressed as mm/min per 100 g LV (nO2). Using linear regression analysis, the relationship was determined between (1) CVR and CS \( P_{CO_2} \) at a constant CS \( P_{O_2} \), (2) CVR and CS \( P_{O_2} \) at a constant CS \( P_{CO_2} \); the slope of each relationship was expressed as units CVR/mm Hg of the respective gas. The combined effect of \( O_2 \) and \( CO_2 \) on CVR was also assessed, using a multiple linear regression analysis according to the relationship CVR = \( a(CS~P_{O2}) + b(CS~P_{CO2}) + C \), in which \( a \) and \( b \) represent the slopes of the relationships CVR/CS \( P_{O2} \) and CVR/CS \( P_{CO2} \), respectively; \( C \) is the intercept of the CVR plane. All values are \( \pm \) SEM.

Results

Effect of \( CO_2 \) Variation on CVR at a Constant CS \( P_{O2} \)

Coronary artery pressure varied inversely with CS \( P_{CO_2} \) (Fig. 2A and 2B). \( CO_2 \) variation was thus observed to have an important effect on CVR, because CVR could double or triple over the range of values of \( CO_2 \) explored (Fig. 3A and 3B; Table 1). Points taken at equilibrium values (filled circles with spines) were found to fall along the same curve as points taken while CS \( P_{CO2} \) and CVR were changing (open circles). Because equilibrium points were obtained only with some difficulty, due to the stringent demands of a constant CS \( P_{O2} \) and the empirical \( O_2 \) adjustments required for each change in \( CO_2 \), the ability to use transient values permitted the CVR-CS \( P_{CO2} \) relationship to be examined more extensively and allowed reliance on transient values. In addition, this indicated that CVR did not have a delayed response to \( CO_2 \) variation, although the exact speed of reaction cannot be determined from these studies. Even if the use of non-steady state values is discounted, the slope of the relation between CVR and CS \( P_{CO2} \) would not be significantly different from that using all points, since in each study an adequate number of equilibrium values were recorded, and their slope alone was not significantly different from that found for the transient values alone.

An inverse, essentially linear relationship was present between CVR and CS \( P_{CO2} \) for most of the \( CO_2 \) range examined. When CS \( P_{CO2} \) exceeded 60–70 mm Hg, there was flattening of this relationship associated with a very low CVR which presumably indicated maximal CVR reduction at the high \( CO_2 \) levels. In general, very high levels of \( CO_2 \) were avoided, since they resulted in loss of CVR reactivity and a rise in left atrial pressure, a finding analogous to that seen as a result of myocardial ischemia. A plateau of maximal CVR was expected during extreme hypocapnia, but this was never observed even though CS \( P_{CO2} \) was reduced to as low as 22 mm Hg (arterial \( P_{CO2} \) of 14 mm Hg). This suggests either that the maximum effect of hypocapnia on CVR occurs at lower values than those we have examined, or that CVR will continue to rise to extreme heights with further \( CO_2 \) reduction. It is conceivable that the very high levels of CVR achieved during hypocapnia might be associated with myocardial ischemia and that, under these conditions, CS \( P_{O2} \) might not properly reflect the tissue \( P_{O2} \) due to transmural blood flow redistribution.

In calculating the slope and regression line for the CVR/CS \( P_{CO2} \) relationship, points in the high \( P_{CO2} \) range, where the relationship flattened, were omitted. Thus, in Figure 3A, all points beyond a CS \( P_{CO2} \) of 60 mm Hg were omitted. Table 1 includes data only for these linear ranges which were examined. The slope of the CVR/CS \( P_{CO2} \) relationship varied from \(-0.0341\) to \(-0.0588\), with a mean of \(-0.0473 \pm 0.005\); the correlation coefficient was above 0.90 in each case. The range of CS \( P_{O2} \) did not exceed 3.5 mm Hg in any experiment and was usually well below this; the mean value was close to the normal value.
of 20 mm Hg in all experiments. Myocardial O₂ consumption and its determinants (heart rate, systolic arterial pressure) showed little change. Data from dog no. 3 were obtained after the administration of intravenous propranolol; continued evidence of reactivity to CO₂ indicates that the changes in CVR reported in this study are not secondary to an altered inotropic state mediated through catecholamines.

While we have chosen to relate blood gas changes in the coronary sinus in these experiments to CVR, it should be pointed out that arterial Pco₂ (A Pco₂) also bore a close relationship to CVR; the slope of the CVR/A Pco₂ relationship varied from -0.043 to -0.105, with a mean of -0.0618 ± 0.012. The mean r was 0.96, with no r value less than 0.89.

**Effect of O₂ Variation While CS Pco₂ was Kept Constant**

CVR was also strongly affected by a variation in O₂ (Fig. 4A and 4B), but this effect was opposite in direction to that achieved by CO₂; also the magnitude of the CVR variation which could be achieved by extreme changes in O₂ did not exceed that resulting from wide CO₂ variation. While CVR rose with increasing O₂, little increase in CVR was observed above an arterial P₀₂ of 90 mm Hg, even though arterial P₀₂ values were carried to 150-200 mm Hg. The best correlation with CVR was observed with CS P₀₂ rather than with arterial P₀₂; a full description of the relationship between CVR and CS P₀₂ is shown in Figure 4A. CVR increases as CS P₀₂ rises within the range of 10-30 mm Hg. Beyond 30-35 mm Hg, no further increases in CVR are seen, indicating that the maximal effect of O₂ on CVR occurs at this value. Similar limits were observed in the other experiments. When CS P₀₂ is decreased to 10 mm Hg, a maximal decrease in CVR is apparent, since further P₀₂ reduction does not further reduce CVR. The simultaneous nature of the onset of anaerobic myocardial metabolism and a minimum CVR during coronary flow reduction has been previously demonstrated;28 in the experiment shown in Figure 4A, a left atrial pressure rise and S-T depression began to occur at a CS P₀₂ of 10 mm Hg and provided similar evidence of the ischemic nature of the lower plateau of this relationship. Reduction of CS P₀₂ to the point of ischemia was avoided in all other experiments, since a prolonged loss of coronary vascular reactivity resulted. CS P₀₂ was thus not reduced below 15 mm Hg (Table 2) in other experiments so that a full CVR curve was not obtained in each dog. However, the maximum CVR obtainable by an O₂ increase did not exceed that observed with hypocapnia in any given dog.

A linear regression analysis between CVR and CS P₀₂ was performed after eliminating points associated with either an upper or lower plateau, since these are no longer areas of changing CVR and therefore are not related to changing blood gas values. The slope of the CVR/CS P₀₂ relationship at a constant CS P₀₂ varied from 0.0874 to 0.1061, with a mean of 0.0986 ± 0.021, and with all r values exceeding 0.92 (Table 2). Thus CVR is approximately twice as sensitive to P₀₂ changes as to Pco₂, expressed per mm Hg of either gas. However, the range of activity of P₀₂ is relatively narrow (approximately 20 mm Hg of CS P₀₂), whereas the range of Pco₂ activity is at least twice as great. No significant changes in myocardial O₂ consumption or its determinants were present; no change was apparent in the response of CVR to O₂ following the administration of intravenous propranolol (Table 2, experiment 7B vs. 7A). The CS Pco₂ was maintained within a range of less than 8 mm Hg, and in most dogs the range was much less than this.

**Combined Effect of CO₂ and O₂ on CVR**

Since both O₂ and CO₂ possessed strong opposing effects on CVR, the multiple regression analysis of their
TABLE 1  Variations in Pco 2 at a Constant CS Po 2

<table>
<thead>
<tr>
<th>Results with dog no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS Po 2 (mm Hg)</td>
<td>21.7-23.6</td>
<td>18.0-21.2</td>
<td>18.2-21.0</td>
<td>18.9-22.0</td>
<td>20.1-23.4</td>
</tr>
<tr>
<td>(mean ± SEM)</td>
<td>(22.6 ± 0.2)</td>
<td>(19.4 ± 0.2)</td>
<td>(19.9 ± 0.1)</td>
<td>(20.4 ± 0.2)</td>
<td>(21.4 ± 0.2)</td>
</tr>
<tr>
<td>CS Pco 2 (mm Hg)</td>
<td>23.1-41.5</td>
<td>23.0-60.7</td>
<td>23.1-49.3</td>
<td>31.4-65.7</td>
<td>33.0-58.0</td>
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<tr>
<td>CVR (U/100 g LV)</td>
<td>2.13-0.87</td>
<td>3.07-1.02</td>
<td>2.22-0.83</td>
<td>2.46-1.26</td>
<td>1.94-0.84</td>
</tr>
<tr>
<td>Slope CVR/CS Pco 2 (b)</td>
<td>-0.0561</td>
<td>-0.0588</td>
<td>-0.0466</td>
<td>-0.0341</td>
<td>-0.0411</td>
</tr>
<tr>
<td>CVR intercept (C)</td>
<td>3.15</td>
<td>4.39</td>
<td>3.10</td>
<td>3.53</td>
<td>3.16</td>
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<tr>
<td>r</td>
<td>0.96</td>
<td>0.93</td>
<td>0.91</td>
<td>0.99</td>
<td>0.97</td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>25</td>
<td>55</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Coronary flow (ml/min per 100 g LV)</td>
<td>92.4</td>
<td>55.8</td>
<td>75.3</td>
<td>63.4</td>
<td>79.8</td>
</tr>
<tr>
<td>nO 2 (mean ± SEM)</td>
<td>(0.373-0.430)</td>
<td>(0.230-0.275)</td>
<td>(0.323-0.396)</td>
<td>(0.319-0.328)</td>
<td>(0.358-0.406)</td>
</tr>
<tr>
<td>(0.402 ± 0.028)</td>
<td>(0.251 ± 0.013)</td>
<td>(0.366 ± 0.011)</td>
<td>(0.324 ± 0.004)</td>
<td>(0.389 ± 0.015)</td>
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</tr>
<tr>
<td>Rate/min</td>
<td>141-146</td>
<td>130-138</td>
<td>124-134</td>
<td>128-140</td>
<td>141-159</td>
</tr>
<tr>
<td>(mean ± SEM)</td>
<td>(144 ± 0.4)</td>
<td>(132 ± 0.6)</td>
<td>(128 ± 0.5)</td>
<td>(133 ± 1.1)</td>
<td>(147 ± 1.2)</td>
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<tr>
<td>A Po 2 (mm Hg)</td>
<td>125-45</td>
<td>99-38</td>
<td>48-39</td>
<td>65-46</td>
<td>179-59</td>
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<tr>
<td>A Pco 2 (mm Hg)</td>
<td>14.0-24.8</td>
<td>15.6-46.5</td>
<td>15.6-35.8</td>
<td>20.5-50.5</td>
<td>23.0-46.5</td>
</tr>
<tr>
<td>CS pH</td>
<td>7.54-7.36</td>
<td>7.53-7.27</td>
<td>7.43-7.24</td>
<td>7.40-7.20</td>
<td>7.41-7.23</td>
</tr>
</tbody>
</table>

nO 2 = myocardial O 2 consumption, ml/min per 100 g LV; r = correlation coefficient. Dog no. 3 was tested after intravenous propranolol.

interrelationship was examined, according to the empirical expression CVR = a (Po 2) + b (Pco 2) + C, in which a and b are the respective slopes of the CVR/Po 2 and CVR/ Pco 2 relationships, or expressed mathematically, a = d (CVR)/d (Po 2) at a constant Pco 2 and b = d (CVR)/d (Pco 2) at a constant Po 2. The value C is a constant for this equation and is presumably related to the intrinsic steady state CVR. Data for this section were obtained from dogs in which both CO 2 and O 2 had been varied individually in the same dog (no. 2, 3, 4) and from two dogs in which gases were randomly varied (no. 7C and 8, Table 3). All points were used which were not clearly associated with a maximal or minimal CVR plateau. Considerable additional data became available from the individually varied gas experiments (no. 2, 3, 4) in which points had previously been omitted since they did not fall within the narrow range of constant CS Po 2 or CS Pco 2 required. Results of the multiple regression analyses for these five dogs are presented in Table 3. The slopes expressing the effect of O 2 and CO 2 for the combined action are similar to those determined through individual variations as presented in Tables 1 and 2. For experiment 8, in which gases were randomly varied, the developed expression would be CVR = 0.0591 (CS Po 2) - 0.0262 (CS Pco 2) + 1.507. A comparison of CVR calculated from this expression and the experimental CVR at the corresponding point (Fig. 5) shows that CVR can be satisfactorily expressed in terms of CS Po 2 and CS Pco 2 providing other factors are unchanged. A consideration of this expression also indicates that CVR cannot be properly interpreted if the level of CO 2 is not taken into consideration.

Discussion

These experiments show that CO 2 can have a major effect on CVR that is fully as great as that resulting from change in O 2 but opposite in direction. This effect of CO 2 on CVR could be mediated through a pH change or through an effect on other unspecified substances, such as an effect on prostaglandin observed for the cerebral
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tion the level of arterial PCO2, which should be held
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The position of the present investigation in the literature relating to CO₂ and coronary flow is unique in that we have employed local control of coronary arterial gases, maintained one gas constant while varying the other, interpreted CVR in terms of the CS concentration of each gas, and presented a mathematical relationship relating CVR, PO₂, and PCO₂. No prior study of this nature has been reported, with the exception of the study of Daugherty et al., in which CO₂ and O₂ were varied so that the authors preferred to relate primary control of perfused coronary artery by means of a donor lung. Their validity of previous studies on coronary flow, such that we may vary widely in response to arterial Pco₂, as we have demonstrated earlier in studies with hyperventilation and CO₂ breathing. These studies raise many important questions regarding the conduct of future studies and the validity of previous studies on coronary flow, such that confirmation of the findings presented here is essential. However, this already exists in a number of older studies, as well as in more recent investigations.

The well-known controlling effect on cerebral flow which is exercised by alterations in arterial Pco₂ value is probably related to prostaglandin synthesis, and it seems reasonable that a similar mechanism could be operative in the coronary circulation. Also, the demonstration that cardiac muscle does not possess extravascular carbonic anhydrase may serve to prolong the myocardial Pco₂ elevation in response to an altered myocardial O₂ consumption, as well as to explain the high myocardial Pco₂ values encountered during myocardial hypoxia.

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