Stenosis differentially affects subendocardial and subepicardial arterioles in vivo

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Received 2 February 2000; accepted in final form 9 November 2000

Merkus, D., I. Vergroesen, O. Hiramatsu, H. Tachibana, H. Nakamoto, E. Toyota, M. Goto, Y. Ogasawara, J. A. E. Spaan, and F. Kajiya. Stenosis differentially affects subendocardial and subepicardial arterioles in vivo. Am J Physiol Heart Circ Physiol 280: H1674–H1682, 2001.—The presence of a coronary stenosis results primarily in subendocardial ischemia. Apart from the decrease in coronary perfusion pressure, a stenosis also decreases coronary flow pulsations. Applying a coronary perfusion system, we compared the autoregulatory response of subendocardial (n = 10) and subepicardial (n = 12) arterioles (<120 μm) after stepwise decreases in coronary arterial pressure from 100 to 70, 50, and 30 mmHg in vivo in dogs (n = 9). Pressure steps were performed with and without stenosis on the perfusion line. Maximal arteriolar diameter during the cardiac cycle was determined and normalized to its value at 100 mmHg. The initial decrease in diameter during reductions in pressure was significantly larger at the subendocardium. Diameters of subendocardial and subepicardial arterioles were similar 10–15 s after the decrease in pressure without stenosis. However, stenosis decreased the dilatory response of the subendocardial arterioles significantly. This decreased dilatory response was also evidenced by a lower coronary inflow at similar average pressure in the presence of a stenosis. Inhibition of nitric oxide production with Nω-monomethyl-L-arginine abrogated the effect of the stenosis on flow. We conclude that the decrease in pressure caused by a stenosis in vivo results in a larger decrease in diameter of the subendocardial arterioles than in the subepicardial arterioles, and furthermore stenosis selectively decreases the dilatory response of subendocardial arterioles. These two findings expand our understanding of subendocardial vulnerability to ischemia.

au toregulation; coronary microcirculation; ischemia

Materials and Methods

All experiments were done in accordance with the guidelines on animal experiments of our institutions. Thirteen mongrel dogs were sedated with an injection of ketamine (10 mg/kg im) and were then given an injection of pentobarbital sodium (25 mg/kg iv) for anesthesia. Depth of anesthesia was monitored by checking reflexes, and additional anesthesia was given when necessary. Dogs were ventilated (after tracheal intubation) with a mixture of room air and oxygen using a jet ventilator. Blood gases and pH were measured regularly, and oxygen and CO2 were kept within physiological limits by adaptation of the ventilation (pH = 7.35–7.45, 1 pCO2 = 30–40 mmHg).

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The PCO₂ system is 2.5–5 on videotape every 33 ms. The spatial resolution of this saline through a small channel of the sheath.

decrease in coronary perfusion pressure. Blood between the entire protocol and prompt responses of the vessels to a direct compression of the microvessels by the needle tip as doughnut-shaped balloon on the tip of the sheath prevents was enclosed in a Silastic 14-Fr double-lumen sheath. A CCD camera as previously described (19). The needle probe Application of Videomicroscope in the first diagonal branch of the left anterior descendingension pressure was measured either with a thin fluid-filled arterial line was destroyed by injection of 40% formaldehyde and the heart was paced at a constant heart rate of 100–120 beats/min.

**Application of System for Controlled Perfusion of Coronary Arteries**

To manipulate coronary arterial pressure and its pulsations, the heart was perfused with blood from the left femoral artery by means of a perfusion system similar to the one described by Spaan (16). To avoid coagulation, heparin was administered (initial dose 3 ml, 5,000 IU/ml iv, followed by continuous administration). An in-line flow probe (Transonic 4-Fr, connected to a T206 Transonic flowmeter) just proximal to the Gregg cannula in the left main coronary artery was used to measure phasic coronary blood flow. Coronary perfusion pressure was measured either with a thin fluid-filled catheter at the cannula tip or a fluid-filled 24-gauge catheter in the first diagonal branch of the left anterior descending coronary artery.

**Application of Videomicroscope**

Subendocardial and subepicardial microvessels were visualized using a needle-probe videomicroscope coupled to a CCD camera as previously described (19). The needle probe was enclosed in a Silastic 14-Fr double-lumen sheath. A doughnut-shaped balloon on the tip of the sheath prevents direct compression of the microvessels by the needle tip as was evidenced by diameter pulsations of the vessels during the entire protocol and prompt responses of the vessels to a decrease in coronary perfusion pressure. Blood between the needle tip and the vessels can be flushed away by injection of saline through a small channel of the sheath.

Images on the CCD camera were monitored and recorded on videotape every 33 ms. The spatial resolution of this system is 2.5–5 μm for ×200 magnification. The maximal depth of field is ~250 μm.

For observation of subepicardial microvessels, the needle probe with inflated balloon was placed gently on the epicardial surface and moved slowly to find microvessels of appropriate size (40–120 μm). For observation of subendocardial microvessels, the needle probe was inserted through an incision in the left atrial appendage via the mitral valve into the left ventricle. The balloon was then inflated and the needle probe was placed gently on the endocardial surface (septum between anterior and posterior papillary muscle) and moved slowly until a microvessel was found. When necessary the blood between the probe and the endocardial surface was flushed away with saline. When a clear image was obtained either of a subendocardial or a subepicardial vessel, an operator manually maintained the probe in the same position by monitoring the image. The vascular image was then stored on the VCR. Arterioles were distinguished from veins by intracoronary injection of the dye indocyanin green with the camera in color mode. The dye appeared first in the arterioles and then in the venules.

**Protocol**

While subepicardial (n = 12, diameter 80.3 ± 5.0 μm (mean ± SE)) or subendocardial (n = 10, diameter 64.5 ± 5.9 μm) arterioles were observed by the videomicroscope, perfusion pressure was lowered stepwise from 100 mmHg (control) to either 70, 50, or 30 mmHg and kept at this level for 20–30 s before being increased back to control level. A screw clamp which caused a pressure drop of ~100 mmHg was applied on the perfusion line to increase pressure pulsations and to decrease flow pulsations which is a pattern essentially similar to a pathological stenosis in the coronary arteries (11). Pressure proximal to the clamp was increased to maintain an average distal (perfusion) pressure of 100 mmHg and then pressure steps were performed as described above. Pressure steps without stenosis were performed in 8 out of 10 subendocardial arterioles and in 10 out of 12 subepicardial arterioles. Pressure steps in the presence of a stenosis were performed for all subepicardial arterioles and in 9 out of 10 subendocardial arterioles.

Left ventricular pressure, aortic pressure, coronary perfusion pressure, and coronary blood flow were measured during the interventions, digitized at a rate of 80 Hz, and stored on a personal computer.

**Adenosine and NG-Monomethyl-L-Arginine Experiments**

At the end of the diameter protocols, adenosine was administered in four experiments and N⁵-monomethyl-l-arginine (L-NMMA) was given in four different experiments. Under these conditions the pressure-step protocols were repeated to establish pressure and flow relations similar to those measured during the diameter-change protocols. No data on diameters are available from these experiments.

**Data Analysis**

At the end of the experiment, the time-sequential images were transferred from videotape to a personal computer. Vascular diameter was determined from the digitized images by manual border tracing. Diameters of the vessels were determined throughout the cardiac cycle from 2.5 s before until 2.5 s after the pressure step downward and during another 3 s after allowing 10–15 s for vasodilation at low pressure. In this period of time, flow reached a new steady state. The diameter was measured in approximately one out of every two images or every image if diameter changed abruptly, which yielded a time resolution of either 33 or 66 ms. During each period of measurement, minimal, maximal, and end diastolic (just before the R wave of the electrocardiogram) diameter were determined for 3–6 consecutive beats. The averages of these measurements were used. All diameters were normalized to their average value at 100 mmHg arterial pressure in control to compare subendocardial and subepicardial arterioles. Both maximal and end-diastolic diameters were used for comparison. The effect of a stenosis was investigated by comparing the maximal diameters at the same mean coronary arterial pressure.

**Statistics**

Data are given as means ± SE. The effects of pressure and stenosis on diameter were determined using ANOVA and paired t-tests. The differences between subendocardial and subepicardial arterioles were tested using unpaired t-tests.
RESULTS

Hemodynamics

Typical examples of a pressure step from 100 to 50 mmHg without stenosis (A) and with stenosis (B). Phasic patterns of perfusion pressure ($P_p$), coronary arterial flow, left ventricular pressure ($P_{lv}$), its derivative ($dP_{lv}/dt$), and aortic pressure ($P_{ao}$) are shown. Left ventricular function does not change during the period of underperfusion as is evidenced by the constant maximal left ventricular pressure.

The application of the needle probe for measurement of subendocardial arterioles did not result in a decrease in left ventricular pressure, indicating that the pump function of the heart was not affected (see the hemodynamic variables in Table 1).

Furthermore, the increase in flow during reactive hyperemia after a 15-s occlusion was 3.1 ± 0.2-fold, indicating that autoregulation was present in our preparation.

Table 1. Hemodynamic parameters before changes in arterial pressure with and without stenosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Minimal Left Ventricular Pressure, mmHg</th>
<th>Maximal Left Ventricular Pressure, mmHg</th>
<th>Coronary Pressure, mmHg</th>
<th>Coronary Flow, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo without stenosis</td>
<td>8</td>
<td>5 ± 1</td>
<td>105 ± 14</td>
<td>100 ± 3</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>Endo with stenosis</td>
<td>9</td>
<td>4 ± 1</td>
<td>98 ± 11</td>
<td>99 ± 9</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Epi without stenosis</td>
<td>10</td>
<td>5 ± 1</td>
<td>88 ± 9</td>
<td>99 ± 2</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Epi with stenosis</td>
<td>12</td>
<td>5 ± 1</td>
<td>85 ± 6</td>
<td>102 ± 4</td>
<td>69 ± 14</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of dogs. Endo, subendocardial microvessels; Epi, subepicardial vessels.
Changes in Arteriolar Diameter

In Fig. 2, the diameter changes of a subepicardial arteriole during stepwise changes in pressure without stenosis (left) and with stenosis (right) are shown. The change in diameter after a pressure step from 100 to 70 mmHg (Fig. 2A) was small. The diameter 10 s after the pressure step was larger than the diameter immediately after the pressure step both in the presence and absence of a stenosis. The diameter change of the same arteriole after a pressure step from 100 to 30 mmHg is also depicted (Fig. 2B). Maximal diameter decreased immediately after the pressure step but increased between 2 and 10 s after the pressure step. The changes in maximal diameter after the pressure steps were similar in the presence and absence of a stenosis.

Phasic Patterns

At high pressure (100 and 70 mmHg), diameter of the subepicardial arterioles increased during systole and decreased in the subsequent diastole (Fig. 2A). At 30 mmHg, the pattern of the diameter variation during cardiac contraction was quite different especially without stenosis (Fig. 2B, left). Diameter decreased sharply at the onset of systole in three of the vessels, increased during the plateau phase of left ventricular pressure, and decreased slowly during diastole. In the remaining vessels, diameter increased gradually during systole at low pressures as well. The stenosis reduced the diameter pulsations at all pressures.

Figure 3 depicts the diameter change of a subendocardial arteriole. In response to a pressure step from 100 to 70 mmHg (Fig. 3A), maximal diameter first decreased and then increased during the next 10 s especially in the absence of a stenosis on the perfusion line (left). Figure 3B again shows the diameter responses to a pressure step from 100 to 30 mmHg with and without a stenosis. The decrease in diameter was larger after the pressure step to 30 mmHg than after the pressure step to 70 mmHg. Maximal diameter 10–15 s after the pressure step was larger than immediately after the pressure step.

The diameter of the subendocardial arteriole decreases during systole at all pressures. These diameter pulsations are slightly less in the presence of a stenosis.

Effects of Pressure

Figure 4 shows the average relation between coronary perfusion pressure and beat-maximal diameter normalized to maximal diameter at 100 mmHg. Normalized diameters of the subendocardial arterioles immediately after the pressure steps were significantly smaller than those of the subepicardial arterioles at the same pressures both with (Fig. 4B) and without (Fig. 4A) stenosis. The diameters of the subendocardial and subepicardial arterioles were similar 15 s after the step without stenosis. Hence the diameter of the subendocardial arterioles initially decreased more than that of the subepicardial arterioles, but the subendocardial arterioles subsequently dilated more resulting in similar normalized diameters 15 s after the pressure change. With stenosis the diameter of the subendocardial arterioles 15 s after the decrease in pressure remained smaller than that of the subepicardial arterioles at 70 mmHg but not at 50 mmHg. Autoregulation was present because flow 15 s after the pressure step was not significantly different between 70 and 100
mmHg but decreased with pressure at 50 and 30 mmHg (Fig. 5C).

Influence of a Stenosis

The effect of the stenosis on maximal diameter and total coronary blood flow is shown in Fig. 5. Two seconds after a reduction in pressure the relations between pressure and diameter for both subendocardial (Fig. 5A) and subepicardial (Fig. 5B) arterioles and the relation between pressure and flow (Fig. 5C) were not influenced by the stenosis. However, 15 s after the reduction in pressure, both total coronary blood flow and diameter of the subendocardial arterioles were significantly smaller in the presence of a stenosis at matched average pressures (49 ± 3 and 49 ± 4 mmHg, stenosis absent and present, respectively), whereas there was no significant difference at higher pressure. The stenosis had no effect on the pressure-flow relations at maximal dilation as is shown in four experiments with adenosine (Fig. 6A). Furthermore, the effect of the stenosis on the pressure-flow relations was abrogated in four experiments with L-NMMA (Fig. 6B).

**DISCUSSION**

**Summary of Findings**

A coronary stenosis has two major hemodynamic effects on myocardial perfusion: a drop in mean perfusion pressure and a decrease in flow pulsatility. We separated these two effects by performing stepwise changes in coronary arterial pressure in the presence and absence of a stenosis. The effects of these pressure steps on mean arterial flow and diameters of subendocardial and subepicardial arterioles were studied. Initially, the maximal diameter of the subendocardial arterioles decreased more in response to a decrease in coronary arterial pressure than the maximal diameter of the subepicardial arterioles both in the presence and absence of a stenosis. The normalized maximal diameter of the subendocardial arterioles 10–15 s after the pressure step was similar to that of the subepicardial arterioles in the absence of a stenosis. However, the stenosis affected dilation of the subendocardial arterioles, whereas the dilation of the subepicardial arterioles remained unchanged after 10–15 s of low pressure. Flow to the myocardium at similar distal perfusion pressure was lower in the presence of a stenosis, which is in agreement with the reduced diameters in the subendocardium.

**Methodological Limitations**

The vessels found in the subendocardium limited our range of vessel diameters to 40–120 μm. From the literature, the dilatory responses are expected to be largest in this diameter range (13, 18).

We have quantified the responses of resistance vessels by maximal diameter during the heartbeat. The initial decrease in diameter is passive and due to a decrease in intravascular pressure because the initial measurements were taken 2 s after a change in pressure that is too fast for changes in tone to occur. This initial decrease in diameter needs to be overcome by vasodilation. We therefore defined vasodilation as the change in diameter between 2 and 15 s after the pres-
sure step. However, full description of a vasodilatory response would require knowledge about local intravascular pressure. An increase in diameter at constant intravascular and extravascular pressures would be vasodilation comparable to that in an isolated vessel experiment. However, intravascular pressure of a resistance vessel somewhere in the arterial tree depends not only on the pressure at the entrance and outlet of the arterial tree but also on the balance of proximal and distal resistances. Dilation is larger in distal vessels than in more proximal vessels. Therefore, it is possible that the intravascular pressure of the vessels we measured actually decreased and that we underestimated the decrease in tone. Unfortunately, no measurements of intravascular pressure in subendocardial arterioles of a beating autoregulating heart are available. In the nonbeating heart without vascular tone, it was shown that pressure in subendocardial arterioles is lower than pressure in subepicardial arterioles of the same size at perfusion pressures ranging from 40 to 100 mmHg (4).

![Fig. 4. Average relation between pressure and normalized maximal diameter for all subendocardial and subepicardial arterioles with (B) and without (A) stenosis. Diameter was normalized to its average value at 100 mmHg before each pressure step. Both subendocardial and subepicardial arterioles dilated significantly at all pressures. Diameter of subendocardial arterioles initially decreased significantly more in response to a decrease in pressure than the diameter of subepicardial arterioles. However, after allowing 10–15 s for dilation, no significant difference between subendocardial and subepicardial arterioles was found without stenosis. Hence subendocardial arterioles dilated more to compensate for the larger initial decrease in diameter. With stenosis, after allowing 10–15 s for dilation, the diameter of subendocardial arterioles was smaller at 70 mmHg than that of subepicardial arterioles.](image)

![Fig. 5. Perfusion with stenosis induced a rightward shift of both the steady-state pressure-flow relationship (C) and the steady-state pressure-diameter relationship of subendocardial arterioles (A) compared with perfusion without stenosis. However, stenosis did not influence the steady-state pressure-diameter relationship of subepicardial arterioles (B). Owing to experimental limitations the pressures with and without stenosis are not the same.](image)
By comparing responses in a normalized and standardized manner, we have tried to minimize circumstantial variations in conditions. We normalized our results to the maximal diameter at an arterial pressure of 100 mmHg with tone intact. Because resistance is inversely proportional to diameter to the power of four, the highest diameter will have the largest positive effect on perfusion. Indeed, maximal diameter does occur in late diastole for the subendocardium and hence at the moment that muscle perfusion is highest. For the subepicardial vessels, maximal diameter was found during systole. However, perfusion of the subepicardium occurs both during systole and diastole, so maximal diameter of the subepicardial arterioles will also be an important parameter for local perfusion (2, 8). We have analyzed the influence of choice of this standardization by also calculating all responses using end-diastolic diameters as is usually done in literature (5, 12). In our data, there is not much difference between subendocardial maximal and end-diastolic diameter, but for the subepicardial vessels there is some difference. However, the changes in diameter for decreases in pressure and with dilation are similar for maximal and end-diastolic diameter (within 2% for all interventions except 30 mmHg without stenosis, in which the difference is 4%). Recalculation of the results using end-diastolic diameter therefore yielded similar results, indicating that dilation is indeed evidenced by an increase in maximal diameter.

Comparison to Literature

There are some major differences between the present study and earlier studies on in vivo coronary resistance vessels. We cannulated the left main coronary artery and used a perfusion system to change coronary arterial pressure. In other studies, coronary arterial pressure was decreased by application of a stenosis around either the left anterior descending or the left circumflex coronary artery (5, 12). Furthermore, we recorded not only steady-state diameter 15 s after the decrease in pressure but also the dynamic change in diameter due to the decrease in pressure, and we measured diameter changes during the whole cardiac cycle.

In steady state we found less dilation of the subepicardial arterioles than previously reported (5, 12). It is important to realize that the dilatory responses are heterogeneous both in our study and in the other studies cited. Although the average data show no dilation at low pressure compared with the diameter of the arterioles at 100 mmHg, some of the individual vessels did dilate (subendocardial: 4, 4, and 2 out of 10 vessels dilated at pressures 70, 50, and 30 mmHg, respectively; subepicardial: 5, 4, and 3 out of 12 vessels dilated at 70, 50, and 30 mmHg, respectively). In the study of Chilian and Layne (5), 65% of the arterioles smaller than 100 μm (n = 9) dilated at 40 mmHg, whereas none of the arterioles smaller than 100 μm (n = 4) dilated at 30 mmHg.

Furthermore, because of the application of the perfusion system which contains a substantial extracorporeal volume, systolic left ventricular pressure is slightly lower than under physiological conditions in the dog. This may have resulted in activation of the baroreceptors in the aortic arch and/or the carotid sinus, which may have resulted in activation of several neurohumoral pathways aiming for an increase in peripheral resistance and an increase in heart rate to maintain blood pressure. Because we kept heart rate constant via atrial pacing, maintenance of blood pressure could only be achieved by vasoconstriction (most likely through activation of the α-adrenoceptors). We cannot exclude that activation of the α-adrenoceptors in the heart may have limited vasodilation in our preparation especially in subendocardium.

Despite the fact that we did not observe dilation compared with the diameter at 100 mmHg, flow was autoregulated at a perfusion pressure of 70 mmHg. Evidently, there are other factors involved in regulation of flow besides the changes in arteriolar diameter in the vessels observed. In a previous study (14) we reported that a global reduction in coronary pressure results in an increase in diastolic duration and therefore reduces extravascular resistance and probably also reduces myocardial oxygen consumption. Based on data from Bache and Cobb (2) and our previous paper (14) we assumed that a 1% increase in the diastolic...
time fraction resulted in a 2.6% decrease in resistance in the maximally dilated coronary vasculature. Using this number and the increase in diastolic time fraction at each pressure we calculated the decrease in resistance due to the increase in the diastolic time fraction (shown as $\Delta R_{\text{DTF}}$ in Table 2). Additionally we calculated the decrease in resistance due to the increase in diameter using Poiseuille’s law ($\Delta R_{\text{di}}$ in Table 2). We compared the sum of these two to the actual change in resistance, based on changes in pressure and flow ($\Delta R_{\text{flow}}$ in Table 2), and this way we could account for 65–99% of the change in resistance. The remaining change in resistance is due to other mechanisms such as recruitment (1). In the other studies (5, 12) in which a segmental preparation was used, extravascular resistance probably increased in the underperfused areas because when part of the heart relaxes earlier, the surrounding normally perfused tissue still contracts and may therefore stretch the part that is already relaxing. This stretch hinders perfusion of the tissue and will therefore increase resistance and require additional vasodilation.

**Differences Between Endocardium and Epicardium**

The subendocardium is more vulnerable to ischemia than the subepicardium. There are several observations in our study that may contribute to the explanation of this larger endocardial vulnerability.

**Response to pressure change.** We found differences between subendocardial and subepicardial arterioles both in the narrowing response of maximal diameter to the initial decrease in pressure and in the subsequent dilation. The initial decrease in maximal diameter is larger for the subendocardial arterioles (Fig. 4). Hence, the subendocardial arterioles must dilate more to compensate for the passive decrease in diameter and therefore use more of their dilatory reserve in response to a similar decrease in pressure. The remaining dilatory reserve of the subendocardial arterioles may therefore fall short when myocardial demand is subsequently increased during an increase in heart rate.

The larger “passive” decrease in diameter in the subendocardium may be attributed to an increase in resistance of the intramural arteries upon a decrease in pressure in the large coronary arteries (6) resulting in a larger decrease in pressure in the subendocardium than in the subepicardium.

**Effect of stenosis.** A stenosis in the coronary arteries not only results in a decrease in distal coronary perfusion pressure but decreases the pulsatility of flow as well. We showed that this hemodynamic aspect of a stenosis affects both subendocardial arterioles and mean coronary flow, whereas no difference in diameter of the subepicardial arterioles was found. Because the effect of a stenosis on mean flow disappears in the presence of L-NMMA, it is likely that it is caused by a change in nitric oxide (NO) production. NO production is directly related to shear stress on the endothelium. Shear stress is not constant during the cardiac cycle. Because flow to the subendocardium is more pulsatile than flow to the subepicardium, the maximal flow and maximal shear stress are likely to be higher as well. Consequently NO production in the subendocardium is higher than in the subepicardium, and perfusion of the subendocardium is more dependent on NO production. A decrease in flow pulsations by the stenosis will compromise NO production and thereby affect the subendocardium more than the subepicardium. In support of this theory are previous data from our group showing that dilation of the subendocardial arterioles in response to an occlusion (which is an extreme form of a stenosis) was more affected by L-NMMA than dilation of the subepicardial arterioles indicating that the perfusion of the subendocardium is indeed more dependent on NO than the subepicardium (18). Our data thereby suggests a mechanism by which pulsatile flow in the coronary circulation favors flow to the subendocardium by selectively increasing subendocardial NO production and thereby decreasing subendocardial resistance.

It is unlikely that the decrease in flow is caused by the difference in the arterial pressure profile (higher

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**Table 2. Changes in resistance without stenosis based on changes in flow, diastolic duration, and diameter**

<table>
<thead>
<tr>
<th>Pressure (mmHg)</th>
<th>$\Delta R_{\text{flow}}$</th>
<th>$\Delta$DTF</th>
<th>$\Delta R_{\text{DTF}}$</th>
<th>Dilation</th>
<th>$\Delta R_{\text{di}}$</th>
<th>$\Delta R_{\text{tot}}$</th>
<th>$\Delta R_{\text{tot}}/\Delta R_{\text{flow}}$</th>
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</thead>
<tbody>
<tr>
<td><strong>Subepicardial arterioles (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>0.48 ± 0.05</td>
<td>0.03 ± 0.01</td>
<td>0.07 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.18 ± 0.05</td>
<td>0.25 ± 0.05</td>
<td>0.65 ± 0.19</td>
</tr>
<tr>
<td>50</td>
<td>0.58 ± 0.05</td>
<td>0.07 ± 0.01</td>
<td>0.18 ± 0.03</td>
<td>0.05 ± 0.02</td>
<td>0.21 ± 0.07</td>
<td>0.39 ± 0.09</td>
<td>0.68 ± 0.19</td>
</tr>
<tr>
<td>30</td>
<td>0.70 ± 0.04</td>
<td>0.12 ± 0.01</td>
<td>0.31 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>0.20 ± 0.08</td>
<td>0.51 ± 0.08</td>
<td>0.75 ± 0.13</td>
</tr>
<tr>
<td><strong>Subendocardial arterioles (n = 8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>0.51 ± 0.04</td>
<td>0.04 ± 0.01</td>
<td>0.10 ± 0.02</td>
<td>0.07 ± 0.02</td>
<td>0.35 ± 0.12</td>
<td>0.45 ± 0.13</td>
<td>0.65 ± 0.16</td>
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<tr>
<td>50</td>
<td>0.62 ± 0.03</td>
<td>0.07 ± 0.03</td>
<td>0.18 ± 0.03</td>
<td>0.06 ± 0.01</td>
<td>0.28 ± 0.04</td>
<td>0.46 ± 0.06</td>
<td>0.69 ± 0.09</td>
</tr>
<tr>
<td>30</td>
<td>0.76 ± 0.09</td>
<td>0.10 ± 0.01</td>
<td>0.27 ± 0.03</td>
<td>0.08 ± 0.04</td>
<td>0.42 ± 0.22</td>
<td>0.69 ± 0.24</td>
<td>0.99 ± 0.30</td>
</tr>
</tbody>
</table>

Data are means ± SE; n, no. of dogs. $\Delta R_{\text{flow}}$, resistance change as calculated from measured flow change between 3 and 15 s after pressure step down; $\Delta$DTF, change in diastolic time fraction between 3 and 15 s after pressure step down; $\Delta R_{\text{DTF}}$, change in resistance due to change in DTF, assuming that each percent increase in diastolic duration results in a 2.6% decrease in resistance (2); Dilation, change in relative diameter between 3 and 15 s after pressure step down; $\Delta R_{\text{di}}$, change in resistance due to dilation assuming that diameter and resistance are related according to Poiseuille’s law; $\Delta R_{\text{tot}}$, sum of $\Delta R_{\text{DTF}}$ and $\Delta R_{\text{di}}$; $\Delta R_{\text{tot}}/\Delta R_{\text{flow}}$, part of total resistance change that can be explained based on changes in diastolic duration and vasodilation.
systolic pressure, lower diastolic pressure) induced by the stenosis (Fig. 1), because the stenosis had no effect on total flow in the presence of adenosine. Our observation that the presence of a stenosis, which increases arterial pressure pulsations, results in a decrease in coronary arterial flow seems in contrast with studies in both isolated arteries (9) and in the whole coronary vascular bed (15), which have shown that perfusion of the myocardium with pulsatile pressure (with an amplitude larger than 60 mmHg) induces vasodilation compared with perfusion at constant pressure. This apparent contradiction may be explained by comparing the effect of pulsatile perfusion pressure on local transmural pressure, being the difference between intravascular and extravascular pressure. Perfusion of the large coronary arteries with pulsatile pressure compared with constant pressure certainly increases the intravascular pressure pulsations to 37 ± 9 mmHg by increasing systolic intravascular pressure and decreasing diastolic intravascular pressure. Because subendocardial extravascular pressure (left ventricular pressure) also increases during systole and decreases during diastole, the difference between intravascular pressure and extravascular pressure becomes smaller both during systole and diastole as is evidenced by the decrease in diameter pulsations in the presence of the stenosis in our study. Therefore, despite the increase in intravascular pressure pulsations, the local subendocardial transmural pulsation amplitude may decrease resulting in constriction of the subendocardial arterioles. Such a specific effect on the subendocardial resistance vessels may therefore be a serious factor in the limitation of subendocardial perfusion in the presence of a stenosis and may contribute to the larger subendocardial vulnerability to ischemia.

In summary, a decrease in pressure results in a larger initial decrease in diameter of the subendocardial arterioles than in the subepicardial arterioles. Furthermore, a stenosis selectively decreases the dilatory response of subendocardial arterioles as well as coronary blood flow. The effect of a stenosis on coronary blood flow may be due to a decrease in NO production caused by the stenosis. These findings are consistent with findings that endocardial perfusion is more reduced by a stenosis than epicardial perfusion.

Assistance of Ms. Ogi with the data analysis is greatly appreciated.

Financial support from the Netherlands Heart Foundation (Grant 92.128) and the Netherlands Organization for Scientific Research (NWO, Grant R90–160) is gratefully acknowledged.

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