Myocardial Oxygen Tension Determines the Degree and Pressure Range of Coronary Autoregulation

WILLIAM P. DOLE AND DANIEL W. NUNO

Experiments were designed to separate effects of myocardial oxygen tension and oxygen consumption on coronary autoregulation. The approach was to measure coronary hemodynamic and metabolic responses to decreases in perfusion pressure during interventions that altered the balance between myocardial oxygen supply and demand. Studies were conducted in anesthetized heart-blocked dogs with the left coronary artery perfused from a pressure-controlled blood reservoir. Decreasing oxygen consumption by lowering heart rate from 120 to 40 bpm increased coronary venous oxygen tension and reduced the degree of flow autoregulation between 120 and 80 mm Hg by threefold. Initial coronary venous oxygen tension but not oxygen consumption was strongly correlated with a quantitative index of autoregulation ($-0.052 \cdot P_{O_2} + 2.01, R^2 = 0.86$) over the pressure range of 120 to 80 mm Hg. When heart rate was lowered to 40 bpm and coronary venous oxygen tension subsequently reduced with vasopressin to control values (120 bpm), autoregulation was completely restored. Parallel studies examined the effects of metabolic and pharmacologic interventions on coronary pressure–flow relations over a wide range of pressures. For each 20 mm Hg decrement in pressure between 160 and 80 mm Hg, lowering heart rate attenuated autoregulation whereas pharmacologic coronary constriction augmented autoregulation. The observed variations in the autoregulation index were largely explained by differences in the prevailing venous oxygen tension. Furthermore, the upper pressure limit for autoregulation was dependent on venous oxygen tension with a threshold oxygen tension for autoregulation of 32 mm Hg. These results indicate that coronary autoregulation is closely coupled to the prevailing venous oxygen tension but not oxygen consumption and is facilitated at low venous oxygen tension. (Circulation Research 1986;59:202–215)

Autoregulation refers to the intrinsic ability of an organ to maintain its blood supply relatively constant following changes in perfusion pressure. Autoregulation of total and transmural myocardial blood flow has been demonstrated in blood-perfused dog hearts in situ. Autoregulation of total coronary flow has also been observed in isolated Langendorff heart preparations perfused with physiological salt solution in the guinea pig, rat, rabbit, and cat.

Both metabolic and myogenic theories have been proposed to explain autoregulation of coronary flow. Based on the metabolic theory, a decrease in coronary artery pressure reduces flow, which results in coronary vasodilation by decreasing myocardial substrate availability or increasing production of metabolites. Based on the myogenic theory, an intrinsic mechanism dependent on venous oxygen tension with a threshold oxygen tension for autoregulation of 32 mm Hg.

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In vascular smooth muscle regulates resistance in response to changes in transmural pressure. Accordingly, a decrease in coronary artery pressure results in coronary vasodilation independent of changes in blood flow. It has been difficult to separate metabolic and myogenic mechanisms of autoregulation in the coronary circulation because changes in coronary perfusion pressure (myogenic stimulus) result in directionally similar transient changes in blood flow (metabolic stimulus). In addition, basal myocardial oxygen demands are high and metabolic factors could potentially mask or inhibit a myogenic response.

In this study we designed experiments to delineate the relative importance of metabolic factors in coronary autoregulation. The experimental approach was to determine the effects on coronary autoregulation of reducing myocardial oxygen demands by lowering heart rate. To separate effects of vascular resistance, myocardial $P_{O_2}$, and $MVO_2$, we compared coronary autoregulation during vasoconstriction produced by lowering metabolic demands and by reducing myocardial blood flow with intracoronary infusion of vasopressin or indomethacin. This approach enabled us to define the relation between coronary autoregulation and coronary venous $P_{O_2}$.

Materials and Methods

Experiments were performed in 46 adult mongrel dogs (20–25 kg). Animals were anesthetized with $\alpha$-chloralose (100 mg/kg, IV), with additional doses of chloralose given as needed throughout the experiment.
The dogs were ventilated with oxygen-enriched room air to keep arterial Po2 between 100 and 125 mm Hg and PCO2 between 30 and 40 mm Hg. Arterial pH was maintained at 7.35–7.45 by an intravenous infusion of sodium bicarbonate (150 mM, 5 ml/kg/hour, IV).25 Aortic pressure was measured through a catheter inserted retrograde from the left femoral artery. Rectal temperature was held constant at 37°C.

The heart was exposed through a thoracotomy in the fifth left intercostal space. Complete atrioventricular heart block was produced by injection of 40% formalin (0.2 cc) directly into the atrioventricular node.36 Pacing wires were sewn to the right ventricular outflow tract and connected to a stimulator. Intravenous lidocaine (1 mg/kg) was used in a few animals to suppress spontaneous ventricular escape beats during reductions in heart rate to 40 bpm.

**Coronary Artery Perfusion**

In 27 animals the left main coronary artery was perfused from a pressurized arterial reservoir through a metal cannula advanced through the right carotid artery. The cannula was tied in place with a ligature passed under the proximal coronary vessel. In 19 animals, the left anterior descending coronary artery was cannulated directly with a short stainless steel tube, secured with a ligature, and connected to the blood reservoir. Coronary artery pressure was measured at the cannula tip through an inner steel tube. Coronary blood flow was measured with an extracorporeal electromagnetic flow transducer (Zepeda Instruments, model SWF-4) in the coronary perfusion line. The reservoir blood was continually stirred and heated to maintain the temperature of the blood entering the cannula at 37°C. Reservoir blood volume was kept constant, and pressure in the reservoir was controlled with two compressed air sources connected in parallel. Heparin (initial dose 500 U/kg IV, then 250 U/kg IV every 1–2 hours) was given to prevent blood coagulation. At the end of each experiment saturated Evans blue solution was injected into the coronary cannula to delineate the area of perfused myocardium which was removed and weighed to calculate coronary flow per 100 g of muscle mass. The flowmeter was calibrated by timed blood volume collections with blood from the experimental animal.

**Measurement of Myocardial Oxygen Tension and Oxygen Consumption**

Coronary venous Po2 was used as an index of average tissue oxygen. For left main coronary artery preparations, the coronary sinus was cannulated with a 7F Sones angiographic catheter inserted through the right jugular vein with the catheter tip positioned 2–3 cm past the bend of the coronary sinus.27 For left anterior descending coronary artery preparations, coronary venous blood was sampled from the great cardiac vein within 1 cm of the origin of the anterior interventricular vein using a 6F Goodale Lubin angiographic catheter inserted through the jugular vein. Sampling of blood from this site reflects venous drainage from the perfusion territory of the left anterior descending artery.28

Coronary arteriovenous oxygen difference was measured continuously by the spectrophotometric method of Shepherd and Burgar.29 Blood was withdrawn simultaneously from the coronary venous catheter and arterial perfusion circuit upstream from the flow probe, pumped at a constant rate of 5 ml/minute through an arteriovenous oxygen difference spectrophotometer (Avox Systems, San Antonio, Texas) and returned to the animal through the right femoral vein. Accuracy of the arteriovenous oxygen difference spectrophotometer was confirmed in separate experiments in which coronary arteriovenous oxygen difference varied over a wide range by changing perfusion pressure or by infusing adenosine or vasopressin into the coronary artery. A close correlation about the line of identity (r = 0.99) was found with measurements obtained using a Lex-O2-Con oxygen content analyzer (Lexington Instruments Corp., Walton, Mass.).

Total oxygen uptake (MV02) was calculated by multiplying the arteriovenous oxygen difference and coronary blood flow during steady state conditions. Coronary venous pH, Po2, and PCO2 were measured with a blood gas analyzer (Instrumentation Laboratory Micro 13) calibrated daily with known gas mixtures. The accuracy of the blood gas analyzer over the Po2 range of 5 to 50 mm Hg was checked using a tonometer (Instrumentation Laboratory Model 237) and equilibrating the dog’s blood with known gas mixtures of nitrogen and oxygen. Measurements were accurate to within 1 mm Hg.

**Quantitation of Coronary Autoregulation**

The degree of coronary autoregulation was quantitated using an index (Arl) (Figure 1) which compares the observed change in vascular conductance for a given change in pressure to the calculated change in conductance assuming that flow remained constant.

\[
Arl = \left( \frac{F - F_i}{P_i} \right) \left( \frac{F_i - F}{P} \right)^{-1} = 1 - \left( \frac{\Delta F}{\Delta P} \right) \left( \frac{F_i}{P_i} \right)^{-1}
\]

where \( F_i \) = initial flow at pressure \( P_i \), \( F \) = flow at pressure \( P \), \( \Delta F = F_i - F \), \( \Delta P = P_i - P \). If conductance is unchanged or decreases when pressure is reduced (passive vascular bed), then Arl ≤ 0 and there is no autoregulation. If conductance increases, then Arl > 0 and the degree of autoregulation will depend on the magnitude of the change in conductance with a maximum value for Arl of 1.0, indicating perfect autoregulation.

Because MV02 decreased with reductions in coronary artery pressure and flow, the autoregulation index was adjusted for such changes in MV02. Values of flow \( F \) at pressure \( P \) were corrected using the slope of the \( F \) vs MV02 relationship obtained by changing heart rate (range 40 to 120 bpm). The corrected flow \( F_c \) was calculated as

\[
F_c = F_m + \left[ \frac{\Delta MVO_2 (PF)}{(\Delta F/\Delta MVO_2)} \right]
\]

Dole and Nuno  Oxygen and Coronary Autoregulation
To separate the effects of coronary vascular resistance, venous Po2, and MVO2 on autoregulation, we compared coronary autoregulation during vasoconstriction produced by 1) decreasing MVO2 by lowering heart rate, and 2) decreasing coronary blood flow with vasopressin or indomethacin at constant heart rate. We anticipated that lowering heart rate would increase coronary vascular resistance and decrease MVO2 with little change or an increase in coronary venous Po2. In contrast, we expected that infusion of vasopressin or indomethacin at a heart rate of 120 bpm would increase coronary vascular resistance and decrease coronary venous Po2 with little or no change in MVO2. In 8 animals (4 left main and 4 left anterior descending preparations), measurements were obtained at heart rates of 120, 40, and 120 bpm during intracoronary vasopressin infusion, and 45 minutes after discontinuing the vasopressin infusion. Lysine vasopressin was infused directly into the coronary perfusion line. The initial infusion rate (0.04–0.07 U/minute) was adjusted to decrease coronary blood flow at a heart rate of 120 bpm and pressure of 120 mm Hg to the flow rate observed at heart rate of 40 bpm before infusion of vasopressin. The concentration of vasopressin was held constant throughout the experiment by using a servo-controlled infusion pump (Harvard, Model 2990) coupled to the voltage output from the electromagnetic flowmeter. This permitted rapid adjustment of the drug infusion rate in proportion to changes in flow. In another group of 6 animals (3 left main and 3 left anterior descending preparations), a similar protocol was employed except that indomethacin was given to produce coronary vasoconstriction. Indomethacin (5 mg/ml) was dissolved in saline and sodium carbonate and the pH adjusted to 7.0–7.5 with the addition of 1 N hydrochloric acid. Hemodynamic and metabolic measurements were obtained during control conditions and 45 minutes after intravenous administration of indomethacin (5 mg/kg).

A third series of experiments was performed to determine whether coronary autoregulation is coupled primarily to the level of myocardial oxygen consumption or to myocardial oxygen tension. If autoregulation depends mainly on tissue Po2, then lowering MVO2 and reducing coronary venous Po2 to control values should restore autoregulation. In 10 animals (6 left main and 4 left anterior descending coronary preparations), we measured coronary hemodynamic and metabolic responses to a decrease in perfusion pressure from 120 to 80 mm Hg at heart rates of 120 bpm (control), 40 bpm, and at 40 bpm during intracoronary infusion of vasopressin. The initial infusion rate of vasopressin (0.04–0.10 U/minute) was adjusted to restore coronary venous Po2, to control values at a pressure of 120 mm Hg. Vasopressin concentration was maintained constant thereafter as described above.

In the final series of experiments we determined the influence of oxygen on both the degree of coronary autoregulation and the pressure range for autoregulation. In 10 animals (6 left main and 4 left anterior descending preparations), steady-state coronary artery
pressure–flow relationships were obtained over the pressure range of 160–40 mm Hg by decreasing pressure in 20 mm Hg steps. Coronary hemodynamic and metabolic parameters were measured during steady-state conditions at each level of pressure. Pressure–flow relations were obtained at heart rates of 120 bpm (control), 40 bpm, and 120 bpm during intracoronary administration of vasopressin. The initial infusion rate of vasopressin (0.04–0.08 U/minute) was adjusted to reduce coronary blood flow to control values at a pressure of 100 mm Hg (midpoint of the pressure–flow curve). Drug concentration was maintained constant thereafter as described above. Following each intervention, coronary hemodynamic and metabolic responses were repeated at a heart rate of 120 bpm and pressures of 120, 100, and 80 mm Hg. Only animals in which repeated measurements of all hemodynamic and metabolic parameters at 120 bpm were within 10% of the values obtained during the control pressure–flow curve were used for subsequent data analysis.

Data Analysis

In each series of experiments, we first tested whether the results obtained with the left main coronary artery preparation differed from those obtained with the left anterior descending coronary preparation using analysis of variance with artery (left anterior descending or left main), experimental intervention (heart rate, drug), coronary pressure, and dog as sources of variation. Because the effect of pressure did not differ significantly between arteries for a given experimental intervention, the data from left main and anterior descending preparations were combined for subsequent analysis.

Differences in effects of reducing coronary artery pressure on hemodynamic and metabolic parameters among experimental interventions were determined by analyses of variance using dogs as a randomized block. Differences were considered statistically significant at the p < 0.05 level using the Bonferroni method. The influence of metabolic factors on coronary autoregulation was assessed by regressing the autoregulation index (Arl) on coronary venous Po2, Pco2, or pH or on MVo2, using analysis of covariance. For each covariable the data were best described using linear or quadratic functions as assessed by comparing standardized R2 values and evaluating the statistical significance of higher-order terms. Standardized R2 values were used to compare the relative effect of the metabolic covariables on autoregulation.

Results

Effects of Lowering Heart Rate on Coronary Autoregulation

Following reduction in pressure at a heart rate of 120 bpm, coronary flow initially decreased and then returned toward control reaching a new steady state within 30 seconds (Figure 2). Oscillations in flow were usually observed prior to reaching steady state. Lowering heart rate from 120 bpm (top panel) to 40 bpm (bottom panel) decreased baseline diastolic flow from 80 to 55 ml/min/100 g. The dynamic and steady-state autoregulatory flow response to pressure reduction at the lower heart rate was markedly attenuated. Also, flow oscillations were observed less frequently and when present were of lower amplitude.

Table 1 summarizes effects of heart rate on coronary hemodynamic and metabolic responses to decreasing perfusion pressure. Lowering heart rate from 120 to 40 bpm reduced myocardial oxygen consumption and increased coronary venous Po2. The autoregulation index (Arl) was reduced at 40 bpm (Table 2). Correction of flows at 80 mm Hg for the change in MVo2 did not qualitatively alter effects of heart rate on pressure-induced changes in flow (Table 2). Lowering heart rate reduced the corrected Arl by threefold from 0.56 ± 0.04 to 0.18 ± 0.05 (p < 0.001).

Effects of Reducing Myocardial Oxygen Demands vs. Pharmacologic Vasoconstriction on Coronary Autoregulation

The effects of intracoronary infusion of vasopressin on coronary responses to decreasing perfusion pressure from 120 to 80 mm Hg are summarized in Table 3. Vasopressin at heart rate 120 bpm decreased initial coronary flow to the same level observed at heart rate 40 bpm with a slight reduction in MVo2. In contrast to metabolic vasoconstriction, which increased coronary venous Po2 and attenuated autoregulation, pharmacological...
logic vasoconstricion decreased venous Po2 and augmented autoregulation (corrected Arl increased from 0.50 ± 0.07 to 0.79 ± 0.05, p < 0.001). Thus, metabolic and pharmacologic interventions produced comparable increases in baseline coronary vascular resistance but had qualitatively different effects on autoregulation and venous Po2. Similar results were obtained in 6 additional animals in which pharmacologic vasoconstriction was produced by intravenous infusion of indomethacin (Table 4).

Figure 3 graphs the corrected Arl over the pressure range of 120 to 80 mm Hg as a function of initial coronary venous Po2 and of initial MVo2. The connected symbols represent data points from individual animals obtained during the three experimental conditions (heart rate 120, 40, and 120 bpm during infusion of vasopressin or indomethacin). In each case there was a strong inverse relation between initial venous Po2 and the autoregulation index over the Po2 range of 40 to 17 mm Hg. Combining both groups of animals (42 observations in 14 dogs), the relation between the corrected autoregulation index and initial coronary venous Po2 was given by: Arl = -0.052 Po2 + 2.01 (R2 = 0.86, p < 0.0001). In contrast, the corrected Arl was poorly correlated with MVo2 (Arl = -0.02 MVo2^2 + 0.75 MVo2 - 3.84, R^2 = 0.30).

Venous Oxygen Tension and Coronary Autoregulation During Reduced Myocardial Oxygen Demands

As in the previous groups of animals, lowering heart rate from 120 to 40 bpm decreased MVo2, increased coronary venous Po2, and decreased Arl. (See Table 5.) Intracoronary infusion of vasopressin at a heart rate of 40 bpm further reduced coronary blood flow and venous Po2 without altering MVo2, and increased Arl. At comparable levels of venous Po2, the Arl at a heart rate of 40 bpm was not significantly different from that at 120 bpm. Thus, while lowering MVo2 attenuates coronary autoregulation, reducing venous Po2 to control values completely restored autoregulation despite the low MVo2. This finding suggests that autoregulation is coupled to Po2 rather than MVo2.

Coronary Pressure-Flow Relationships

Analysis of variance indicated that effects of pressure on coronary flow, arteriovenous O2 difference, MVo2, and venous Po2 did not differ significantly between the 6 left main and 4 left anterior descending coronary preparations for a given experimental condition. The effects of 20 mm Hg step reductions in coronary artery pressure from 160 to 40 mm Hg on coronary hemodynamic and metabolic parameters for all 10 animals are summarized in Figure 4. Lowering heart

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### Table 1. Effects of Reducing Myocardial Oxygen Demands by Lowering Heart Rate on Coronary Hemodynamic and Metabolic Responses to Decreasing Perfusion Pressure from 120 to 80 mm Hg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heart Rate 120</th>
<th>Heart Rate 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean coronary artery pressure (mm Hg)</td>
<td>120: 84±5</td>
<td>120: 64±4†</td>
</tr>
<tr>
<td></td>
<td>80: 66±3*</td>
<td>80: 40±2*†</td>
</tr>
<tr>
<td>Mean coronary flow (ml/min/100 g)</td>
<td>120: 1.43 ±0.07</td>
<td>120: 1.88 ±0.12</td>
</tr>
<tr>
<td></td>
<td>80: 1.21 ±0.05*</td>
<td>80: 2.01 ±0.10†</td>
</tr>
<tr>
<td>Mean coronary resistance (mm Hg/ml/min/100 g)</td>
<td>120: 1.43 ±0.07</td>
<td>120: 1.88 ±0.12</td>
</tr>
<tr>
<td></td>
<td>80: 1.21 ±0.05*</td>
<td>80: 2.01 ±0.10†</td>
</tr>
<tr>
<td>Diastolic coronary flow (ml/min/100 g)</td>
<td>120: 110±6</td>
<td>120: 74±5†</td>
</tr>
<tr>
<td></td>
<td>80: 92±4*</td>
<td>80: 47±3*†</td>
</tr>
<tr>
<td>Arteriovenous O2 difference (ml/100 ml)</td>
<td>120: 10.8±0.6</td>
<td>120: 8.7±0.5†</td>
</tr>
<tr>
<td></td>
<td>80: 12.3±0.6*</td>
<td>80: 10.9±0.5*†</td>
</tr>
<tr>
<td>Myocardial O2 consumption (ml/min/100 g/min)</td>
<td>120: 8.8±0.4</td>
<td>120: 5.6±0.3*†</td>
</tr>
<tr>
<td></td>
<td>80: 7.9±0.4*</td>
<td>80: 4.5±0.3*†</td>
</tr>
<tr>
<td>Coronary venous O2 tension (mm Hg)</td>
<td>120: 29±1</td>
<td>120: 35±2*†</td>
</tr>
<tr>
<td></td>
<td>80: 24±2*</td>
<td>80: 28±1*†</td>
</tr>
<tr>
<td>Coronary venous CO2 tension (mm Hg)</td>
<td>120: 46.3±1.3</td>
<td>120: 42.6±1.4†</td>
</tr>
<tr>
<td></td>
<td>80: 47.6±1.3</td>
<td>80: 44.2±1.4†</td>
</tr>
<tr>
<td>Coronary venous pH</td>
<td>120: 7.38±0.01</td>
<td>120: 7.38±0.01</td>
</tr>
<tr>
<td></td>
<td>80: 7.38±0.01</td>
<td>80: 7.39±0.01</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>120: 85±4</td>
<td>120: 66±4*</td>
</tr>
<tr>
<td></td>
<td>80: 85±3</td>
<td>80: 44±2*</td>
</tr>
</tbody>
</table>

Values are mean ± SE, n = 12.
*p < 0.05 vs corresponding value at 120 mm Hg.
†p < 0.05 vs corresponding value at heart rate 120 bpm.

### Table 2. Effects of Reducing Myocardial Oxygen Demands by Lowering Heart Rate on Coronary Autoregulation Over the Pressure of 120–80 mm Hg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ΔF (ml/min/100 g)</th>
<th>ΔF/Fi</th>
<th>Arl</th>
<th>ΔMVo2 (ml/min/100 g)</th>
<th>ΔMVo2/Fi</th>
<th>ΔF/Fi</th>
<th>Arl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate 120</td>
<td>-19±3</td>
<td>-0.21 ±0.02</td>
<td>0.35±0.06</td>
<td>-0.9±0.2</td>
<td>-12±1</td>
<td>-0.14±0.01</td>
<td>0.56±0.04</td>
</tr>
<tr>
<td>Heart rate 40</td>
<td>-25±2*</td>
<td>-0.37 ±0.02*</td>
<td>-0.10±0.06*</td>
<td>-1.1±0.2</td>
<td>-17±2*</td>
<td>-0.27±0.02*</td>
<td>0.18±0.05*</td>
</tr>
</tbody>
</table>

ΔF = change in coronary flow following a decrease in coronary pressure from 120 to 80 mm Hg; Fi = initial coronary flow at 120 mm Hg; Arl = autoregulation index; ΔMVo2 = change in myocardial oxygen consumption following the decrease in coronary pressure and flow.

Values are mean ± SE, n = 12.
*p < 0.05 vs heart rate 120 bpm.
### Table 3. Effects of Reducing Myocardial Oxygen Demands and of Coronary Vasoconstriction with Vasopressin on Coronary Hemodynamic and Metabolic Responses to Decreasing Perfusion Pressure from 120 to 80 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>Heart rate 120</th>
<th>Heart rate 40</th>
<th>Heart rate 120 + vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>Mean coronary artery pressure (mm Hg)</td>
<td>87 ± 7</td>
<td>67 ± 5*</td>
<td>87 ± 7</td>
</tr>
<tr>
<td>Mean coronary flow (ml/min/100 g)</td>
<td>1.38 ± 0.10</td>
<td>1.19 ± 0.08*</td>
<td>1.80 ± 0.15†</td>
</tr>
<tr>
<td>Mean coronary resistance (mm Hg/ml/min/100 g)</td>
<td>112 ± 9</td>
<td>86 ± 7*</td>
<td>78 ± 9†</td>
</tr>
<tr>
<td>Diastolic coronary flow (ml/min/100 g)</td>
<td>10.0 ± 0.8</td>
<td>11.5 ± 0.8*</td>
<td>8.0 ± 0.9†</td>
</tr>
<tr>
<td>Arteriovenous O₂ difference (ml/100 ml)</td>
<td>8.6 ± 0.8</td>
<td>7.4 ± 0.6*</td>
<td>5.6 ± 0.5†</td>
</tr>
<tr>
<td>Myocardial O₂ consumption (ml/min/100 g)</td>
<td>29 ± 2</td>
<td>26 ± 1*</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Coronary venous O₂ tension (mm Hg)</td>
<td>44.3 ± 2.1</td>
<td>45.8 ± 2.0</td>
<td>41.4 ± 2.3†</td>
</tr>
<tr>
<td>Coronary venous CO₂ tension (mm Hg)</td>
<td>7.39 ± 0.02</td>
<td>7.39 ± 0.02</td>
<td>7.41 ± 0.02</td>
</tr>
<tr>
<td>Coronary venous pH</td>
<td>87 ± 8</td>
<td>86 ± 7</td>
<td>75 ± 7</td>
</tr>
<tr>
<td>Autoregulation index</td>
<td>0.31 ± 0.07</td>
<td>-0.24 ± 0.09*</td>
<td>0.64 ± 0.06*</td>
</tr>
<tr>
<td>Corrected autoregulation index</td>
<td>0.46 ± 0.04</td>
<td>0.05 ± 0.05*</td>
<td>0.82 ± 0.04†</td>
</tr>
</tbody>
</table>

Values are mean ± SE, n = 8.
* p < 0.05 vs corresponding value at pressure 120 mm Hg.
† p < 0.05 vs corresponding value at heart rate 120 bpm.
‡ p < 0.05 vs corresponding value at heart rate 40 bpm.

### Table 4. Effects of Reducing Myocardial Oxygen Demands and of Coronary Vasoconstriction with Indomethacin on Coronary Hemodynamic and Metabolic Responses to Decreasing Perfusion Pressure from 120 to 80 mm Hg

<table>
<thead>
<tr>
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<th>Heart rate 120 + indomethacin</th>
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<tr>
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<td>29 ± 2</td>
<td>26 ± 1*</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Coronary venous O₂ tension (mm Hg)</td>
<td>44.3 ± 2.1</td>
<td>45.8 ± 2.0</td>
<td>41.4 ± 2.3†</td>
</tr>
<tr>
<td>Coronary venous CO₂ tension (mm Hg)</td>
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<td>7.41 ± 0.02</td>
</tr>
<tr>
<td>Coronary venous pH</td>
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<td>0.46 ± 0.04</td>
<td>0.05 ± 0.05*</td>
<td>0.82 ± 0.04†</td>
</tr>
</tbody>
</table>

Values are mean ± SE, n = 6.
* p < 0.05 vs corresponding value at pressure 120 mm Hg.
† p < 0.05 vs corresponding value at heart rate 120 bpm.
‡ p < 0.05 vs corresponding value at heart rate 40 bpm.
rate from 120 to 40 bpm increased the slope of the pressure–flow curve between 160 mm Hg and 80 mm Hg whereas coronary constriction with vasopressin decreased the slope of the pressure–flow curve over this pressure range. Between 60 and 40 mm Hg the slope was less at heart rate 40 compared to that during vasopressin infusion. Coronary arteriovenous oxygen difference (A – VΔO₂) increased linearly with decreasing coronary artery pressure at heart rate 120 bpm (slope -0.038 ± 0.002). Lowering heart rate to 40 bpm increased the relative change in A – VΔO₂ when pressure was reduced (slope -0.051 ± 0.003, p < 0.001). In contrast, coronary constriction with vasopressin decreased the change in A – VΔO₂ with pressure reduction (slope -0.019 ± 0.002, p < 0.001). Myocardial oxygen consumption fell as coronary artery pressure and flow were reduced during all three experimental conditions. Changes in MVO₂ tended to be less during vasopressin infusion over the pressure range of 120 to 80 mm Hg and greater between 60 and 40 mm Hg. During all 3 experimental conditions, coronary venous Po₂ fell linearly as coronary artery pressure was reduced.

In Figure 5, values for coronary flow were adjusted for pressure and flow related changes in MVO₂. These flow values were used to construct pressure–flow relationships at constant MVO₂ (left panel) and to calculate the corrected autoregulation index for each 20 mm Hg change in pressure which was plotted as a function of initial pressure (right panel). Lowering heart rate attenuated the autoregulatory response for initial pressures between 160 and 80 mm Hg and decreased the upper pressure limit for autoregulation from 150 to 118 mm Hg (p < 0.001). Vasopressin infusion augmented the autoregulatory response and increased the upper pressure limit for autoregulation to greater than 160 mm Hg (p < .01).

Figure 6 plots the corrected autoregulation index for a 20 mm Hg reduction in pressure as a function of coronary venous Po₂ for each initial pressure (P). Several observations can be made. First, there is a strong inverse relationship between the autoregulation index...
TABLE 5. Effects of Restoring Coronary Venous Oxygen Tension on Coronary Autoregulation During Reduced Myocardial Oxygen Demand Over the Pressure Range of 120 to 80 mm Hg

<table>
<thead>
<tr>
<th>Mean coronary artery pressure (mm Hg)</th>
<th>Mean coronary flow (ml/min/100 g)</th>
<th>Mean coronary resistance (mm Hg/ml/min/100 g)</th>
<th>Arteriovenous O2 difference (ml/100 ml)</th>
<th>Myocardial O2 consumption (ml/min/100 g)</th>
<th>Coronary venous O2 tension (mm Hg)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Autoregulation index</th>
<th>Corrected autoregulation index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate 120</td>
<td>120</td>
<td>84 ± 5</td>
<td>1.43 ± 0.08</td>
<td>12.1 ± 0.7</td>
<td>9.9 ± 0.5</td>
<td>96 ± 5</td>
<td>0.58 ± 0.05</td>
<td>0.72 ± 0.04</td>
</tr>
<tr>
<td>Heart rate 40</td>
<td>80</td>
<td>72 ± 5*</td>
<td>1.11 ± 0.07*</td>
<td>13.1 ± 0.7*</td>
<td>9.3 ± 0.6</td>
<td>95 ± 5</td>
<td>-0.01 ± 0.09*</td>
<td>0.24 ± 0.02*</td>
</tr>
<tr>
<td>Heart rate 40 + vasopressin</td>
<td>120</td>
<td>67 ± 6†</td>
<td>1.80 ± 0.14†</td>
<td>9.0 ± 0.5†</td>
<td>6.1 ± 0.5†</td>
<td>80 ± 5†</td>
<td>0.48 ± 0.05‡</td>
<td>0.70 ± 0.03‡</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>45 ± 5*†</td>
<td>1.78 ± 0.17†</td>
<td>11.3 ± 0.7†</td>
<td>5.2 ± 0.6†</td>
<td>80 ± 6†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE, n = 10.

*p < 0.05 vs corresponding value at pressure 120 mm Hg.

†p < 0.05 vs corresponding value at heart rate 120 bpm.

‡p < 0.05 vs corresponding value at heart rate 40 bpm.

and initial venous PO2 for each of the initial pressures between 160 and 100 mm Hg (R2 = 0.63 - 0.80). Since the variation due to differences among dogs was small (R2 = 0.05 - 0.15), the observed effects of lowering heart rate and of vasopressin mediated constriction on coronary autoregulation (Figure 5) can be largely explained by differences in prevailing venous PO2. Second, the venous PO2 at which ArI is zero (threshold for autoregulation) for initial pressures between 160 and 100 mm Hg did not differ significantly (PO2 = 30–34 mm Hg). Thus, the upper pressure limit for coronary autoregulation is strongly influenced by

![Figure 4](http://circres.ahajournals.org/)

**Figure 4.** Dependence of coronary blood flow (CBF), coronary arteriovenous oxygen difference (AVDO2), myocardial oxygen consumption (MV02), and coronary venous PO2 (CVP02) on coronary artery pressure over the pressure range of 160–40 mm Hg. Each variable is plotted as a function of the corresponding pressure. Data are mean ± SE at heart rate (HR) 120 bpm (), HR 40 bpm (A), and HR 120 bpm during vasopressin (VPN) infusion (O). * = significant differences (p<0.05) from control values at HR 120 bpm. † = significant differences from values at HR 40 bpm.
venous Po2, and the threshold Po2 for autoregulation averaged 32 mm Hg. Finally, in contrast to the influence of venous Po2 on autoregulation at initial pressures of 160–100 mm Hg, small changes in venous Po2 had little effect on autoregulation at initial pressures of 80 and 60 mm Hg.

Discussion

In this study experiments were designed to separate effects of coronary vascular resistance, MVo2, and myocardial (coronary venous) Po2 on coronary autoregulation. A major finding was that lowering heart rate from 120 to 40 bpm attenuated coronary autoregulation when perfusion pressure was reduced from 120 to 80 mm Hg (Figure 2, Tables 1 and 2). In contrast to effects of bradycardia, coronary constriction resulting from vasopressin or indomethacin infusion augmented the autoregulatory response to pressure reduction (Tables 3 and 4). Since both metabolic and pharmacologic interventions produced comparable increases in baseline resistance but had qualitatively opposite effects on autoregulation, we conclude that changes in resistance cannot explain the attenuation of autoregulation during bradycardia.

In each of the animals studied, there was a strong inverse relationship between initial coronary venous Po2 and the degree of coronary autoregulation (Arl) over the pressure range of 120–80 mm Hg. However, there was only a very weak association between MVo2 and Arl (Figure 3). Such data suggest that the critical metabolic determinant of coronary autoregulation is myocardial Po2 and not MVo2. To further test the hypothesis that coronary autoregulation is coupled to myocardial Po2 rather than MVo2, we compared autoregulatory responses at a control heart rate of 120 bpm and at 40 bpm before and after restoring venous Po2 with vasopressin to control values. At comparable levels of venous Po2, Arl between 120 and 80 mm Hg was the same at both heart rates, despite significant differences in MVo2, evidence that autoregulation is coupled to Po2.

Additional evidence supporting a role for oxygen in coronary autoregulation is provided by the experiments examining effects of myocardial metabolic demands and of coronary vasoconstriction with vasopressin on coronary pressure–flow relations over a wide range of pressures. An important finding was that at each level of initial pressure between 160 and 100 mm Hg, there was a strong inverse relationship between the degree of autoregulation and coronary venous Po2 (Figure 6). Indeed, most of the variation in Arl associated with lowering heart rate or vasopressin mediated coronary constriction (Figure 5) could be explained by differences in the prevailing venous Po2. The data indicate a threshold venous Po2 for autoregulation of 30–34 mm Hg.

Interestingly, bradycardia and vasopressin mediated constriction had little effect on corrected Arl for pressure reduction below 80 mm Hg. While this could be interpreted to mean that oxygen is not important for autoregulation at low pressures, it is also possible that the effects of Po2 are maximum at low flow rates. Values for coronary venous Po2 at pressures between 80 and 40 mm Hg were well below the threshold Po2 for autoregulation.

Correlations of Arl with coronary venous PCO2 (R2 = 0.66) or pH (R2 = 0.23) were not as strong as correlations with coronary venous Po2 (R2 = 0.86, p < 0.001). A number of studies have shown that arterial hypercapnia results in coronary vasodilation independent of changes in MVo2. However, the sensitivity of coronary resistance to changes in venous PCO2...
Coronary Venous PCO₂ (mmHg) vs. Corrected Autoregulation Index

**Figure 6.** Corrected autoregulation index for 20 mm Hg change in pressure as a function of venous PO₂ for each initial pressure Pᵢ. Symbols represent individual data points at heart rate (HR) 120 bpm (○), 40 bpm (△), and 120 bpm during vasopressin (VPN) infusion (□). The slope (S) and multiple R² for each regression are indicated at the bottom of the graphs. All slopes differed significantly from zero (p < 0.01). For each initial pressure between 160 and 100 mm Hg, the venous PO₂ at which Arl = 0 (threshold PO₂ for autoregulation) did not differ significantly, averaging 32 mm Hg (range 30–34 mm Hg).

Quantitation of Autoregulation

The autoregulation index (Arl) used in this study is the same as that employed by Norris et al. The index compares the observed change in vascular conductance between two pressures to the calculated change in conductance assuming that flow remained constant. Based on this definition, autoregulation in response to a decrease in perfusion pressure occurs when conductance at the lower pressure is increased (or resistance decreased) compared to initial values. Such an approach to quantitating autoregulation differs from using the shape or slope of the pressure-flow curve. Differences between slopes of two pressure-flow seg-

is only about half of that found for PO₂ under constant flow conditions. The coronary vasodilator potency of CO₂ may be even less during free flow conditions. In the present study, although coronary venous PCO₂ tended to increase when perfusion pressure was reduced from 120 to 80 mm Hg, the change of less than 2 mm Hg was not statistically significant and would be of insufficient magnitude to explain the observed decrease in resistance. Furthermore, a recent preliminary report indicated that the myocardial volume of distribution for CO₂ is considerably larger than for O₂. Following a 50% step decrease in coronary flow, coronary venous PO₂ reached 90% of its change in 13 seconds compared to 58 seconds for venous PCO₂. This means that changes in tissue CO₂ are probably too slow to explain the rapid changes in vascular resistance which occur during coronary autoregulation (Figure 2).
ments may not always indicate different degrees of autoregulation depending on initial pressure and flow (Figure 1). Also, a parallel shift in a pressure–flow relationship may not necessarily indicate that autoregulation is unchanged. This is because the slope of a pressure–flow curve is influenced not only by autoregulation but also by initial vasomotor tone. For example, in a markedly constricted vascular bed, the slope of a pressure–flow segment may be the same or less than that of a more vasodilated bed; however, the degree of autoregulation could be less if there is relatively little or no change in initial conductance or resistance.

Some of our studies used the cannulated left anterior descending coronary artery. The development of intrarterial pressure gradients could have resulted in collateral flow into or out of the region perfused by the left anterior descending artery. It is unlikely, however, that collateral flow significantly influenced the experimental results. The minimum intrarterial pressure gradient at which collateral flow can be detected with radiolabelled microspheres in the presence of forward flow is 60–85 mm Hg. In the present study we did not observe pressure gradients of this magnitude in left anterior descending artery preparations in which coronary pressure was varied between 120 and 80 mm Hg (Tables 1–5). In the 10 animals used to examine coronary pressure–flow relations over the range of 160–40 mm Hg, intrarterial pressure gradients exceeding 60 mm Hg did occur at a coronary pressure of 160 mm Hg in the 4 left anterior descending artery preparations. However, in this and other protocols, the effects of pressure on coronary hemodynamic and metabolic parameters did not differ significantly between the left anterior descending and left main coronary artery preparations for a given experimental intervention.

One problem in attempting to quantitate coronary autoregulation is that decreasing coronary perfusion pressure and flow may result in a small reduction in MVo2 even in the absence of myocardial ischemia (Gregg phenomenon18, 39). Accordingly, any pressure-induced change in coronary flow would be influenced not only by the degree of autoregulation but also by the change in MVo2. To account for the effects of MVo2 on autoregulation, data were also analyzed after adjusting coronary flow values for pressure and flow related changes in MVo2. The adjusted flow values were used to calculate a corrected autoregulation index which assumes constant MVo2. However, caution must be used in interpreting the corrected autoregulation index at low pressures, because changes in MVo2 could be due, in part, to myocardial ischemia.

Another potential problem in interpreting the experimental results is that heart rate, in addition to altering MVo2, also affects the extravascular component of coronary vascular resistance which could influence autoregulation. However, when steady state diastolic flow (200 to 300 msec after the aortic dicrotic notch) was used instead of mean flow to calculate the autoregulation index, the effects of lowering heart rate and of pharmacological vasoconstriction on the diastolic ArI were qualitatively similar to results obtained using mean flow values. Thus, lowering heart rate significantly reduced diastolic ArI, and pharmacologic coronary vasoconstriction increased diastolic ArI. Furthermore, there was a strong inverse correlation between diastolic ArI and coronary venous Po2 (R² = 0.94) over the pressure range of 120–80 mm Hg.

Although the autoregulation index provides a useful means of quantitating autoregulation, our major conclusions regarding the effects of oxygen on coronary autoregulation do not depend solely on this index. First, the dynamic flow response to a sudden reduction in pressure was dependent on the prevailing venous Po2. Thus, bradycardia which increased venous Po2 attenuated the flow response to an abrupt decrease in pressure as evidenced by a slower rate of rise in flow (Figure 2) whereas vasopressin or indomethacin which decreased venous Po2 resulted in a more rapid flow adjustment. Second, the absolute change in mean (and diastolic) coronary flow between pressures of 120 and 80 mm Hg during steady state conditions was greatest during bradycardia and high venous Po2 and least during pharmacological vasoconstriction and low venous Po2 (Tables 1–5). Finally, the shape of the pressure–flow curve was altered by the experimental interventions, the slope being steeper at high venous Po2 and flatter at low venous Po2 (Figure 5).

Consideration of Previous Studies

Schubert et al13 measured tissue Po2 with an oxygen microelectrode at two levels of perfusion pressure in the autoregulating isolated saline perfused cat heart. Decreasing coronary artery pressure from 113 to 78 mm Hg did not cause a statistically significant change in average tissue oxygen tension in those hearts which autoregulated. However, there were more locally hypoxic areas (tissue Po2 < 5 mm Hg) at the lower perfusion pressure. These results were interpreted as being consistent with a common microvascular control mechanism which operates to achieve oxygen mass balance with locally hypoxic areas of the myocardium acting as a feedback signal for microvascular adjustments. Although these data would seem to rule out average tissue Po2 as a mediator for coronary autoregulation, as Belloni has pointed out, extrapolation to the in situ blood-perfused heart is limited by use of a high Po2-low oxygen content saline perfusate.

Recently, Drake-Holland et al40 examined pressure–flow relationships over the autoregulatory range at ventricular rates between 60 and 180 bpm. Reducing coronary perfusion pressure resulted in a decrease in coronary vascular resistance that was accompanied by a widening of the arteriovenous oxygen difference and a slight reduction in MVo2. Although the investigators state that heart rate shifted the entire pressure–flow curve in a nearly parallel fashion, close inspection of the curves (Figure 2 of that study) suggests that the slopes between 150 and 60 mm Hg may be greater at the lower heart rates (60–100 bpm) compared to the higher heart rates (140 and 180 bpm). Calculation of the autoregulation index between 120 and 80 mm Hg
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in that study indicates a progressive decrease from a value of 0.75 at the heart rate of 180 bpm to 0.31 at the heart rate of 60 bpm. Increasing heart rate resulted in metabolic vasodilation and was accompanied by a slight increase in arteriovenous oxygen difference and presumably a decrease in venous PO₂. The investigators demonstrate a direct relation between coronary vascular resistance and venous oxygen content or tension. Such a relation has been previously demonstrated by Berne et al for coronary sinus oxygen contents below 5.5 ml/100 ml. These observations are consistent with those in the present study and suggest that coronary autoregulation is closely coupled to myocardial PO₂.

Implications Regarding Local Regulation of Myocardial Oxygenation

Based on the metabolic theory, myocardial metabolism provides a local feedback mechanism for maintaining tissue oxygenation following changes in oxygen supply or demand. Accordingly, vascular resistance (flow) and capillary exchange capacity (oxygen extraction) are modulated by changes in tissue PO₂ directly or through release of one or more vasoactive metabolites. The finding in the present study that autoregulation is closely coupled to venous PO₂ during changes in metabolic demands or oxygen delivery is consistent with such a metabolic mechanism. When venous PO₂ was relatively high (≥ 32 mm Hg) pressure-induced changes in flow resulted in increases in oxygen extraction with little or no flow autoregulation. In contrast, as venous PO₂ was lowered below 32 mm Hg, the degree of flow autoregulation increased and the relative change in oxygen extraction decreased in response to reduction in perfusion pressure. The relative sensitivity of coronary resistance as well as exchange vessels to pressure-induced changes in flow would appear to depend on the prevailing venous PO₂ (Figure 7). At high PO₂, myocardial oxygenation is regulated mainly by capillary exchange vessels, whereas at lower PO₂ the contribution of resistance vessels becomes more important. This observed influence of venous PO₂ on the relative contribution of resistance and exchange vessels to myocardial oxygenation is quite similar to that reported for skeletal muscle and intestine.

In the resting skeletal muscle, the degree of flow autoregulation (venous PO₂ ≥ 40 mm Hg) was found to be minimal. However, when venous PO₂ was lowered during muscle contraction, catecholamine-induced vasoconstriction, or mild hypoxia, the degree of flow autoregulation following pressure reduction was significantly augmented. More recently, Sullivan and Johnson measured arteriolar diameter and red blood cell velocity in individual microvessels of cat sartorius muscle when ambient oxygen tension and perfusion pressure were altered. Elevating ambient PO₂ reduced or abolished autoregulation in all orders of arterioles, consistent with the hypothesis that changes in tissue oxygen tension are responsible for autoregulation in skeletal muscle. A similar effect of ambient PO₂ on autoregulation has been reported in the cerebral circulation for cat pial vessels.

The myogenic hypothesis proposes that vascular resistance is proportional to transmural pressure presumably due to the effects of stretch on vascular smooth muscle. While our data for coronary autoregulation are consistent with a metabolic mechanism, they do not exclude a potential role for myogenic factors in autoregulation. However, the observation that metabolic and pharmacologic vasoconstriction have qualitatively opposite effects on coronary flow autoregulation is difficult to explain based on a myogenic mechanism unless myogenic induced vasodilation is facilitated at low venous PO₂ independent of the initial vascular resistance. Studies in intestine indicate that arterial hypoxia attenuates or has no effect on myogenic responses elicited by elevating venous pressure. Although studies on the effects of metabolic rate on myogenic responses in the intestine are conflicting, a systematic study in skeletal muscle demonstrated that myogenic responses of resistance vessels were abolished when the resting muscle was stimulated to contract.

Recently, Khayyal et al reported that pharmacologic coronary vasoconstriction with high-dose vasopressin that resulted in myocardial ischemia augmented coronary autoregulation. The investigators interpret the demonstration of autoregulation as well as reactive hyperemia in the presence of myocardial ischemia as evidence supporting a myogenic mechanism. An alternative explanation is that vasopressin reduced myocardial PO₂ and that subsequent reduction in coronary pressure and flow resulted in enhanced metabolic vasodilation.

**Figure 7.** Effects of initial venous PO₂ on coronary responses to decreasing perfusion pressure from 120 to 80 mm Hg. Symbols are mean values ± SE (n = 14) at heart rate (HR) 120 bpm (○), 60 bpm (△), and 120 bpm during intracoronary vasopressin (VPN) or indomethacin (IND) (□). The relative contributions (%) of flow and O₂ extraction to myocardial oxygenation during reduction in coronary perfusion pressure were dependent on the prevailing coronary venous PO₂.
In summary: The results of the present study indicate that coronary autoregulation is closely coupled to the prevailing coronary venous Po2 and is facilitated at low Po2 within the physiologic range. The findings are consistent with a metabolic mechanism for coronary autoregulation in which myocardial oxygen tension directly or through release of vasoactive metabolites results in coronary vasodilation when perfusion pressure is reduced.

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References


**Key Words** • coronary autoregulation • myocardial oxygen tension • myocardial oxygen consumption • perfusion pressure • coronary hemodynamics • coronary metabolic responses
Myocardial oxygen tension determines the degree and pressure range of coronary autoregulation.

W P Dole and D W Nuno

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