Serotonin Selectively Aggravates Subendocardial Ischemia Distal to a Coronary Artery Stenosis During Exercise

Robert J. Bache, MD; Randall P. Stark, MD; and Dirk J. Duncker, MD

Background. The coronary circulation has been shown to remain responsive to vasodilator and vasoconstrictor stimuli during myocardial ischemia. Because serotonin possesses both vasodilator and vasoconstrictor properties, we examined its effect in the coronary circulation distal to an arterial stenosis that resulted in myocardial hypoperfusion during exercise.

Methods and Results. Seven chronically instrumented dogs were studied during treadmill exercise in the presence of a stenosis that reduced distal left circumflex coronary artery perfusion pressure to 42±1 mm Hg. Myocardial blood flow was assessed with radioactive microspheres during exercise before and during intracoronary infusion of 0.4 and 2.0 μg/kg·min-1 serotonin. The stenosis was adjusted to maintain distal coronary pressure constant during control exercise and with the two doses of serotonin. In seven dogs, the effect of serotonin (2.0 μg/kg·min-1) was also studied during exercise with normal arterial inflow. During control exercise, the stenosis decreased mean myocardial blood flow to 45% of flow in the normally perfused region. This decrease was most pronounced in the subendocardium (endo-epicardial ratio 0.36±0.06 versus 1.46±0.14 in the control region; p<0.01). With no change in pressure distal to the stenosis, serotonin decreased subendocardial flow from 0.51±0.09 ml/min·g-1 to 0.41±0.12 (p<0.05) and then to 0.35±0.08 ml/min·g-1 (p<0.05) and tended to increase subepicardial flow from 1.47±0.17 to 1.91±0.23 and 1.85±0.21 ml/min·g-1 (p=0.08) during infusions of 0.5 and 2.0 μg/kg·min-1, respectively, with no change in total arterial inflow. In contrast, in the absence of a stenosis, serotonin (2.0 μg/kg·min-1) increased subendocardial flow from 2.43±0.25 to 3.73±0.25 ml/min·g-1 (p<0.01) and subepicardial flow from 1.88±0.20 to 5.29±0.38 ml/min·g-1 (p<0.01).

Conclusions. During normal arterial inflow, serotonin dilated coronary resistance vessels and increased flow to all myocardial layers. During hypoperfusion, a vasodilator response was still present in the subepicardium, but vasoconstriction was then observed in the subendocardium. Our data suggest that serotonin constricts the intramural penetrating arteries, thereby selectively increasing resistance to subendocardial blood flow. (Circulation 1992;86:1559–1565)

Key Words • blood flow, coronary • vasoconstriction, coronary • stenosis, coronary • vessels, intramural • microspheres • ischemia

Platelets aggregating at the site of a coronary artery stenosis can induce myocardial ischemia by causing narrowening of the stenosis and by releasing thromboxane A2 and serotonin, which causes constriction of the stenotic arterial segment.1 In the setting of myocardial ischemia, these platelet products were considered to have little effect on the distal coronary vasculature because ischemia has generally been thought to cause intense microvascular dilation, which renders these vessels unresponsive to vasoactive stimuli. However, recent studies have demonstrated that even during ischemia, the coronary resistance vessels retain some degree of vasomotor tone2–5 and are capable of responding to vasoconstrictor stimuli.6–9 Serotonin dilates coronary resistance vessels but causes constriction of the larger coronary arterial segments.10,11 This arterial vasoconstriction may be facilitated in the presence of a coronary stenosis when flow-mediated or direct endothelium-dependent vasodilation is deficient or absent.10,12,13 The present study was undertaken to examine the effect of serotonin in the coronary circulation distal to an arterial stenosis that results in myocardial hypoperfusion during exercise.5,8,9 To avoid passive changes in subendocardial perfusion resulting from changes in poststenotic perfusion pressure, a stenosis was used that maintained coronary pressure constant at 40–45 mm Hg.

Methods

Studies were performed in 10 adult mongrel dogs weighing 20–27 kg and trained to run on a motor-driven treadmill. All experiments were performed in accordance with the Guiding Principles in the Care and Use of Laboratory Animals as approved by the Council of...
the American Physiological Society (DHEW Publication No. [NIH] 8023, 1980) and under the supervision of the Animal Care Committee of the University of Minnesota.

**Surgical Preparation**

After sedation with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), animals were anesthetized with sodium pentobarbital (30–35 mg/kg i.v.), intubated, and ventilated with a mixture of oxygen (30%) and room air (70%). Respiratory rate and tidal volume were adjusted to keep arterial blood gases within physiological limits. A left thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. A polyvinyl chloride catheter (3.0-mm o.d.) filled with heparinized saline was inserted into the left internal thoracic artery and advanced into the ascending aorta. Similar catheters were introduced into the left atrium through the atrial appendage and the left ventricle through the apical dimple and secured with purse-string sutures. A solid-state micromanometer (model P5, Konigsberg Instrument Company, Pasadena, Calif.) was also introduced into the left ventricle through the area of the apex. Approximately 1.5 cm of the proximal left circumflex coronary artery was dissected free, and a Doppler flow probe (Craig Hartley, Houston, Tex.) was positioned around the artery. Immediately distal to the flow probe, a hydraulic occluder (3.0-mm o.d.) was placed around the vessel. A silicone catheter (0.3-mm i.d.) bonded to a larger silicone catheter (1.6-mm i.d.) was introduced into the left circumflex artery immediately distal to the hydraulic occluder. The pericardium was then loosely closed, and the catheters and electrical leads were tunneled subcutaneously to exit at the base of the neck. The chest was closed in layers, and the pneumothorax was evacuated. Catheters were flushed daily with heparinized saline to maintain patency.

**Hemodynamic Measurements**

Studies were performed 2–3 weeks after surgery with the animals exercising on the platform of a motor-driven treadmill. Recordings of phasic and mean aortic pressure and coronary perfusion pressure were measured with Gould P23XL pressure transducers positioned at midchest level. Left ventricular pressure was measured with the micromanometer and calibrated with the fluid-filled left ventricular catheter. Left ventricular dP/dt was obtained via electrical differentiation of the left ventricular pressure signal. Data were recorded on an eight-channel direct writing oscillograph (Coulbourn Instruments, Lehigh Valley, Pa.). Left ventricular pressure was recorded at both normal and high gain for measurement of left ventricular end-diastolic pressure.

**Myocardial Blood Flow**

Myocardial blood flow was measured with microspheres 15 μm in diameter and labeled with $^{125}$I, $^{113}$Ce, $^{51}$Cr, $^{85}$Sr, $^{99}$Nb, or $^{99}$Se (3M Company, St. Paul, Minn.). Approximately $3 \times 10^6$ microspheres were injected into the left atrial catheter and flushed with 8 ml of normal saline for each measurement. Before injection, microspheres were agitation for at least 10 minutes in an ultrasonic bath. An arterial reference sample was withdrawn from the aortic catheter at a constant rate of 15 ml/min starting 5 seconds before injection and continuing for 90 seconds. At the end of each study, the region perfused by the left circumflex coronary artery was identified by injection of 10 ml of Evans blue dye into the coronary artery catheter, and the animals were given an overdose of sodium pentobarbital. The hearts were excised and fixed in 10% buffered formalin. Then the atria, aorta, right ventricular free wall, and large epicardial blood vessels were dissected from the left ventricle and discarded. The left ventricle was divided into four transverse rings from base to apex. Myocardial samples were obtained from the center of the blue-stained region perfused by the left circumflex artery and divided into four transmural layers of equal thickness from epicardium to endocardium. The resulting specimens were weighed on an analytical balance and placed into vials for counting. Similar specimens were obtained from the anterior left ventricular wall in the region perfused by the left anterior descending coronary artery to serve as controls. Myocardial and blood reference samples were counted in a gamma spectrometer with multichannel analyzer (model 5912, Packard Instrument Company, Downers Grove, Ill.). Counts per minute and corresponding sample weights were entered into a digital computer programmed to correct for background activity and contaminant activity contributed by the associated nuclides and to calculate the corrected counts per minute per gram of myocardial tissue.

Blood flow to the myocardial specimen ($Q_m$, milliliters per minute per gram of myocardium) was computed as

$$Q_m = Q_v \cdot C_m / C_i$$

where $Q_v$ equals rate of withdrawal of reference blood sample (milliliters per minute), $C_m$ equals counts per minute per gram of the myocardial specimen, and $C_i$ equals counts per minute of the reference blood sample.

**Experimental Protocols**

The effects of serotonin on myocardial perfusion distal to a coronary artery stenosis were studied in seven of the 10 dogs. Dogs initially underwent a 5-minute period of warm-up exercise during which the speed and grade of the treadmill were gradually increased until a heart rate of 190–200 beats per minute was achieved. After dogs were subsequently allowed to rest on the treadmill for 10–15 minutes, exercise was restarted at the predetermined level. After 3 minutes of exercise, when heart rate and pressures had reached a steady state, the hydraulic occluder was inflated with saline using a micrometer-driven syringe to produce a degree of stenosis that resulted in a distal coronary pressure of 40–45 mm Hg. After coronary pressure had been maintained at a stable level for 2 minutes, microspheres were injected for the assessment of myocardial blood flow. Exercise was continued for 90 seconds, after which the stenosis was released and exercise was discontinued. After the animals were allowed 60 minutes of rest, an infusion of serotonin was begun into the coronary artery catheter at a dose of 0.4 μg/kg⁻¹·min⁻¹. Serotonin was dissolved in physiological saline to deliver 0.4 μg/kg⁻¹·min⁻¹ at a rate of 0.3 ml/min. Two minutes after beginning the infusion of
TABLE 1. Effects of Intracoronary Serotonin Infusion on Systemic and Coronary Hemodynamics of Exercising Dogs in the Absence and Presence of a Left Circumflex Coronary Artery Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Exercise (no stenosis)</th>
<th>Exercise + stenosis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Resting (n=7)</td>
<td>Control (n=7)</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>127±6</td>
<td>197±3*</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>97±3</td>
<td>111±5*</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>124±6</td>
<td>146±6*</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>4±1</td>
<td>7±2</td>
</tr>
<tr>
<td>LV dP/dt max (mm Hg/sec)</td>
<td>2,150±210</td>
<td>3,600±320*</td>
</tr>
<tr>
<td>Coronary pressure (mm Hg)</td>
<td>97±7</td>
<td>102±7</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>37±3</td>
<td>57±4*</td>
</tr>
</tbody>
</table>

LV, left ventricle; LV dP/dt max, maximal rate of rise of left ventricular pressure. Data have been presented as mean±SEM; *p<0.05 exercise control vs. resting; †p<0.05 exercise + serotonin or exercise + stenosis control vs. exercise control. There was no significant effect of serotonin on any of the parameters during exercise in the presence of a stenosis.

serotonin, exercise was begun at the previous level while infusion was continued. The coronary occluder was inflated to produce approximately the previously applied level of coronary artery stenosis; infusion of serotonin was interrupted for 2–3 seconds at 20-second intervals to allow measurement of distal coronary pressure and adjustment of the severity of stenosis as needed to achieve a coronary pressure equal to that during the control intervention. When coronary perfusion pressure had remained stable for 2 minutes, microspheres were again injected for measurement of myocardial blood flow. After a 60-minute recovery period, the above protocol was repeated, but serotonin was infused into the coronary catheter at a dose of 2.0 μg/kg·min⁻¹.

To study the effect of serotonin on myocardial perfusion during exercise in the absence of a coronary artery stenosis, the exercise protocol was performed in seven dogs (four of which were also studied in the coronary stenosis protocol) while serotonin was infused at a rate of 2.0 μg/kg·min⁻¹.

**Results**

**Systemic and Coronary Hemodynamics**

Hemodynamic data are presented in Table 1. Heart rate increased from 127±6 beats per minute at rest to 197±3 beats per minute during control exercise (p<0.01), mean aortic pressure increased from 97±3 mm Hg to 111±5 mm Hg (p<0.01), left ventricular systolic pressure increased from 124±6 mm Hg to 146±6 mm Hg (p<0.01), and left ventricular dP/dt max increased from 2,150±210 mm Hg/sec to 3,600±320 mm Hg/sec (p<0.01). Neither inflation of the occluder nor infusion of serotonin resulted in significant changes of these hemodynamic variables during exercise. Left ventricular end-diastolic pressure was 4±1 mm Hg at rest and did not change significantly during control exercise but increased during application of the coronary artery stenosis to 12±2 mm Hg (p<0.05). Infusion of serotonin in either the absence or presence of a stenosis had no effect on end-diastolic pressure. Under resting conditions and during control exercise, mean coronary pressure was not different from mean aortic pressure (Table 1), although the increase in coronary pressure during exercise tended to be less than that of aortic pressure. Coronary blood flow increased from 37±3 ml/min at rest to 57±4 ml/min during control exercise (p<0.05). Inflation of the hydraulic occluder to produce a coronary pressure of 42±1 mm Hg decreased proximal left circumflex coronary artery flow to 29±3 ml/min (p<0.01 versus control exercise). Infusions of serotonin at doses of 0.4 and 2.0 μg/kg·min⁻¹·g⁻¹ had no effect on coronary flow when the stenosis maintained perfusion pressure at 42±1 mm Hg. In contrast, in the absence of a stenosis, the drug almost doubled coronary flow (p<0.01 versus control exercise).

**Myocardial Tissue Blood Flow**

During exercise in the presence of a left circumflex coronary stenosis, mean blood flow in the normally perfused anterior left ventricular region was 2.25±0.10 ml/min⁻¹·g⁻¹. Blood flow to the inner layers exceeded...
that to the outer layers, resulting in an endocardial/epicardial (endo/epi) flow ratio of 1.46±0.14 ml/min⁻¹·g⁻¹. Infusion of serotonin into the left circumflex coronary artery had no effect on mean transmural myocardial blood flow or its distribution in the anterior region (Table 2). The posterior wall of the left ventricle perfused by the stenosed left circumflex artery received approximately 45% of the flow measured in the anterior wall (Table 2). The decrement in flow was, however, not evenly distributed across the wall. In the outermost layer, flow was 80–85% of the corresponding layer in the control segment, but flow decreased progressively to 15–20% of control in the inner layer, yielding an endo/epi flow ratio of 0.36±0.06 (p<0.01 versus control area) (Figure 1). Although infusion of serotonin did not affect mean myocardial blood flow, maldistribution of myocardial flow was aggravated as indicated by a further decrease in endo/epi ratio to 0.20±0.04 (p<0.01) (Figure 1). This decrease was primarily due to a reduction in subendocardial flow from 0.51±0.09 ml/min⁻¹·g⁻¹ to 0.41±0.12 and 0.35±0.08 ml/min⁻¹·g⁻¹ (p<0.05) during 0.4 and 2.0 μg/kg⁻¹·min⁻¹ infusions of serotonin, respectively (Table 2). ANOVA did not reveal a statistically significant change in subepicardial flow, but flow in the outermost layer increased in six of seven animals from 1.47±0.17 to 1.85±0.21 ml/min⁻¹·g⁻¹ (p=0.08 vs. Wilcoxon matched-pair samples and Bonferroni correction) during infusion of the highest dose. These effects of serotonin on myocardial perfusion were not different between the two doses.

When serotonin was infused at a rate of 2.0 μg/kg/min in the absence of a coronary artery stenosis, transmural myocardial blood flow was twice that in the control region (Table 3). Although flow increased in all layers in response to serotonin, the drug did not uniformly affect the four myocardial layers as the endo/epi ratio decreased to 0.72±0.05 versus 1.30±0.04 in the control region (p<0.01).

**Discussion**

This study documents the effects of serotonin on myocardial perfusion during exercise with normal arterial inflow and in the presence of a flow-limiting coronary stenosis. During unimpeded coronary inflow, serotonin caused vasodilation with an increase in blood flow to all transmural myocardial layers. In contrast, in the presence of a stenosis, serotonin tended to increase subepicardial blood flow but paradoxically decreased

<table>
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<tr>
<th>TABLE 2. Effects of Intracoronary Serotonin Infusion on Myocardial Blood Flow in Seven Exercising Dogs With Left Circumflex Coronary Artery Stenosis</th>
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<tbody>
<tr>
<td>Control</td>
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<tr>
<td>LV anterior wall (control region)</td>
</tr>
<tr>
<td>Subendocardium</td>
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<tr>
<td>Inner middle layer</td>
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<td>Outer middle layer</td>
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<tr>
<td>Subepicardium</td>
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<td>LV posterior wall (ischemic region)</td>
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<tr>
<td>Subepicardium</td>
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</tbody>
</table>

Myocardial blood flow measured in milliliters per minute per gram of myocardial tissue. LV, left ventricle. Data are presented as mean±SEM; *p<0.05 ischemic region vs. control region; †p<0.05 serotonin vs. control; ‡p=0.08 serotonin vs. control using Wilcoxon signed rank test with Bonferroni correction.

**TABLE 3. Effects of Intracoronary Serotonin Infusion on Myocardial Blood Flow in Seven Exercising Dogs in the Absence of Left Circumflex Coronary Artery Stenosis**

| Control | Serotonin 2.0 μg/kg⁻¹·min⁻¹ |
|---------|-----------------|-------------------------------|
| Subendocardium                                | 2.43±0.25                    | 3.73±0.25*                   |
| Outer middle layer                            | 2.54±0.27                    | 4.64±0.33*                   |
| Inner middle layer                            | 2.39±0.24                    | 5.18±0.33*                   |
| Subepicardium                                 | 1.88±0.20                    | 5.29±0.38*                   |
| Mean                                            | 2.28±0.23                    | 4.72±0.27*                   |
| Endocardial/epicardial ratio                   | 1.30±0.04                    | 0.72±0.05*                   |

Myocardial blood flow measured in milliliters per minute per gram of myocardial tissue. Data are presented as mean±SEM; *p<0.05 vs. control.
flow to the subendocardium. The mechanism by which serotonin produced this decrease in subendocardial perfusion in the presence of a stenosis will be consid-
ered in detail.

Effects of Serotonin on the Normal Coronary Vasculature

Previous studies in anesthetized dogs in which coronary blood flow was directly measured have reported that serotonin is a potent small vessel dilator. Thus, intracoronary administration of serotonin in doses of 0.04–4 μg/kg, either per minute or as a bolus injection, resulted in a 15–100% increase in coronary blood flow.11,15,16 In the present study, administration of serotonin caused a doubling of coronary blood flow in the absence of a stenosis, even when exercise had already resulted in substantial vasodilation of the coronary resistance vessels. Lamping et al11 demonstrated that the increase in coronary flow produced by serotonin results from vasodilation of resistance vessels smaller than 100 μm in diameter. In contrast to the vasodilator response of the resistance vessels, serotonin causes vasoconstriction of larger coronary artery segments. Thus, in vivo studies of epicardial conductance vessels 2–3 mm in diameter have reported that serotonin caused 25–45% reductions in arterial cross-sectional area.10,15 Arterial vasoconstriction induced by serotonin was enhanced by removal of the endothelium.10 This occurred because serotonin causes both direct17,18 and flow-mediated12 release of endothelium-derived relaxing factor, which opposes its direct vasoconstrictor action. Serotonin-induced vasodilation is mediated by endothelial S1-like receptors, whereas large epicardial artery constriction involves either S1-like receptors16,19 or S2 receptors20,21 located on vascular smooth muscle cells.

Serotonin increased blood flow to all myocardial layers, but the increase in flow to the subepicardium exceeded that to the subendocardium. This could result from the unique pharmacological effects of serotonin or could be a nonspecific effect of a vasodilator in the presence of tachycardia. Pharmacological vasodilation of the coronary resistance vessels interferes with the normal ability of the subendocardial vessels to undergo selective vasodilation to compensate for the decreased diastolic perfusion interval during tachycardia.22 However, unpublished data from our laboratory show that the increase in flow produced by intracoronary adeno-
sine during exercise is associated with a lesser decrease in endo/epi ratio than that produced by serotonin. This suggests that the reduction in endo/epi ratio in the present study was in part related to the specific pharmacological profile of serotonin. Transmural differences in receptor density could result in nonuniform vasodila-
tion across the left ventricular wall. Alternatively, vasoconstriction of penetrating arteries could limit the increase in flow to the subendocardium.

Response of the Coronary Resistance Vessels During Hypoperfusion

The coronary circulation has generally been viewed as an array of conductance and resistance vessels, of which the latter are under metabolic control. Myocardial ischemia was thought to cause maximal vasodilation of the resistance vessels, which would override any competing vasoconstrictor influences. However, recent studies in swine and dogs have documented that even in ischemic myocardium, vasodilator reserve can be demon-
strated during adenosine administration, indicating that vasodilation is not maximal.2–5 Furthermore, α1-adrenoceptor stimulation8 or α2-adrenoceptor stimulation6 or the thromboxane A2 mimetic U466197,9 can produce vasoconstriction in ischemic myocardium and aggravate contractile dysfunction.6,9 Of particular interest was the observation that the increase in coronary blood flow produced by α1-adrenoceptor blockader,23 was enhanced by the presence of myocardial ischemia. Similarly, U46619 decreased blood flow only in the presence of myocardial ischemia but not during unim-
peded arterial inflow.9 These findings can be explained by vasoconstriction in arterial segments that are not under metabolic control but which contribute signifi-
cantly to total coronary resistance. Chilian et al24 have shown that approximately 25% of total coronary resistance resides in vessels >170 μm in diameter, whereas metabolic vasodilation occurs predominantly in vessels <100 μm in diameter.25 During normal conditions, vasoconstriction of the larger arterial segments may be compensated for by vasodilation of vessels <100 μm in diameter.6,26 However, when hypoperfusion has already caused metabolic vasodilation of the vessels <100 μm in diameter, vasoconstriction of larger segments can no longer be compensated for by further dilation of these smallest arterioles. In this situation, vasoconstriction of the larger arterial vessels would aggravate hypoperfusion. In addition to vasomotor tone in vessels that are not under metabolic control, recent evidence suggests that vasomotor tone may persist even in vessels that are under metabolic control. Thus, Chilian and Layne27 observed that even during severe hypoperfusion, adeno-
sine caused vasodilation in vessels <150 μm in diameter. Furthermore, Chilian28 observed that whereas α1- and α2-adrenoceptor stimulation had no effect on vessels <100 μm in diameter during normal arterial inflow, myocardial hypoperfusion resulted in unmasking of both α1- and α2-adrenoceptor-mediated vasoconstriction in vessels of this size.

Effect of Serotonin on Distal Vessels in the Presence of Coronary Artery Stenosis

Coronary blood flow and its transmural distribution.

Two previous studies have evaluated the effect of sero-
totonin on coronary blood flow in the presence of an arterial stenosis in open-chest dogs. Ichikawa et al10 used a coronary stenosis that caused a 30-mm Hg reduction in coronary pressure and a 15% decrease in coronary blood flow. Intracoronary infusion of serotonin (1.0 μg/kg min−1) which had produced a dou-
bled blood flow in the absence of a stenosis, still caused a 20% increase in blood flow in the presence of the stenosis. In contrast, Woodman13 reported that an intracoronary bolus injection of serotonin (2.0 μg/kg), which caused a 70% increase in flow under normal inflow conditions, resulted in a 12% decrease of flow in the presence of a critical coronary stenosis. Neither study examined the transmural distribution of myocar-
dial blood flow. In the present study, serotonin caused a decrease in flow to the subendocardium and tended to increase flow to the subepicardium with no change in total blood flow to the ischemic region. It can be argued
that the disparate responses to serotonin in the inner and outer layers were the result of ischemia in the inner but not the outer layer at a coronary pressure of 42 mm Hg. In this case, greater autoregulatory reserve in the subepicardial small vessels could better compensate for the large vessel constriction produced by serotonin. However, earlier studies using a similar experimental model revealed that both intracoronary adenosine and $\alpha_1$-adrenoceptor blockade produced an increase in blood flow that was essentially uniform in all transmural layers, suggesting that vasoconstrictor reserve is evenly distributed along the left ventricular wall at this perfusion pressure. Because both serotonin and adenosine dilate arterioles with diameters $<100$ $\mu$m, serotonin might have been expected to also increase flow in all transmural layers. Although serotonin caused the expected increase in flow in the subepicardium, the stenosis unmasked an unexpected vasoconstrictor action of serotonin in the subendocardium.

**Role of intramural penetrating arteries.** Recently, Chilian reported that in the normal heart, intravascular pressure in arterial segments of 100 $\mu$m is considerably lower in the subendocardium than in the subepicardium. This indicates that a significant pressure drop occurs across the penetrating arteries that traverse the left ventricular wall to deliver blood to the subendocardium. These penetrating arteries range from 50 to 500 $\mu$m in diameter, with most around 200 $\mu$m. Serotonin is known to constrict vessels $>100$ $\mu$m in diameter; vasodilation of the penetrating arteries by serotonin would increase resistance to blood flow in the innermost layers. In the normal heart, the major portion of coronary resistance resides in arterioles $<100$ $\mu$m. Dilatation of these resistance vessels by serotonin would outweigh the effect of constriction of the penetrating arteries. In contrast, in the presence of a flow-limiting coronary stenosis, the arterioles $<100$ $\mu$m in diameter have already undergone ischemic vasodilation. Vasodilation of the penetrating arteries by serotonin would now outweigh any slight additional vasodilation of the arterioles $<100$ $\mu$m in diameter, causing a decrease of subendocardial flow. Although the arterial vessels that supply the subepicardial microvasculature would also be constricted by serotonin, these vessels travel a much shorter distance, so their contribution to subepicardial resistance is less than the contribution of the penetrating arteries to subendocardial resistance.

**Transmural steal.** Vasodilation of coronary resistance vessels distal to a flow-limiting arterial stenosis can result in passive redistribution of blood flow away from the subendocardium. This phenomenon is dependent upon the decrease in coronary perfusion pressure, which occurs when the stenosis prevents flow from increasing in response to distal vasodilation. Interaction between the decreased intravascular distending pressure and extravascular compressive forces (which are highest in the subendocardium) results in passive redistribution of flow away from the subendocardium. To prevent this phenomenon, coronary pressure was maintained constant in the present study. Thus, passive redistribution of flow across the left ventricular wall cannot explain the observed decrease in subendocardial perfusion during serotonin infusion.

**Blood Concentrations of Serotonin**

To know whether the effects observed in the present study might occur in the clinical setting, it is important to determine whether the concentrations of serotonin used in this study could be achieved during platelet aggregation. Using the measured flow rates to compute dilution factors, the doses of 0.4–2.0 $\mu$g/kg$^{-1}$·min$^{-1}$ of serotonin used in the present study correspond to blood concentrations of approximately 1.5–7.5$\times10^{-8}$ M. Benedict et al. reported coronary sinus plasma serotonin levels of 2$\times10^{-8}$ M during in vivo coronary artery thrombus formation in dogs. In vitro aggregating platelets in numbers found in human blood yield serotonin concentrations as high as 6$\times10^{-8}$ M. These data indicate that the concentrations of serotonin used in our study can be achieved during in vivo platelet aggregation.

**Clinical Implications**

Transcardiac serotonin concentrations can be increased in patients with occlusive coronary artery disease, especially with irregular eccentric atherosclerotic lesions. Studies in open-chest dogs have shown that local serotonin blood levels are elevated at the site of a coronary artery stenosis that produces cyclic flow variations. Serotonin liberated during platelet aggregation can worsen the stenosis severity by causing vasoconstriction of large epicardial coronary arteries, especially when the endothelium is damaged. The present study shows that in addition to increasing stenosis resistance, serotonin can worsen hypoperfusion of the subendocardium, probably by causing vasoconstriction of the penetrating arteries that deliver blood to the deeper myocardial layers. Distal coronary artery constriction has recently been identified as a cause for myocardial ischemia in patients with stable angina pectoris. It is possible that in the presence of a coronary stenosis, constriction of intramural penetrating arteries by serotonin could contribute to the development of subendocardial ischemia.

**References**


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Circulation. 1992;86:1559-1565
doi: 10.1161/01.CIR.86.5.1559

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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