Importance of Intraluminal Pressure on Hemodynamics and Vasoconstriction Responses of Stenotic Arteries

Massroor Ghods, MD; Rakesh Mangal, MD; Ami S. Iskandrian, MD; and William P. Santamore, PhD

Background. Clinical and morphological studies clearly indicate that most human coronary artery stenoses are capable of vasomotion. Variable ischemic thresholds, ischemia unrelated to work load, and variant angina further show the presence and importance of vasoconstriction in coronary artery stenosis. Despite the importance of vasoconstriction, the effect of intraluminal pressure on the hemodynamic response to vasoconstrictors has not yet been examined. Intraluminal pressure is a primary determinant of vessel size and the force opposing vasoconstriction. Accordingly, we examined the effects of intraluminal pressure on the hemodynamic response to norepinephrine (NE)-induced vasoconstriction.

Methods and Results. In canine carotid arteries perfused with physiological salt solution, pressures at the proximal and distal ends of the artery, as well as flow, were continuously recorded. We altered intraluminal pressure using three diverse interventions: changes in perfusion pressure, decreasing distal resistance, and collaterals. In normal, nonstenotic arteries, NE decreased the external vessel diameter but did not reduce flow. Perfusion pressure changes did not affect the ED₅₀ of the NE–diameter relation. After an intraluminal stenosis was created, NE-induced constriction decreased flow. The threshold concentration of NE needed to decrease flow decreased as the perfusion pressure decreased (38.5±17.9, 2.3±1.3, and 0.12±0.1X₁₀⁻⁷ mol/l for 125, 100, and 75 mm Hg of perfusion pressure, respectively; p<0.05). Lowering distal resistance decreased stenotic pressure and decreased the threshold NE concentration from 5.4±1.9 to 0.34±0.2X₁₀⁻⁷ mol/l (p<0.05), and increasing stenotic pressure with collaterals increased the threshold NE concentration from 2.6±1.4 to 7.5±4.6X₁₀⁻⁷ mol/l (p<0.05).

Conclusions. In stenotic arteries, interventions that lowered the intraluminal pressure decreased the threshold NE concentration needed to decrease flow, and interventions that raised the intraluminal pressure increased the threshold NE concentration. This pressure-dependent constrictor sensitivity affects the vasomotor tone and is important in pathophysiology of ischemia occurring with hypotension (low perfusion pressure) or mild increase in myocardial oxygen demand (low distal arteriolar resistance). The results also suggest that collaterals, by maintaining stenotic pressure, could decrease the constrictor sensitivity and prevent ischemia. (Circulation 1992;85:708–716)

Although often overlooked, intraluminal pressure is a primary determinant of vessel size: increasing pressure significantly increases vessel size, and decreasing pressure decreases vessel size.¹ For coronary arteries, the pressure-induced vessel dimension changes are equal in magnitude to the vasoconstriction-induced dimensional changes. For example, at normal arterial pressure, maximal vasoconstriction decreases coronary diameter by 10–16%, and a 50 mm Hg reduction in pressure decreases coronary diameter by 12%.¹ Furthermore, the efficacy of vasoconstrictors is inversely related to intraluminal pressure. Increasing intraluminal pressure decreases diameter shortening, and decreasing intraluminal pressure increases diameter shortening.

Morphological and clinical studies clearly indicate that most human coronary artery stenoses are capable of vasomotion.²–⁷ Variations in angina threshold, silent myocardial ischemia, and angina at rest further demonstrate the importance of vasomotion in patho-
physiology of angina pectoris. Despite this importance of vasomotor tone, no one has examined the effects of intraluminal pressure on the hemodynamic response to vasoconstrictors. Accordingly, in this study, we examined the effects of intraluminal pressure on stenotic hemodynamic responses to norepinephrine (NE)—induced vasoconstriction. We used three diverse interventions (changes in perfusion pressure, decreasing distal resistance, and collaterals) to alter intraluminal pressure, and examined both normal and stenotic arteries in an in vitro artery preparation capable of vasmotion.

Methods

Preparation

An in vitro artery preparation was used to eliminate distal vasculature, neural, humoral, and systemic effects. Random-source dogs were anesthetized with Innovar Vet (0.1 mg/kg i.m.) and sodium pentobarbital (30 mg/kg i.v.). The carotid arteries were removed and connected to the perfusion system (Figure 1). The system consisted of a flow pump (Masterflex model 7013, Cole-Palmer International, Chicago), proximal and distal pressure transducers, an arterial bath, a reservoir, and a distal resistance. The perfusate and arterial bath (physiological salt solution, PSS) consisted of (mmol/l) NaCl 119, KCl 4.7, CaCl 2.5, NaH2PO4 1.2, MgSO4 1.2, NaHCO3 22.6, EDTA 0.05, and glucose 1 g/l; it was maintained at pH 7.4 and 37°C while being aerated with 95% room air–5% CO2.

Pressures proximal and distal to the arterial segment were measured. The pressure transducers (Spectramed Inc., Critical Care Division, Oxnard, Calif.) were carefully calibrated to ensure equal sensitivity by simultaneously exposing the pressure transducers to the same pressure. All data were recorded on an Electronics for Medicine recorder (Model VR-6, Electronics for Medicine/Honeywell, White Plains, N.Y.). The proximal and distal pressure signals were processed with an analog-to-digital converter (model STA-AP Board, Metra-Byte, Taunton, Mass.) and supplied to an Apple II+ microcomputer (Apple Computer Company, Cupertino, Calif.). Under feedback control, the computer maintained a perfusion pressure of 100 mm Hg. The output signal from the feedback control circuit (Figure 1) also provided perfusion flow rates and was calibrated by timed collections with a graduated cylinder.

In every experiment, a constant perfusion pressure (100 mm Hg) was applied initially to the arterial segment, and the artery was allowed to stabilize for 2 hours. The 22 experiments were divided randomly into three groups. NE dose–response relations were determined at three levels of perfusion pressure (75, 100, and 125 mm Hg) in eight experiments, at low and high distal resistance in five experiments, and with and without collaterals in nine experiments. A stenosis was created by partially inflating with contrast material (Hypaque-76, Winthrop Pharmaceuticals, N.Y.) a coronary dilatation balloon catheter (2 cm long, 4 mm maximal diameter) within the arterial segment. In the perfusion pressure experiments, the coronary dilatation balloon catheter was partially inflated to create a pressure gradient of approximately 10 mm Hg across the arterial segment, while in the other experiments, a pressure gradient of 20 mm Hg was created. For a dynamic stenosis, the pressure gradient across the vessel is inversely related to the perfusion pressure.9–11 Our preliminary studies indicated that an initial pressure gradient of 20 mm Hg at 100 mm Hg perfusion pressure would be too severe a pressure gradient at 75 mm Hg perfusion pressure. Thus, in the perfusion pressure experiments, the initial pressure gradient was set to approximately 10 mm Hg. This level of balloon inflation was kept constant throughout subsequent interventions.

Protocol

Effects of perfusion pressure. In these experiments (n=8), perfusion pressure was randomly set to 75, 100, or 125 mm Hg. For each perfusion pressure, NE was added incrementally to the perfusate to obtain molar concentrations ranging from 10⁻⁹ to 10⁻⁵ mol/l.
Each NE concentration was maintained for at least 2 minutes or until a steady-state response was obtained. Hemodynamic variables were recorded continuously throughout the study. Proximal and distal pressures were analog-to-digitally converted every second, and the data were stored in an Apple II+ microcomputer. After the NE dose-response relation was obtained, the perfusate and arterial bath solutions were replaced with fresh physiological salt solution, and the artery was allowed to stabilize for 2 hours.

NE dose–response relation was again determined at another level of perfusion pressure randomly selected from 75, 100, or 125 mm Hg. For example, if the artery was initially perfused at 100 mm Hg, the artery would then be perfused at either 125 or 75 mm Hg. The perfusate was replaced with fresh physiological salt solution, and the artery was allowed to recover for 2 hours. Last, the NE dose–response relation was determined at the last level of perfusion pressure.

**Effects of distal resistance.** Normally, a 20-gauge needle was used as the distal resistance in the perfusion apparatus. This needle allowed an initial flow rate of 30–40 ml/min. The distal resistance was lowered by switching to an 18-gauge needle to allow a maximal flow rate of 50–70 ml/min. In these experiments \( (n=5) \), the NE dose–response relations were obtained randomly at both levels of distal resistance.

**Effects of collaterals.** The experimental model of collateral circulation consisted of a reservoir at 100 mm Hg and a fixed resistance in its perfusion line. This line was attached to a point distal to the arterial segment to provide a flow of 5 to 10 ml/min with a 20 mm Hg gradient across the arterial segment. A second pump returned the solution to the reservoir (Figure 1). In these experiments \( (n=9) \), the NE dose–response curve was determined randomly with and without collateral flow.

**Effects of perfusion pressure on normal (nonstenotic) vessel dimensions.** In these experiments \( (n=4) \), the arterial diameter was continuously monitored with 5-MHz ultrasonic crystals placed on either side of the artery. The distance between the crystals was measured with a sonomicrometer (Triton Technology Inc., San Diego, Calif.). Hemodynamic variables were also monitored. Perfusion pressure was randomly set to 75, 100, or 125 mm Hg. For each level of perfusion pressure, the NE dose–diameter response was determined.

**Data Analysis**

For the normal arteries, the diameter data were approximated by a four-parameter logistic equation:

\[
Y = \frac{a - d}{1 + (X/c)^b} + d
\]

where \( X \) and \( Y \) are the NE concentration and response, respectively, and \( a, b, c, \) and \( d \) are the four fitted parameters: \( a \), response at zero dose; \( b \), slope factor; \( c \), 50% maximally efficient dose or \( ED_{50} \); and \( d \), response at "infinite" dose.

For the stenotic arteries, the stenotic resistance was calculated as the pressure gradient across the arterial segment (proximal pressure minus distal pressure) divided by flow. The mean and SEM were calculated for distal pressure, flow, and stenotic resistance at baseline (response at zero dose) and at the highest NE dose that resulted in maximal response and caused near total cessation of flow. For the stenotic arteries, the whole response (flow decrease) generally occurred at one incremental dose of NE.\(^{11} \) Thus, rather than trying to calculate an \( ED_{50} \) value, we used this threshold concentration of NE. In each experiment, the incremental dose of NE that resulted in an abrupt 50% or greater reduction in flow was determined. The mean and SEM were calculated for the threshold NE concentration. The distal pressure, flow, stenotic resistance, and threshold NE concentration values were compared with a one-way analysis of variance for repeated measurements with a Bonferroni-corrected \( t \) test for the perfusion pressure studies and by a paired \( t \) test for the collateral and distal resistance studies.

**Results**

Figure 2 shows the typical response of arterial dimensions to NE-induced constriction in a nonstenotic artery. Using ultrasonic crystals, external vessel diameter was recorded at three levels of perfusion pressure while NE was added incrementally to the perfusate. As might be expected, increasing the perfusion pressure increased the initial vessel size and decreased the amount of diameter shortening induced by NE. Yet the concentration of NE needed to induced vasoconstriction was unaltered. In this
TABLE 1. Summary of Diameter Data: Effects of Perfusion Pressure on Dimensions of Nonstenotic Arteries

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Perfusion pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Initial (mm)</td>
<td>4.11±0.2*†</td>
</tr>
<tr>
<td>Final (mm)</td>
<td>3.91±0.2*†</td>
</tr>
<tr>
<td>Shortening (mm)</td>
<td>0.20±0.01*†</td>
</tr>
<tr>
<td>NE dose–diameter ED50 (×10^-8 mol/l)</td>
<td>9.8±6.1</td>
</tr>
</tbody>
</table>

NE, norepinephrine. Values are mean±SEM.  
*<0.05 vs. 100 mm Hg.  
†p<0.05 vs. 10 mm Hg.
	nonstenotic artery, the hemodynamic variables (distal pressure and flow) were unaltered by NE-induced vasoconstriction.

Table 1 summarizes the dimensional data for the nonstenotic arteries. Increasing the perfusion pressure increased the initial diameters and decreased the magnitude of diameter shortening induced by NE, and decreasing the perfusion pressure decreased the initial diameters and increased the magnitude of diameter shortening induced by NE. However, changing the perfusion pressure did not affect the ED50.

For a stenotic artery, Figure 3 shows the typical hemodynamic responses to vasoconstriction at three different levels of perfusion pressure. In Figure 3A, the arterial segment was perfused at 75 mm Hg. NE was added incrementally to the perfusate. At an NE concentration of 10^-8 mol/l, the distal pressure, which is almost identical to the pressure within the stenosis, began to decrease. The next incremental concentration of NE (3.16×10^-8 mol/l) resulted in a large decrease in distal pressure and near total cessation of flow. This is very typical of stenotic vasoconstriction responses; most of the response occurs with one incremental dose of agonist.8,11,13

Figure 3B shows the same artery perfused at 100 mm Hg. At this perfusion pressure, the control distal pressure and flow increased, and the pressure gradient across the artery decreased. As in previous studies for a dynamic stenosis, the pressure gradient decreased as the perfusion pressure increased.9-11 Once again, NE was added incrementally to the perfusate. A higher NE concentration (3.16×10^-7 mol/l) was required to cause a significant reduction in distal pressure and flow. In Figure 3C, the perfusion pressure was set to 125 mm Hg. At this level of

![Computer printout of proximal and distal pressures and flow vs. time. At the arrows, norepinephrine (NE) was incrementally added to the perfusate. Panel A: Hemodynamic response to NE at 75 mm Hg perfusion pressure. The NE concentration of 3.16×10^-8 mol/l reduced distal pressure and flow. Panel B: With the artery perfused at 100 mm Hg, 3.16×10^-7 mol/l NE was required to reduce flow. Panel C: Hemodynamic response at 125 mm Hg perfusion pressure: only 3.16×10^-6 mol/l NE was required to reduce flow.](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.82.3.711)
perfusion pressure, a still higher concentration of NE (3.16×10⁻⁶ mol/l) was required to cause a relatively mild decrease in flow and distal pressure. For the data presented in Figures 3A, 3B, and 3C, the artery was initially perfused at 100 mm Hg, then at 75 mm Hg, and last at 125 mm Hg.

Figures 4A and 4B show the typical hemodynamic responses with a high and a low distal resistance, respectively. In Figure 4A, NE was added incrementally to the perfusate. At an NE concentration of 10⁻⁷ mol/l, distal pressure and flow decreased. In Figure 4B, the distal resistance was lowered. This resulted in a significant decrease in the initial distal pressure, an increase in flow, and an increase in the pressure gradient across the stenosis. NE was then added to the perfusate. With a lower distal resistance, less NE (10⁻⁸ mol/l) was required to decrease flow and distal pressure.

Figure 5 shows the typical effects of “collateral” flow on the stenotic responses. In Figure 5A, the artery was perfused at 100 mm Hg without any collateral flow distal to the stenosis. NE was added incrementally to the perfusate. At an NE concentration of 10⁻⁸ mol/l, flow and distal pressure decreased. In Figure 5B, collateral flow was added distal to the stenosis (see Figure 1). As a result, distal pressure increased and pressure gradient across the arterial segment decreased. Because of collateral flow, the flow throughout the arterial segment decreased. NE was then added incrementally to the perfusate of
both reservoirs. In the presence of collateral flow, a higher NE concentration ($10^{-7}$ mol/l) was required to decrease flow and distal pressure.

Table 2 summarizes the hemodynamic responses in the stenotic arteries. It shows the initial and final (after NE-induced constriction) values for distal pressure, flow, and stenotic resistance and the threshold concentration of NE needed to reduce flow. As expected, the three experimental conditions altered the initial distal pressure and flow. Lowering the perfusion pressure decreased the initial distal pressure and flow. The distal pressure decrease was proportionally greater than the flow decrease, however, resulting in an increase in stenotic resistance. Lowering distal resistance decreased the distal pressure, increased the flow through the arterial segment, and increased the stenotic resistance. In the presence of collaterals, the pressure gradient across the artery and stenotic resistance decreased. Flow through the vessel decreased slightly. The collaterals helped to maintain the intraluminal stenotic pressure and increased the initial distal pressure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perfusion pressure (mm Hg)</th>
<th>Low distal resistance</th>
<th>Collaterals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 125</td>
<td>Control Low distal</td>
<td>Control</td>
</tr>
<tr>
<td>Distal pressure (mm Hg)</td>
<td></td>
<td>resistance</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>115±1.7</td>
<td>85.9±3.1</td>
<td>79.6±3.1</td>
</tr>
<tr>
<td>Final</td>
<td>44.5±15.8*</td>
<td>32.7±8.6*</td>
<td>25.7±3.9*</td>
</tr>
<tr>
<td>Flow (ml/min)</td>
<td>39.3±1.8</td>
<td>30.8±2.1</td>
<td>25.3±0.8</td>
</tr>
<tr>
<td>Stenotic resistance</td>
<td>18.7±4.2*</td>
<td>16.1±4.3*</td>
<td>13.6±1.3*</td>
</tr>
<tr>
<td></td>
<td>(mm Hg/ml/min)</td>
<td>(mm Hg/ml/min)</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>0.17±0.02</td>
<td>0.46±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Final</td>
<td>4.50±1.1*</td>
<td>4.7±0.9*</td>
<td>6.1±0.9*</td>
</tr>
<tr>
<td>NE dose ($\times 10^{-7}$ mol/l)</td>
<td>38.5±17.9</td>
<td>5.4±1.9</td>
<td>2.6±1.4</td>
</tr>
</tbody>
</table>

For all three protocols, NE-induced constriction decreased the distal pressure and flow and increased the stenotic resistance. Also, the threshold NE concentration needed to decrease flow was related to perfusion pressure. Decreasing the perfusion pressure from 125 to 100 mm Hg caused a 17-fold decrease in the threshold NE concentration, and decreasing perfusion pressure from 100 to 75 mm Hg caused a 19-fold decrease in threshold NE concentration, for a total 320-fold change. Lowering distal resistance caused a 16-fold change in the threshold NE concentration. Collaterals prevented a large distal pressure decrease with NE-induced constriction and caused a threefold increase in threshold NE concentration.

Figure 6 combines the data from all three experimental protocols. This figure plots the changes in initial distal pressure from control value versus the log of threshold NE concentration intervention/control ratio. For example, in Figure 4b, decreasing the distal resistance decreased the initial distal pressure from 86 to 57 mm Hg (~29 mm Hg) and changed the

![Effects of Change in Pressure on Threshold to Norepinephrine](image)
Figure 7. Graph of initial intraluminal pressure decreased by the effects of the atherosclerotic plaque in a stenotic artery. This initial decrease in intraluminal pressure makes constriction more effective. Further, localized vasoconstriction decreases the intraluminal pressure. As the vessel constricts, the pressure decrease leads to further vessel shortening. Thus, the constriction is along a decreasing pressure line. The combination of an initial decrease in intraluminal pressure together with pressure decreases as the vessel constricts causes exaggerated constriction within the stenosis.

Threshold NE concentration from $10^{-7}$ to $10^{-8}$ mol/l (log of threshold NE concentration I/C ratio: −1). The other data points were obtained similarly for all three interventions. Despite the diverse interventions (changing perfusion pressure, distal resistance, collaterals), changes in stenotic pressure were significantly related to changes in the threshold NE concentration. Interventions that lowered stenotic pressure decreased the threshold NE concentration, while interventions that raised stenotic pressure increased the threshold NE concentration.

Discussion

In this study, we examined whether changes in intraluminal pressure could alter the hemodynamic responses to a vasoconstrictor. In normal arteries, even at maximal concentration, NE did not decrease flow. Increasing intraluminal pressure did increase the initial vessel size and decrease the diameter shortening induced by NE. The ED$_{50}$ of the NE dose–diameter response was unaltered, however.

In contrast, in stenotic arteries, changing stenotic pressure altered the hemodynamic response to NE. Increasing the perfusion pressure or adding collaterals increased the stenotic intraluminal pressure, and decreasing the perfusion pressure or decreasing distal resistance decreased the stenotic intraluminal pressure. Interventions that raised stenotic pressure increased the threshold concentration of NE required to reduce flow, and interventions that lowered stenotic pressure decreased the threshold concentration of NE dose–flow response. This is the first study to demonstrate that pressure alters the hemodynamic responses to a constrictor in stenotic arteries, a phenomenon that does not occur in normal arteries.

Mechanism

Figure 7 shows the pattern of constriction that, we believe, occurs within normal and stenotic coronary arteries. Figure 7 presents the pressure–diameter relation for a dilated and constricted coronary artery. The force opposing arterial constriction is the intraluminal pressure. In normal (nonstenotic) arteries, this pressure is the systemic arterial pressure, which is relatively constant. Localized contraction does not change systemic pressure. We believe that this is the reason why changing the perfusion pressure did not affect the ED$_{50}$ of the NE dose–diameter relation.

Within a stenosis, the pressure is initially less than systemic pressure, which by itself results in greater shortening for any given amount of agonist. More importantly, local vasoconstriction further decreases this pressure. Thus, in a stenotic artery, as the artery begins to shorten, the stenotic pressure opposing vasoconstriction decreases dramatically. This decrease in stenotic pressure leads to further diameter shortening with a resulting decrease in cross-sectional area and stenotic pressure: a positive feedback mechanism.

For this positive feedback mechanism to occur, the vessel must first shorten. For this initial shortening, the vessel must exceed its afterload, which is determined primarily by its intraluminal pressure. Thus, anything that decreases intraluminal pressure will cause abrupt flow decreases to occur at lower concentrations of a vasoconstrictor, whereas interventions that increase intraluminal pressure will delay or prevent these flow decreases. We believe that this attenuated shortening with higher intraluminal pressure and augmented shortening with lower pressure caused the observed change in threshold NE concentration.

Comparison With Literature

In a previous study, Li et al showed that stenotic pressure changes exaggerated constriction within an arterial stenosis. Diameters proximal to and within an arterial stenosis were measured by quantitative angiographic techniques. For the same vasoconstriction stimulus, the stenotic diameter changes were significantly greater than the proximal diameter changes. Furthermore, stenotic diameter changes were significantly related to stenotic pressure changes, whereas proximal diameter changes were unrelated to stenotic hemodynamics. Li et al, by holding the intraluminal pressure constant, verified that the accentuated vasoconstriction was a result of intraluminal pressure changes. When the stenotic pressure was held constant, the constriction responses in the proximal and stenotic diameters were similar. Thus, maintaining the stenotic pressure constant eliminated the accentuated vasoconstriction.

In another study, we compared the response to denudation in isolated arterial rings and in stenotic...
arteries. In isolated arterial rings, denudation increased the maximal isometric tension but did not change the sensitivity to serotonin. In contrast, in stenotic arteries, denudation increased the sensitivity to serotonin. Since this change in sensitivity did not occur in isolated arterial rings, the change in sensitivity did not occur at the cellular level. Thus, in stenotic arteries, this augmented contraction presented itself as an apparent increase in the sensitivity to serotonin, similar to the results of the present study.\textsuperscript{14}

**Clinical Implications**

**Effects of arterial blood pressure.** In stenotic coronary arteries, a substantial reduction in intraluminal pressure occurs even with normal levels of aortic pressure. Lowering aortic pressure causes a further decrease in the stenotic pressure. As described in this paper, this decrease in pressure would decrease the threshold vasoconstrictor concentration and might cause ischemia. In our review of the literature, all the experimental studies showed that lowering arterial blood pressure can have detrimental effects on coronary blood flow and myocardial performance.\textsuperscript{9,10,15–19} The clinical studies showed that in patients with severe coronary artery disease undergoing cardiovascular surgery, the majority of perioperative ischemic events were temporally related to hemodynamic disturbances. In these studies, up to 25\% of perioperative myocardial ischemic events were preceded by a fall in arterial blood pressure greater than 20\%, and hypotension was as important a cause of ischemia as hypertension or tachycardia.\textsuperscript{20–23}

**Effects of low distal resistance.** Clinical interventions that lower distal arteriolar resistance decrease stenotic intraluminal pressure and can decrease the threshold vasoconstrictor concentration. Large coronary arteries are under tonic vasomotor tone, and decreasing intraluminal pressure could accentuate this tone. Consistent with these ideas, Stone\textsuperscript{24} has speculated that a combination of increased myocardial oxygen demands (decreased distal arteriolar resistance) and increased vasomotor tone might explain the high incidence of myocardial ischemia upon awakening. The results of this present study would suggest that these two components may act synergistically rather than just additively. Lowering the distal resistance decreased the stenotic intraluminal pressure. This decrease in pressure, in turn, decreased the threshold vasoconstrictor concentration.

Arteriolar-type vasodilators (e.g., dipyridamole, adenosine) decrease arteriolar resistance in both peripheral and coronary beds. Lowering peripheral arteriolar resistance decreases systemic arterial pressure and therefore stenotic intraluminal pressure. In addition, lowering coronary arteriolar resistance further lowers the stenotic intraluminal pressure. This decrease in stenotic intraluminal pressure could accentuate the coronary vasomotor tone and, in addition to coronary steal, could induce myocardial ischemia. Thus, arteriolar vasodilators, rather than being beneficial, are clinically used in radionuclide imaging to detect potentially ischemic regions.

**Effects of collaterals.** In the presence of coronary stenosis, collateral vessels provide flow distal to stenosis and can thereby prevent ischemia. However, with increased myocardial oxygen demands in the normal region, shunting of blood away from the collaterals occurs, which can lead to ischemia (coronary steal). Although these ideas are well established, the importance of collaterals in maintaining intraluminal pressure has received less attention. In an experimental study, Schwartz et al\textsuperscript{25} showed that eliminating collateral flow decreased the pressure within the stenosis. This pressure decrease caused the stenosis to collapse, leading to a large flow decrease through the stenotic artery. Thus, collaterals help to maintain pressure within the stenosis, and this increase in intraluminal pressure would increase the threshold vasoconstrictor concentration and may help prevent acute vessel closure.

**Critique of Method**

As mentioned above, most coronary artery stenoses (75\%) are capable of vasomotion. Thus, to examine the effects of vasodilators and vasoconstrictors on stenotic hemodynamics, a stenosis capable of vasomotion must be used. The most commonly used experimental stenosis is an external snares. However, an external snares is totally nonresponsive to vasoconstriction by the stenosis.\textsuperscript{26} The intraluminal stenosis provides the only acute experimental stenotic model that would respond to vasoconstriction and to vasodilation. In previous studies from our laboratory, we directly compared the hemodynamic responses to vasoconstriction and to intraluminal pressure changes obtained with the intraluminal balloon with the responses observed in human stenotic arteries.\textsuperscript{11,27} Both qualitatively and quantitatively, the responses were similar. We also examined the endothelium. Scanning electron microscopy showed only minimal endothelial damage, and normal vasodilation responses to acetylcholine were obtained.\textsuperscript{14} We did not directly measure pressure within the stenosis. In a previous study, we directly measured the pressure within the stenosis\textsuperscript{13} and observed that the stenotic pressure was almost identical to the distal pressure. There was little, if any, pressure recovery distal to the stenosis.

Since the intraluminal stenosis is the only acute experimental stenosis capable of vasomotion, we used an intraluminal stenosis in these studies. Obviously, care should be taken when experimental data are extrapolated to the clinical situation.

**References**


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