Tissue Acidosis
Role in Sustained Arteriolar Dilatation Distal to a Coronary Stenosis

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This study tested the hypothesis that myocardial tissue acidosis is responsible for maintenance of reduced arteriolar tone distal to a severe coronary arterial stenosis. Domestic swine (n=10) were instrumented with a coronary arterial stenosis that reduced vessel diameter 80%. Measurements of hemodynamic indexes were made 1) before stenosis, 2) at 5, 20, and 60 minutes after stenosis placement, and 3) after each of three, 20-minute NaOH infusions (0.05 M, 0.1 M, and 0.5 M) distal to the stenosis (group 1). Intracellular pH at the end of 30 minutes of 0.5 M NaOH infusion distal to the stenosis was measured in a second group (n=6) of swine (group 2). After stenosis placement in group 1, endocardial blood flow declined significantly, and evidence of regional acidosis (increased coronary venous PCO₂ and decreased coronary venous pH) and ischemia (lactate production) developed. One hour later, evidence of acidosis persisted, though to a lesser extent. Myocardial oxygen and lactate metabolism exhibited similar patterns. Infusion of 0.5 M NaOH (0.38 ml/min) reduced (p<0.01) distal zone epicardial blood flow but did not change endocardial flow. Regional myocardial oxygen extraction (75±8%, mean±SD) and consumption (8.2±2.3 ml/min/100 g) also declined significantly (p<0.01) in response to 0.5 M NaOH infusion compared with 60 minutes after stenosis (86±4 and 12.4±2.8 ml/min/100 g respectively). The pH of coronary venous blood (7.41±0.05) was elevated (p<0.01) by 0.5 M NaOH above prestenosis (7.36±0.03) and 60-minute poststenosis levels (7.33±0.04). Measurement of intracellular pH (¹⁴C-DMO³H-inulin technique) in group 2 animals showed that distal zone pH (7.00±0.11) after 0.5 M NaOH infusion was at a level similar to that in normal myocardium in a nonstenosed region of the heart. Thus, because endocardial blood flow was unchanged during 0.5 M NaOH infusion, even though pH of coronary venous blood reached systemic levels and intracellular pH increased significantly, tissue acidosis is probably not required for maintenance of arteriolar dilation distal to a severe coronary arterial stenosis. The data support the hypothesis that tissue acidosis capable of mediating acute changes in coronary arteriolar tone does not have a major role in the long-term maintenance of reduced vascular tone distal to a coronary arterial stenosis. (Circulation 1989;79:890–898)

For some time, acute changes in arterial blood pH and PCO₂ have been known to influence coronary arteriolar tone and myocardial blood flow.¹–¹⁵ The results of several recent studies, however, indicate that mediators of acute changes in coronary arteriolar tone may not have an important role in more long-term adjustments of the coronary circulation to sustained changes in either myocardial oxygen supply or demand.¹⁶–¹⁸ Thus, coronary vasodilation is maintained during sustained isoproterenol infusion even though adenosine release by the myocardium peaks rapidly during the initial phase of the infusion and then returns to control levels.¹⁶ In addition, adenosine deaminase inhibits, in part, the initial flow increase observed in response to isoproterenol but has no effect on the sustained flow response to the drug.¹⁷ The concentration of potassium ion also has increased in coronary venous blood in response to vasodilation stimuli (e.g., pacing and ischemia) and then returned to control levels even though coronary vasodilation persists.¹⁸ Whether or not similar changes occur in coronary venous pH and PCO₂

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Supported in part by Grant HL-29951 from the National Heart, Lung, and Blood Institute. H.G. is an Established Investigator of the American Heart Association.

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Received July 25, 1988; revision accepted November 22, 1988.
after imposing a severe coronary arterial stenosis is unknown. The purpose of this investigation, therefore, was to test the hypothesis that 1) acute changes in acid-base and aerobic metabolism after imposing a severe coronary arterial stenosis may revert toward baseline (i.e., prestenosis) levels over time despite constant regional myocardial blood flow and external determinants of myocardial oxygen demand and 2) tissue acidosis does not have an essential role in the long-term maintenance of arteriolar dilation distal to the stenosis. Experiments were performed in closed-chest, sedated domestic swine instrumented with a severe coronary arterial stenosis.17,19-21

**Methods**

**Animal Preparation**

Farm-bred domestic swine (n = 10; mean weight, 42 kg; range, 37–49 kg) were premedicated with ketamine (25 mg/kg i.m.) and sodium thiamylol (total dose, 0.5–1.0 g i.v.), intubated, and anesthetized with halothane (0.5–1.5%) and nitrous oxide (60:40 mixture with oxygen). The animals were ventilated with a volume-cycled respirator through which supplemental oxygen was delivered at 2–3 l/min mixed with room air and anesthetic gases. Arterial blood gases were monitored frequently and were maintained at appropriate levels (pH 7.38–7.45, PCO2 at 35–45 mm Hg, and PO2 at 100–125 mm Hg) throughout each study. After induction of anesthesia, each animal was anticoagulated with heparin (225 IU/kg i.v.). Full anticoagulation was maintained by administering approximately half the initial loading dose every 2–3 hours.

The animal was instrumented for the study as follows. A 7F catheter was advanced under fluoroscopic control into the left atrium. This catheter was used for administering radioactive microspheres for measurements of regional myocardial blood flow. Another 8F catheter was positioned in the aorta to monitor arterial blood gases and for reference withdrawal for microsphere determinations of regional myocardial blood flow. A pigtail catheter was placed at the apex of the left ventricle to monitor pressure. The femoral veins were cannulated bilaterally to administer fluids and medications during the study. Another 7F catheter was positioned in the midportion of the anterior interventricular vein (AIV). Next, a 7F pacing catheter was placed in the coronary sinus to maintain the animal’s heart rate at 135–140 beats/min throughout the study.

Before placement of the coronary arterial stenosis (see below), halothane and nitrous oxide were discontinued, and the animal was permitted to awaken sufficiently to breathe spontaneously and exhibit modest tremulousness. A constant intravenous infusion of sodium thiamylol was begun at 1–13 mg/min to maintain sedation and to ensure the animal was free of pain. Once the animal had stabilized for approximately 20 minutes, the experimental protocol was begun.

**Experimental Protocol**

A period of hemodynamic and arterial blood gas stability was documented by obtaining measurements of arterial and AIV blood gases with recordings of hemodynamic indexes (i.e., heart rate and arterial and left ventricular pressures) every 5 minutes for 15–20 minutes. After showing that three successive measurements of arterial and AIV pH differed by less than 0.1–0.2% (arterial vs. arterial, AIV vs. AIV), initial measurements of all experimental variables were obtained, which included hemodynamic output, regional myocardial blood flow (microspheres), arterial and AIV blood gases, and pH, lactate, and oxygen content of arterial and AIV blood.

Next, a rigid plastic stenosis that reduced vessel diameter by 80% was inserted within the lumen of the animal’s left anterior descending coronary artery as previously described.17,19-21 Experimental variables were measured again at 5, 20, and 60 minutes after stenosis placement. After completion of measurements at the 60-minute point, an intracoronary infusion of 0.05 M NaOH distal to the stenosis was begun at a rate of 0.38 ml/min. The infusion was continued for 20 minutes, and at the end of this period, all experimental variables were measured again. Arterial and AIV pH and blood gases and hemodynamic measurements also were obtained 10 minutes after beginning NaOH infusion. Once data acquisition at the 20-minute point had been completed, another 20-minute infusion was begun at 0.38 ml/min but with 0.1 M NaOH. Again, arterial and AIV pH and blood gases and all other experimental variables were measured at the midway point and at the end of the infusion. After this, the sequence was repeated again but with an infusion of 0.5 M NaOH.

Once the final set of measurements had been obtained, myocardium distal to the stenosis was marked by injection of radiolabeled microspheres through the coronary infusion catheter attached to the stenosis.17,19-21 Afterward, the animal was given a large intravenous dose of sodium thiamylol and killed 5 minutes later by intravenous injection of potassium chloride. Next, the chest was opened, and the location of the distal end of the AIV catheter was diagrammed in relation to the position of the stenosis in the left anterior descending coronary artery. The stenosis-catheter system was removed from the left anterior descending coronary artery, and the vessel itself was inspected for evidence of gross intimal damage. Afterward, the heart was rinsed thoroughly in tap water, refrigerated in buffered saline, and sectioned for determination of microsphere activity (see below).
Regional Myocardial Blood Flow

For each experimental condition, approximately 4×10⁸ radiolabeled microspheres (15-μm diameter, 85–105 μCi total radioactivity) were injected into the left atrial catheter to determine regional myocardial blood flow.²² Seven determinations of flow were made in each animal. A different radioisotope was chosen at random from a collection of eight radiolabels (¹ⁱ⁷Co, ⁶⁵Cr, ⁶⁰⁵Sn, ⁸⁶⁵Rb, ²⁶⁷Sc, ⁹⁵⁶Nb, ¹ⁱ⁴²In, and ¹⁵³⁵Gd) for each flow determination. A more detailed description of microsphere methodology used in our laboratory has been published.¹⁹

Coronary arteriolar resistance in endocardium distal to the stenosis was calculated by dividing distal coronary mean diastolic pressure minus mean left arterial pressure plus 7 mm Hg²³ by distal zone endocardial blood flow. Distal zone epicardial and transmural resistances were calculated in the same fashion except that distal coronary mean pressure and distal zone epicardial and transmural flows, respectively, were used in the computation. Resistances in the circumflex zone were calculated with aortic instead of distal coronary pressure.

Regional Myocardial Oxygen Metabolism

Paired samples (2–3 ml) of arterial and AIV blood were obtained for determining oxygen content (Lex-O₂, CON Instrument, Lexington Instruments, Waltham, Massachusetts) during each phase of the study. Oxygen content (vol%) was determined in duplicate for each sample, and values were accepted only when the difference between them was 0.2 ml O₂/dl or less. Regional myocardial oxygen consumption (ml/min/100 g) was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial and AIV oxygen difference.

Regional Myocardial Lactate Metabolism

Lactate concentration in arterial and AIV blood was determined by a spectrophotometric method with commercially available kits (Calbiochem Rapid Lactate Reagents, Calbiochem-Behring, La Jolla, California). Samples of blood (5 ml) were immediately deproteinized by placing them in cold perchloric acid (8% vol/vol). The samples were centrifuged, and the supernatant was frozen for subsequent analysis in duplicate. Regional lactate consumption was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial and AIV lactate difference.

Regional Myocardial Acid and Base Metabolism and Intracellular pH Study

A Corning blood gas machine (Corning, New York) was used to measure pH, Po₂ and Pco₂ in arterial and AIV blood. Blood samples were obtained simultaneously (artery and AIV) under anaerobic conditions, immediately placed on ice, and then analyzed as rapidly as possible (within 10–20 minutes).

Calculation of pH and Pco₂ in left anterior descending coronary artery blood. The extent to which NaOH infusion altered the pH and Pco₂ of arterial blood in the left anterior descending coronary artery distal to the stenosis was determined in three separate in vitro studies. Known quantities of NaOH were added to arterial blood under anaerobic conditions, and resulting pH and Pco₂ were measured. Next, pH (or Pco₂) was plotted as a function of micromoles of NaOH added per liter of blood. The data from each in vitro study were fit to a second-order polynomial with a commercially available computer program (Sigmaplot, Jandel Scientific, Sausalito, California). The coefficients for the first- and second-order terms were very similar for each curve and so were averaged to provide a general model for predicting arterial pH (or Pco₂) based on micromoles of NaOH added per liter of arterial blood.

The models used were as follows:

\[ \text{pHe} = p\text{Ho} + 2.2 \times 10^{-2}(\text{NaOH}_a) + 3.0 \times 10^{-4}(\text{NaOH}_a) \]  

\[ \text{Pco}_2 = \text{Pco}_2o - 1.3(\text{NaOH}_a) + 1.4 \times 10^{-3}(\text{NaOH}_a) \]  

where pH is corrected pH; pHo is measured pH; Pco₂ is corrected Pco₂; Pco₂o is measured Pco₂; and NaOHₐ is final, added NaOH concentration in arterial blood.

Because concentration of NaOH in the syringe and its infusion rate were known and because transmural blood flow distal to the stenosis was measured, it was possible to estimate micromoles of NaOH added per liter of arterial blood perfusing myocardial distal to the stenosis.

Measurements of intracellular pH. A separate group of six domestic swine was studied to measure the effect of intracoronary NaOH (0.5 M) infusion on myocardial intracellular pH. Intracellular pH was measured by a modification of the ¹⁴C-5,5-dimethyl-2,4-oxazolidinedione (DMO)/³H water method of Scholerb and Grantham²⁴ and was calculated as follows:

\[ \text{pHi} = pK' + \log_{10}[(A - B)/B] \]  

where pHi is intracellular pH; pK' is DMO dissociation constant, temperature corrected; A is [¹⁴C-DMOtotal – ¹⁴C-DMOecf]/(H₂Ototal – H₂Oecf); and B is [¹⁴C-DMOecf]/[10^(pHecf+pK') + 1].

Note: 1) measured concentration of ¹⁴C-DMO and ³H-inulin in coronary venous plasma was used to approximate extracellular space (ecf) concentration; 2) pHecf is measured coronary venous pH; 3) H₂Ototal is tissue wet weight – tissue dry weight; 4) H₂Oecf is ³H-inulin in coronary venous plasma; and 5) ¹⁴C-DMOecf is (¹⁴C-DMOecf*H₂Oecf). The protocol used was as follows:

First, the animal was anesthetized with halothane and nitrous oxide and then instrumented for the study as described above. Before stenosis place-
ment, paired samples of arterial and AIV blood were obtained for pH, blood gas, and background liquid scintillation counting measurements. Next, the artificial stenosis (80% lumenal diameter reduction) was positioned in the animal's left anterior descending coronary. Five minutes after stenosis placement, repeat arterial and AIV blood samples were obtained for blood gas and pH measurements, and hemodynamic indexes were recorded. Next, 75 μCi of 14C-DMO and 50 μCi 3H-inulin were injected intravenously. An intracoronary infusion (0.38 ml/min) of 0.5 M NaOH distal to the stenosis was begun immediately after isotope injection. The infusion was continued for 30 minutes to allow time for tracer equilibration.25 Hemodynamic indexes were monitored continuously and remained stable during the infusion period. At the end of 30 minutes, repeat samples of arterial and AIV blood were obtained for measurements of all experimental variables. Next, the chest was opened, and the heart was exposed to obtain a transmural biopsy (about 1.5×2.5 cm) of myocardium distal to the stenosis.

Myocardial tissue was immediately blotted dry, cut into four layers (from endocardium to epicardium) each weighing 0.1–0.2 g, placed in preweighed vials, reweighed, and processed for liquid scintillation counting. Tissue processing included decolorization (30% H2O2), digestion (0.6N NCS, Amersham, Arlington Heights, Illinois), and pH adjustment followed by temperature and dark adaptation before counting.

To calculate intracellular pH in myocardium distal to the stenosis (distal zone) certain assumptions were used. First, because interstitial fluid pH and tracer concentration could not be measured directly, we used AIV plasma pH and tracer activities in the calculation of distal zone intracellular pH. Others have used the same assumption in conjunction with this method.26 Second, in preliminary studies involving overnight drying of tissue samples \( n = 181 \) at 50°C the dry:wet weight ratio was determined to be 0.23±0.01 (mean±SD). Accordingly, in all but one experiment of the present series, an assumed dry:wet weight ratio of 0.23 was used in calculating intracellular pH. The weighted mean value of intracellular pH for each tissue sample in the distal zone was used to compute an average transmural value of intracellular pH for the entire zone.

**Statistical Methods**

The significance of differences in group mean values was assessed by blocked, one-way analysis of variance and Newman-Keuls or Dunnett's test.26 Results were considered statistically significant at a \( p \) value less than 0.05. All values are expressed as mean±SD.

**Results**

**Hemodynamics**

In comparison with prestenosis levels, no changes occurred in heart rate, mean aortic pressure, mean left atrial pressure, or tension time index during the 1st hour after stenosis insertion (Table 1). Mean pressure distal to the stenosis exhibited a modest but statistically significant \( (p<0.05) \) increase at 20 and 60 minutes after stenosis placement compared with values observed 5 minutes after stenosis insertion.

Intracoronary infusion of NaOH at 0.05 and 0.1 M doses was not associated with significant changes (vs. 60 minutes after stenosis) in any hemodynamic index. In contrast, infusion of 0.5 M NaOH resulted in modest but statistically significant changes in heart rate (increase 2%, as a result of a slight increase in sinus rate above the paced rate, \( p<0.05 \) vs. 60 minutes after stenosis), tension time index (decrease 10%, \( p<0.01 \) vs. 60 minutes), and aortic mean pressure (decrease 6%, \( p<0.05 \) vs. 60 minutes after stenosis).

**Regional Myocardial Blood Flow**

Before stenosis insertion, flows were similar in respective layers of the distal and circumflex zones (1.62±0.56, 1.28±0.49, and 1.48±0.53 ml/min/g; endocardium, epicardium, and transmural, respectively). Circumflex zone flows did not change compared with control flows at any time during the study. Five minutes after placement of the stenosis, there was a significant reduction \( (p<0.01) \) in distal zone endocardial and transmural flows compared

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<th>Table 1. Hemodynamics Indexes</th>
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<td>Heart rate (min)</td>
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<td>LAD mean pressure (mm Hg)</td>
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<td>LA mean pressure (mm Hg)</td>
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<td>Tension time index (mm Hg*sec)</td>
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LAD, left anterior descending coronary artery; LA, left atrium.

* \( p<0.05 \) vs. 60 minutes poststenosis; † \( p<0.05 \) vs. 5 minutes poststenosis; ‡ \( p<0.01 \) vs. 60 minutes poststenosis.
with control levels (Figure 1). In contrast, epicardial flow in the distal zone did not change significantly when comparing control values with values during the 1st hour after stenosis placement. Both endocardial and transmural flow distal to the stenosis increased between 5 and 60 minutes after stenosis. The changes, however, were not statistically significant.

Endocardial flow distal to the stenosis did not change when comparing the 60-minute poststenosis level with levels during or after NaOH infusion at any dose. Distal zone epicardial blood flow also did not change when comparing the 60-minute poststenosis value with the levels in response to either 0.05 or 0.10 M NaOH infusion. In contrast, infusion of 0.5 M NaOH distal to the stenosis resulted in a significant reduction (p<0.01) in epicardial flow compared with the 60-minute poststenosis value.

**Coronary Vascular Resistance**

Distal zone endocardial resistance declines significantly (p<0.01) when comparing prestenosis levels with 5-minute poststenosis levels, and after 5 minutes, resistance was unchanged for the remainder of the study. NaOH infusion did not change endocardial resistance either 5 or 60 minutes after stenosis at any dose level.

Epicardial resistance in the distal zone also declined significantly (p<0.01) when comparing prestenosis values with 5-minute poststenosis values, and after 5 minutes, resistance was unchanged for the remainder of the 60-minute observation period. Infusion of 0.05 and 0.1 M NaOH doses failed to cause any change compared with 60-minute poststenosis levels in epicardial resistance. However, epicardial resistance did increase significantly (p<0.05) when comparing the 60-minute poststenosis value to the value at 0.5 M NaOH. Finally, circumflex zone resistance in each myocardial layer remained constant when comparing respective prestenosis levels (endocardium, 78±38; epicardium, 103±45; transmural, 88±40 mm Hg/ml/min/g); for the entire study.

**Regional Myocardial Acid-Base Balance**

Arterial and AIV oxygen tension remained unchanged when comparing prestenosis values (113±20 and 19±3 mm Hg, respectively) with 60-minute poststenosis values. Similarly, arterial CO₂ tension remained constant when comparing prestenosis levels (43±4 mm Hg) with the 60-minute poststenosis levels. In contrast, AIV CO₂ tension increased significantly (p<0.05) when comparing the prestenosis levels with the 5-minute poststenosis values (Figure 2). During the next 55 minutes, CO₂ tension in AIV blood returned to values that did not differ significantly from prestenosis values. The pH of arterial blood did not differ significantly when comparing prestenosis levels (7.43±0.02) with poststenosis levels throughout the entire study. In contrast, the pH of AIV blood was reduced significantly when comparing prestenosis values to poststenosis values at 5 (p<0.01), 20 (p<0.01), and 60 (p<0.05) minutes (Figure 2).

There was no change when comparing the 60-minute poststenosis values in arterial oxygen and in CO₂ tension (117±17 and 42±4 mm Hg, respectively) during NaOH infusion. AIV blood gas tension and pH were unchanged by 0.05 M NaOH compared with respective levels 60 minutes after stenosis. Similar results were obtained in response to 0.1 M NaOH infusion (Figure 2).
Infusion of 0.5 M NaOH significantly \((p<0.01)\) reduced CO\(_2\) tension measured in the AIV (Figure 2) and calculated for left anterior descending coronary artery blood (41 ± 4 to 35 ± 4 mm Hg). In addition, the pH (and Po\(_2\)) of AIV blood increased significantly compared with 60 minutes after stenosis (Figure 2) as did calculated pH of left anterior descending coronary artery blood (7.42 ± 0.03 to 7.54 ± 0.08).

**Intracellular pH Measurements**

After 30 minutes of intracoronary infusion of 0.5 M NaOH distal to the stenosis, the average value of distal zone intracellular pH (transmural) was 7.00 ± 0.11. The value is within the range of baseline levels for normal myocardium as determined both by the DMO method\(^\text{25}\) and by phosphorus nuclear magnetic resonance.\(^\text{27}\) Also of note, the value of distal zone interstitial fluid volume determined with \(^3\)H-inulin (0.238 ± 0.044 ml/g left ventricle) agreed very closely with the value of this constant (0.217) determined by other methods.\(^\text{28}\)

**Regional Myocardial Oxygen Metabolism**

Compared with prestenosis levels, no significant change occurred in arterial (13.4 ± 1.5 ml/dl) or AIV (2.2 ± 0.6 ml/dl) oxygen content during the 1st hour after stenosis placement. Regional myocardial oxygen extraction distal to the stenosis also remained unchanged during the 1st hour after stenosis placement compared with prestenosis levels (84 ± 5%). In contrast, regional myocardial oxygen consumption declined significantly \((p<0.01)\) when comparing prestenosis levels with levels 5 minutes after place-

**Regional Myocardial Lactate Metabolism**

Arterial lactate levels remained unchanged for the duration of the study compared with prestenosis levels (0.75 ± 0.23 mM). AIV lactate concentration increased significantly \((p<0.01)\) 5 minutes after place-

**Figure 2.** Bar graphs of anterior interventricular vein (AIV) \(\text{PCO}_2\) and AIV pH changes during the study. Note at 5 minutes, \(\text{PCO}_2\) is elevated and pH is reduced compared with prestenosis levels. NaOH infusion (0.5 M) elevated AIV pH to systemic levels and caused a modest reduction in AIV \(\text{PCO}_2\). *\(p<0.05\) vs. PRE; **\(p<0.01\) vs. PRE; ###\(p<0.01\) vs. 60 minutes.

**Figure 3.** Bar graphs of regional myocardial oxygen consumption (M\(\text{VO}_2\)) and lactate consumption and production. Immediately after stenosis placement, there was evidence of 1) reduced M\(\text{VO}_2\) that remained unchanged during the 1st hour of the study and 2) substantial lactate production that declined over time and was not changed by NaOH infusion. *\(p<0.05\) vs. PRE; **\(p<0.01\) vs. PRE; ###\(p<0.01\) vs. 60 minutes; #\(p<0.05\) vs. 5 minutes.
stentosis placement (1.43 ± 0.76) compared with pre-
stentosis concentrations (0.40 ± 0.10). Similarly, lac-
tate consumption occurring before stenosis changed
to production 5 minutes after stenosis insertion
(p < 0.01) (Figure 3). During the next 55 minutes,
both AIV lactate concentration (0.85 ± 0.24 at 60
minutes) and myocardial lactate production declined
significantly compared with respective levels at 5
minutes after stenosis. Infusion of NaOH at each
dose level produced no significant change compared
with 60 minutes after stenosis either in AIV lactate
concentration or myocardial lactate production.

Discussion

The role of pH and PCO₂ in the regulation of
myocardial blood flow has been considered by
previous investigators.1-15 In addition, a comprehen-
sive review of the subject has been written by
Feigl.29 Important differences between earlier inves-
tigations and the present one should be reviewed,
however, before summarizing the findings of previ-
ous studies. First, all of the published work has
involved experimental models with normal coro-
nary circulation. We are unaware of any data on
this subject specifically pertaining to the stenosed
coronary circulation. Second, previous studies fre-
fently have used open-chest, anesthetized models
often with pump-perfused coronary circulation and
with exposure to extremes of pH or PCO₂ or both.
Accordingly, the results of such experiments may
not be applicable to more intact preparations.29
Third, the focus of earlier studies has been on the
role of pH or PCO₂ or both as acute mediators of
coronary tone. The role, if any, of these factors in
more long-term adjustments of the coronary circu-
lation, particularly in the stenosis setting, has been
given relatively little attention.

Data obtained from earlier studies, nevertheless,
indicate that acutely increasing PCO₂ or lowering pH
of arterial blood perfusing the coronary circulation
or both results in coronary vasodilation.3-5,12 How-
ever, lowering pH or increasing PCO₂ of arterial
blood will produce a rightward shift (Bohr effect) of
the oxygen-hemoglobin dissociation curve. In turn,
a rightward shift of the curve would be expected to
cause coronary vasoconstriction because more oxy-
gen would be released from blood, thereby increas-
ing myocardial oxygen delivery, at any given tissue
oxygen tension.29 The fact that acidosis generally
elicits coronary vasodilation and not vasoconstric-
tion, therefore, underscores the need to perform
experiments to determine the effects of altering
blood pH and PCO₂ on coronary flow regulation.

Alkalizing arterial blood, whether by base in-
suffusion or hyperventilation, would be expected to
cause an acute left shift of the oxygen-hemoglobin
dissociation curve and thereby elicit coronary vaso-
dilation. Although such a result was observed in an
isolated heart-lung model,10 hyperventilation in
dogs1,14 and humans11 caused coronary vasoconstric-
tion. In addition, although alkalization of arterial
blood with sodium bicarbonate caused an increase
in myocardial blood flow in one study,14 heart rate
and tension time index increased substantially and
could have been responsible, at least in part, for
augmentation of myocardial blood flow. Further-
more, because bicarbonate infusion causes intracel-
lular acidosis along with extracellular alkalosis, the
former also may have contributed to the observed
increase in myocardial blood flow. Thus, the results
of previous experiments in this area do not always
conform to theoretical expectations, and additional
work is required, particularly in the realm of tissue
acidosis as a long-term mediator of coronary tone in
the stenosis setting.

The results of this study show that abrupt imposi-
tion of a severe stenosis on the coronary circula-
tion may result in a reduction in endocardial blood
flow with no change or even an increase in epica-
drial flow. The reduction in endocardial blood flow
was accompanied by evidence of tissue acidosis as
manifested by increase in coronary venous PCO₂ and
reduction in coronary venous pH. A decline in
myocardial oxygen consumption and a change from
lactate consumption to lactate production (i.e., me-
tabolic evidence of myocardial ischemia) also was
documented. Both endocardial and epicardial resis-
tance decreased (vs. prestenosis) after insertion of
the stenosis, although the reduction in endocardial
resistance was less than maximal.28,30 Accordingly,
the data are consistent with a role for tissue acidosis
in the acute reduction of arteriolar tone immediately
after stenosis placement.

By observing the animals over time, it was pos-
sible to gain some insight into the potential role of
tissue acidosis as a more long-term mediator of
reduced arteriolar tone distal to a severe coronary
arterial stenosis. As noted earlier, very little infor-
mation is available in this regard. The data obtained
in the present study and an earlier one describing
the natural history of myocardial ischemia in this
animal model31 show that metabolic evidence of
myocardial ischemia and tissue acidosis declines
over the course of an hour but does not resolve fully
(Figures 2 and 3). Between 1 and 3 hours after
stenosis placement in the natural history study,31
there was evidence of additional improvement in
tissue acidosis and reduction in myocardial isch-
emia, although the changes were modest compared
with those that occurred between 5 and 60 minutes
after stenosis. The fact that arteriolar tone distal to
the stenosis remained unchanged over time despite
evidence of a reduction in both tissue acidosis and
metabolic evidence of myocardial ischemia sug-
gests either that tissue acidosis plays only a modest
role in the chronic reduction of arteriolar tone in the
stenosis setting or that once a certain degree of
acidosis is attained, further reductions in arteriolar
tone are not produced even if the acidosis increases.
If the latter hypothesis were correct, a spontaneous
or induced lessening of tissue acidosis would not be
accompanied by an increase in coronary arteriolar
tone unless acidosis were corrected beyond some "critical level."

Information obtained in the second half of this study during which NaOH was infused into the coronary circulation distal to the stenosis is helpful in choosing between the hypotheses outlined above. Distal zone endocardial blood flow failed to decline in response to NaOH at any dose level tested. It should be recalled that infusion of 0.5 M NaOH was sufficient to raise distal zone intracellular pH to levels that have been reported for normal, nonstenosed myocardial regions.\(^{25,27}\) In addition, the pH of coronary venous blood was elevated to systemic levels (i.e., 7.41) during 0.5 M NaOH infusion. Thus, NaOH infusion (0.5 M) was capable of raising intracellular and tissue pH and could do so to an extent that should have removed the stimulus for vasodilatation if tissue acidosis functioned in that role. Because endocardial blood flow and resistance were not influenced by NaOH infusion, it is unlikely that tissue acidosis has an essential role in more long-term adjustments of the coronary circulation to the presence of a severe stenosis.

The fact that epicardial blood flow distal to the stenosis declined in response to a high dose of (0.5 M) NaOH does not necessarily contradict the argument advanced above. Myocardial oxygen consumption and extraction declined significantly during 0.5 M NaOH, an observation that indicates that primary myocardial depression (induced by NaOH) was responsible for epicardial flow reduction. Primary vasoconstriction should have been associated with either no change or an increase in myocardial oxygen extraction, and so attributing the decline in epicardial flow to that mechanism is difficult. A leftward shift of the oxygen-hemoglobin dissociation curve could not have been responsible for the results because both myocardial oxygen extraction and blood flow declined. A leftward shift by itself should have caused an increase in epicardial flow (which is possible in this model\(^{20,30,31}\)) with no change in myocardial oxygen consumption. Furthermore, the change in coronary arterial pH (from 7.41 to 7.54) and P\(_{CO_2}\) (from 42 to 35 mm Hg) induced by 0.5 M NaOH would have reduced the P\(_{20}\) of arterial blood only modestly (i.e., from about 27 mm Hg to about 24 mm Hg\(^{10}\)). The fact that myocardial ischemia failed to worsen with the decline in epicardial flow also supports the hypothesis that primary myocardial depression (as opposed to primary vasoconstriction) was induced by NaOH. Finally, failure of endocardial flow to decline during infusion of 0.5 M NaOH may reflect the fact that depression of myocardial function was more severe in the endocardium and that as a result, endocardial flow was less susceptible to further depression by NaOH.

The mechanism responsible for apparent NaOH-induced depression of myocardial function cannot be stated with certainty. An earlier natural history study,\(^{31}\) however, excluded the possibility of a time-dependent spontaneous deterioration of distal zone function as an alternative explanation for the observed decline in regional myocardial oxygen consumption during NaOH infusion. Similarly, although a high-dose base infusion was associated with a reduction in certain external determinants of myocardial oxygen demand (Table 1), the absolute changes were small and were not associated with autoregulatory reductions in circumflex zone blood flow. Accordingly, reduced distal zone epicardial blood flow and oxygen consumption during 0.5 M NaOH infusion probably cannot be explained by observed small changes in external determinants of oxygen demand. Further, because NaOH was administered by slow (0.38 ml/min) infusion into the blood (an excellent buffer) and because calculated pH of blood in the left anterior descending coronary artery increased to no more than 7.55, a direct caustic effect of NaOH on the myocardium or vasculature probably would not account for the result. Rather, it is more likely that myocardial contractility was adversely affected by the pH effect of base infusion, which presumably interfered with availability of calcium to the contractile apparatus.

In conclusion, even though tissue acidosis may be chronically present under resting conditions in the setting of a severe coronary arterial stenosis, data obtained in this study show that increased hydrogen ion concentration or P\(_{CO_2}\) tension or both is not essential for long-term maintenance of reduced arteriolar tone distal to the stenosis. Although other mediators may substitute for low pH or elevated P\(_{CO_2}\), results of earlier studies conducted in our laboratory indicate that sustained elevation of interstitial fluid adenosine concentration\(^{19}\) or increased prostacyclin production\(^{32}\) also are not essential for long-term maintenance of reduced arteriolar tone distal to a severe coronary arterial stenosis. Thus, the results of the present investigation are best understood in the context of a series of experiments,\(^{16-19,31,32}\) which indicate that known mediators of acute changes in coronary arteriolar tone may not have an important role (either alone or in combination) in the long-term maintenance of reduced arteriolar tone distal to a severe coronary arterial stenosis. The mechanism(s) involved in maintenance of reduced coronary arteriolar tone in this setting is unknown but could involve alterations in one or more proteins responsible for regulation of vascular smooth muscle contraction and relaxation. Additional biochemical studies are required to test this hypothesis.

**Acknowledgments**

We thank the staff of the Cardiac Research Laboratory, Rhode Island Hospital, for excellent technical assistance and Mrs. Christine Abatiello for the preparation of the manuscript. Donald Jackson, PhD, (Brown University) provided helpful advice and criticism.
References

**Key Words** • coronary flow regulation • pH • pCO2 • coronary flow • maintenance of arteriolar dilation
Tissue acidosis: role in sustained arteriolar dilatation distal to a coronary stenosis.
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Circulation. 1989;79:890-898
doi: 10.1161/01.CIR.79.4.890

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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