Reactive Dilation of Large Coronary Arteries in Conscious Dogs

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SUMMARY. To study the response of large coronary arteries to short periods of myocardial ischemia a pair of ultrasonic dimension transducers, a flow probe and a hydraulic occluder were implanted around the left circumflex coronary artery for the instantaneous and continuous measurement of external coronary artery dimensions and coronary blood flow, respectively. At 6.1 ± 0.4 seconds after release of a 15-second occlusion, mean coronary blood flow increased by 255 ± 30% from a preocclusion flow of 32 ± 4.1 ml/min. At this time, large coronary arterial cross-sectional area was unchanged but increased slowly, reaching a peak 28 ± 4.4% above preocclusion levels 61 ± 3.2 seconds after occlusion, i.e., reactive dilation. During maximal reactive dilation, coronary blood flow had already returned to control levels, and heart rate, mean arterial pressure, left ventricular systolic pressure, and left ventricular dP/dt were not different from control. The reactive dilation was not affected if the occlusion occurred proximal or distal to where diameter was measured, or by combined α- and β-adrenergic receptor blockade, ganglionic blockade, inhibition of prostaglandin synthesis, or by aminophylline. When the reactive hyperemia was prevented by constricting the coronary artery upon release of the coronary occlusion, the reactive dilation was not observed. Thus, large coronary arteries respond to brief periods of occlusion with reactive dilation. The time course of this response is distinctly different from the accompanying reactive hyperemia, and could be eliminated by preventing the marked increase in coronary blood flow following release from the brief period of coronary artery occlusion. (Circ Res 54: 50-57, 1984)

REACTIVE hyperemia, the striking vasodilation in response to a brief arterial occlusion, is a fundamental characteristic of the coronary circulation, and has been characterized extensively in open-chest anesthetized, and in intact, conscious animals (Olsson and Gregg, 1965). Although there is controversy over whether the mechanism of reactive hyperemia is myogenic or metabolic (Katz and Lindner, 1936; Gregg and Fisher, 1965; Berne and Rubio, 1979; Schwartz et al., 1982), this phenomenon is thought to involve only resistance vessels, and not the large conductance vessels. In fact, prior studies in anesthetized animals with an open chest indicated that large coronary artery resistance does not decrease following the release of a brief coronary occlusion (Winbury et al., 1969; Fam and McGregor, 1969; Takeda et al., 1977). Recently, techniques have become available to assess changes in the dimensions of large coronary arteries in intact, conscious animals (Vatner et al., 1980). These techniques have been utilized to demonstrate that the caliber of large coronary arteries changes in response to interventions that directly affect these vessels and also in response to alterations in myocardial metabolism, e.g., heart rate, wall tension (Macho et al., 1981). The goal of this study was to determine whether large coronary arteries dilate after brief periods of coronary artery occlusion in the conscious dog. A second goal was to determine the mechanism of the dilation by (1) comparing responses to occlusions of the large coronary arteries distal and proximal to the segment of vessel where diameter was measured, since during the latter, but not the former conditions, distending pressure falls, (2) comparing the effects of increasing duration of coronary artery occlusion, (3) repeating occlusion after autonomic blockade, inhibition of prostaglandin synthesis with indomethacin, and inhibition of the action of adenosine with aminophylline, and (4) maintaining blood flow constant at preocclusion levels by only partially releasing the hydraulic occluder following coronary artery occlusion. This latter maneuver was considered important in light of prior studies demonstrating flow-dependent dilation of large arteries (Ingebrigtsen and Leraand, 1970; Lie et al., 1970; Gerova et al. 1980).

Methods

Mongrel dogs (n = 12) were operated upon using general anesthesia with pentobarbital sodium (30 mg/kg), and sterile surgical techniques, and a left thoracotomy approach. Tygon catheters (Norton Plastics and Synthetics Division) were implanted in the descending thoracic aorta and left atrium. Solid state miniature pressure gauges (Konigsberg Instruments) were implanted in the apex of the left ventricle and in the thoracic aorta. The left circum-
flex coronary artery was isolated 3–6 cm from its origin for the placement of an electromagnetic (n = 8) flow probe (Zepada Instruments) or a Doppler ultrasonic flow probe (n = 4). Ultrasonic dimension transducers, 7 MHz piezoelectric crystals (1 x 2 mm x 12 mg) attached to a dacron backing, were sutured to opposing surfaces of the circumflex coronary artery using 5-0 suture (Ethicon, Inc.). Alignment of the crystals was ensured at surgery by monitoring the ultrasonic signal with an oscilloscope. An hydraulic occluder was placed between the flow probe and piezoelectric crystals in all 12 dogs (i.e., distal to the flow probe, and proximal to the implanted crystals). In four of the dogs, a second occluder was also placed distal to the ultrasonic dimension transducers.

Arterial and left atrial pressures were measured with the implanted catheters attached to a strain gauge manometer (Statham P23Db, Statham Instruments, Inc.). Aortic and left ventricular pressures were measured with the implanted solid state transducers. These transducers were calibrated in vitro against a mercury manometer and cross-calibrated in vivo using the arterial and left atrial catheters. Instantaneous and continuous measurements of external coronary diameter were obtained with an improved ultrasonic transit-time dimension gauge (Patrick et al., 1974). The instrument generates a voltage linearly proportional to the transit-time of acoustic impulses traveling at the sonic velocity of 1.55 mm/µsec in tissue, and, thus, continuously records dimensions. The original dimension gauge was modified to measure coronary arterial dimensions (Vatner et al., 1980; Macho et al., 1981). Coronary blood flow was measured with a Benton Square wave electromagnetic flowmeter (Benton Instruments) or Doppler ultrasonic flowmeter. Zero flow reference was established during each coronary artery occlusion.

The experiments were conducted 1–3 weeks after operation, when the animals were healthy and trained to lie quietly in the laboratory. The left circumflex coronary artery was occluded for 15 seconds proximal to the dimension crystals in 12 dogs. The left circumflex coronary artery was occluded for periods of 5, 10, 15, and 20 seconds in eight dogs. The left circumflex coronary artery was occluded for 15 seconds proximal and distal to the site of implantation of the piezoelectric crystals in four dogs. Occlusions of 15 seconds were also examined before and after 0-adrenergic receptor (propranolol, 1 mg/kg, iv) blockade in nine dogs, before and after combined α-(phenolamine, 2 mg/kg) and β-adrenergic receptor blockade in five dogs, before and after ganglionic blockade with hexamethonium (30 mg/kg, iv) in three dogs, before and after prostaglandin synthesis inhibition (indomethacin 7.5 mg/kg, iv) in five dogs, and before and after aminophylline (10 mg/kg, iv) which is thought to block adenosine receptors (Atosno, 1970; Dutta and Mustafa, 1980), in nine dogs. Aminophylline was administered after β-adrenergic receptor blockade (propranolol, 1 mg/kg) to prevent the tachycardia and subsequent large coronary dilation which occurs with this drug. The adequacy of α- and β-adrenergic receptor blockade was confirmed by the absence of pressor and inotropic responses, respectively, to injection of norepinephrine (0.2 µg/kg), of ganglionic blockade by the absence of reflex tachycardia to injection of nitroglycerin (10 µg/kg, iv), and of adenosine receptor blockade by injection of adenosine (0.47 µmol/kg, iv). In four dogs, flow was held constant by inflation of an hydraulic occluder during injection of adenosine (0.47 µmol/kg, iv) after release of a 15-second occlusion, and during a step-wise increase in heart rate induced by electrical stimulation of the left atrium. In two additional dogs, flow was held constant by partially inflating a proximal occluder after release of a 15-second proximal occlusion.

Data were recorded on magnetic tape (Bell and Howell, Inc., Datatape Division) and played back on a multichannel tape recorder (Gould-Brush). Mean pressure and coronary diameter were derived using R-C filters with a 2-second time constant. LV dp/dt was derived from the LV pressure signal using Flühbruck operational amplifiers (Teledyne Flühbruck) connected as a differentiator and having a frequency response of 700 Hz. A triangle wave was substituted for the pressure signal to calibrate the differentiator directly. Heart rate was measured with a cardiotachometer (Beckman Instruments) triggered by the LV pressure pulse. Internal coronary cross-sectional area was calculated, knowing the wall volume, the blood vessel density, the mass of the artery, and the instantaneous external diameter (Vatner et al., 1980). Late diastolic coronary resistance, an index of changes in small coronary vessel dimensions, was calculated as the quotient of late diastolic aortic pressure and late diastolic coronary blood flow.

Any drift in the dimension gauge, tape-recording system, or the strip chart recorder was eliminated by frequent calibration during the experiment. The received ultrasonic dimension signal was monitored continuously during the experiment using an oscilloscope. In this way, any change in crystal alignment could be detected and invalidate the experiment.

Although analog signals were recorded continuously, data were analyzed before occlusion, just prior to release of the occluder, at the time of maximum coronary blood flow, and at maximum coronary dimensions. The area under the reactive dilation above preocclusion values, was computed by planimetry. The peak reactive dilation and area under the coronary diameter curve and area of the reactive hyperemia were compared for proximal and distal occlusions, and for proximal occlusions before and after adrenergic receptor blockade, ganglionic blockade, prostaglandin synthesis inhibition, and adenosine receptor blockade with aminophylline. Statistical analysis was performed by a multiple-way analysis of variance to determine significance between groups and by one-way analysis of variance for linear contrasts. Significance was determined by Scheffe’s test (Armitage, 1973).

**Results**

A typical response to a 20-second period of coronary artery occlusion is shown in Figure 1. In 12 dogs, during 15-second occlusion, coronary blood flow fell to zero, and rapidly rose upon release, increasing by an average of 255 ± 30% above control (32 ± 4.1 ml/min) by 6.1 ± 0.4 seconds, and demonstrating a 460 ± 31% repayment of the flow debt. This occurred in the absence of significant changes in heart rate, arterial pressure, LV pressure, or LV dp/dt (Table 1). During the 15-second period of proximal coronary artery occlusion, mean coronary diameter and coronary cross-sectional area (CSA) fell by 6.2 ± 0.9% from 3.80 ± 0.15 mm, and by 24 ± 3.4% from 5.65 ± 0.45 mm² (P < 0.01), respectively. After release at the time of peak reactive hyperemic flow, mean coronary diameter and...
FIGURE 1. The effects of a 20-second coronary occlusion of the left circumflex coronary artery proximal to the measurement of left circumflex coronary arterial diameter are shown on recordings of phasic and mean coronary dimensions (CD), phasic and mean coronary blood flow (CBF), mean arterial pressure (AP), left ventricular (LV) pressure (P), and LV dP/dt. After release of the coronary occlusion, CBF increased dramatically, resulting in a typical reactive hyperemia. Coronary dimensions increased slowly after release of the occlusion, reaching a peak approximately 60 seconds later, at a time when coronary blood flow had already returned to control.

CSA were not significantly different from pre-occlusion values (Fig. 2). Coronary diameter and CSA then began to increase reaching a maximum 6.7 ± 1.0% and 28 ± 4.4% above control 61 ± 3.2 seconds after release of the occlusion (Fig. 2). At the time of maximum reactive dilation of the large coronary artery, coronary blood flow and calculated vascular resistance had already returned to control (Fig. 2), and heart rate, arterial pressure, LV systolic and end-diastolic pressures, and LV dP/dt remained at control levels. Coronary diameter returned to control by 257 ± 11 seconds.

FIGURE 2. The effects of release of 15-second coronary artery occlusion proximal to the coronary dimension transducers on mean coronary blood flow (MCF) and calculated coronary cross-sectional area (CSA) and late diastolic coronary resistance (LDCR) are shown during peak reactive hyperemia (upper panel) and during peak reactive dilation (lower panel). Values are expressed as percent change from control. Control values are shown below each bar. Asterisks indicate values significantly different from control (P < 0.01). Note that the scales for the two panels are different.

Effects Of Increasing Duration Of Coronary Artery Occlusion

With increasing duration of coronary artery occlusion from 5 to 20 seconds in eight dogs, there was a progressive increase in the peak coronary diameter (4.1 ± 1.0%, 5.0 ± 1.3%, 5.8 ± 1.4%, 6.7 ± 1.4%) and CSA (17 ± 4.3%, 21 ± 5.6%, 25 ± 6.0%, 31 ± 7.3%), as well as of the area of the reactive dilation.

TABLE 1

<table>
<thead>
<tr>
<th>Change from Control at Time of</th>
<th>Control</th>
<th>Occlusion</th>
<th>Peak flow</th>
<th>Peak diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92 ± 2.5</td>
<td>+0.5 ± 0.4</td>
<td>+0.3 ± 0.8</td>
<td>+0.2 ± 0.7</td>
</tr>
<tr>
<td>Late diastolic pressure (mm Hg)</td>
<td>78 ± 1.8</td>
<td>+0.8 ± 1.0</td>
<td>−0.8 ± 0.8</td>
<td>+0.0 ± 0.0</td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td>119 ± 4.1</td>
<td>−1.3 ± 0.6</td>
<td>+0.7 ± 0.8</td>
<td>−0.1 ± 0.8</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>7.01 ± 0.47</td>
<td>+0.5 ± 0.1*</td>
<td>−0.2 ± 0.4</td>
<td>−0.4 ± 0.3</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3363 ± 173</td>
<td>−369 ± 87*</td>
<td>+61 ± 60</td>
<td>+41 ± 31</td>
</tr>
<tr>
<td>Mean coronary diameter (mm)</td>
<td>3.80 ± 0.15</td>
<td>−0.23 ± 0.03*</td>
<td>−0.03 ± 0.01</td>
<td>+0.24 ± 0.03*</td>
</tr>
<tr>
<td>Mean coronary CSA (mm²)</td>
<td>5.65 ± 0.45</td>
<td>−1.28 ± 0.15*</td>
<td>−0.13 ± 0.07</td>
<td>+1.47 ± 0.18*</td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min)</td>
<td>32 ± 4.1</td>
<td>0.0</td>
<td>+84 ± 15*</td>
<td>+1.5 ± 1.3</td>
</tr>
<tr>
<td>LDCR (mm Hg/ml per min)</td>
<td>2.54 ± 0.39</td>
<td>−1.80 ± 0.32*</td>
<td>−0.20 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 4.8</td>
<td>+1.4 ± 0.9</td>
<td>+3.6 ± 2.0</td>
<td>+0.2 ± 1.5</td>
</tr>
</tbody>
</table>

* Different from control, P < 0.01.
Flow

Duration of Occlusion (sec)

p<0.01

p<0.01

p<0.01

Diameter

Duration of Occlusion (sec)

p<0.01

p<0.01

p<0.01

FIGURE 3. Increasing the duration of coronary artery occlusion from 5 to 20 seconds caused proportional increases in planimetered area of reactive hyperemia (upper panel), and planimetered area of reactive dilation (lower panel). The areas are expressed in arbitrary units.

FIGURE 4. Occlusion of the left circumflex coronary artery for 15 seconds proximal to (left panel) or distal to (right panel) the segment of coronary artery where diameter was measured caused similar increases in coronary artery diameter (CD) after occlusion. However, during coronary artery occlusion, coronary diameter decreased and increased with proximal and distal occlusions, respectively.

and the area of the reactive hyperemia (Fig. 3). In addition, the time to peak dilation for 5-, 10-, 15-, and 20-second occlusions was 41 ± 2.0, 53 ± 2.0, 62 ± 3.6, and 68 ± 4.0 seconds, respectively.

Comparison Of Proximal And Distal Coronary Artery Occlusions

The effects of 15-second coronary artery occlusions proximal and distal to the segment of coronary artery where diameter was measured are shown in Figure 4. During coronary artery occlusions in these four dogs, mean coronary arterial diameter and CSA fell with proximal but not distal occlusion. However, the two post-occlusive responses were essentially identical. The time-to-peak dilation was 54 ± 5.3 and 54 ± 3.9 seconds; the areas of the reactive dilations were 77 ± 6.9 and 74 ± 8.1 units; the time to return to control was 275 ± 11 and 261 ± 17 seconds; and the peak increases in coronary diameter were 3.86 ± 0.76% and 3.77 ± 0.99% from 4.38 and 4.35 mm and the peak increases in CSA were 16 ± 3.2% and 16 ± 4.3% from 7.37 and 7.20 mm², for proximal and distal occlusions, respectively.

Effects of Autonomic Blockade

In the same nine dogs studied before and after β-adrenergic receptor blockade, peak CSA increased with reactive dilation by 30 ± 6.2% from 6.55 ± 0.66 mm², before β-adrenergic receptor blockade and by 30 ± 6.4% from 6.17 ± 0.69 mm² after blockade. The time-to-peak dilation and the area of the reactive dilation were also unaffected by β-adrenergic receptor blockade (Fig. 5).

In the same five dogs studied before and after combined α- and β-adrenergic receptor blockades, the increases in CSA with reactive dilation before (31 ± 5.4% from 5.81 ± 0.85 mm²) as compared to after (35 ± 6.8% from 5.37 ± 0.72 mm²) were not different. The time-to-peak dilation and the time to return to control were unaffected by combined α- and β-adrenergic receptor blockades. The area of the reactive dilation was 101 ± 21 units before and 92 ± 21 units after combined α- and β-adrenergic receptor blockades. The area of the reactive hyperemia was 36 ± 2.6 units before and 23 ± 1.2 units after (P < 0.05) after combined α- and β-adrenergic receptor blockades.

In the same three dogs studied before and after
Inhibition of Prostaglandin Synthesis

In the same seven dogs studied before and after indomethacin, the increases in CSA with reactive dilation were 34 ± 3.4% from 5.04 ± 0.85 mm² before inhibition of prostaglandin synthesis and 38 ± 4.9% from 6.47 ± 0.88 mm², as were the time-to-peak dilation and the time to return to control. The areas of the reactive dilation before (103 ± 21 units) and after (112 ± 14 units) ganglionic blockade were also similar.

Effects of Aminophylline

Aminophylline reduced (P < 0.01) the vasodilation of large coronary arteries and the increases in mean coronary blood flow in response to injected adenosine in nine dogs. Before aminophylline, adenosine increased mean coronary flow by 243 ± 41% from 29 ± 3.3 ml/min and large coronary CSA by 31 ± 5.4% from 5.13 ± 0.51 mm². After aminophylline, adenosine increased mean coronary blood flow by 44 ± 12% from 27 ± 3.3 ml/min and increased large coronary arterial CSA by only 7.2 ± 3.3% from 5.34 ± 0.59 mm². In the same nine dogs studied before and after aminophylline, the increases in CSA with reactive dilation were 40 ± 3.9% from 4.72 ± 0.44 mm² before aminophylline and 32 ± 5.4% from 5.25 ± 0.65 mm² after aminophylline. The time-to-peak dilation and time to return to control were unchanged after aminophylline. The planimetered area of the reactive hyperemia decreased significantly (P < 0.01) by 19 ± 3.0% (i.e., from 43 ± 1.5 to 32 ± 2.7 units) after the administration of aminophylline, whereas the area of the reactive dilation (Fig. 5) was reduced by only 13 ± 4.0% (NS).

Effects of Barbiturate Anesthesia

In three dogs studied acutely after operation with sodium pentobarbital anesthesia (30 mg/kg, iv), large coronary arterial diameter and CSA did not rise from baseline values of 3.86 ± 0.53 mm and 5.95 ± 1.63 mm² after release of the coronary artery occlusion.

Constant Flow Experiments

In the same four dogs studied with and without constant coronary blood flow, the increases in large coronary CSA following release of occlusion were 30 ± 2.4% from 5.43 ± 1.01 mm² when flow was allowed to increase by 306 ± 27% from 30 ± 3.8 ml/min. In contrast, following release of occlusion, CSA did not change significantly (−6.1 ± 4.3%) from a control of 5.43 ± 1.00 mm² when coronary blood flow was held constant at 31 ± 3.0 ml/min by constricting the coronary artery distal to the diameter measurement (Fig. 6). In the two dogs in which flow was held constant at 32 ml/min by constricting the coronary artery proximal to the diameter measurement, CSA did not change from control of 6.86 ± 1.53 mm² after release of occlusion. Injection of adenosine, 0.47 pmol/kg, increased large coronary CSA by 24 ± 2.6% from 5.34 ± 0.72 mm² and mean coronary blood flow by 177 ± 47%.
from 30 ± 1.8 ml/min when flow was allowed to increase. With coronary blood flow constant large coronary CSA increased by 13 ± 2.6% from 5.25 ± 0.74 mm² (P < 0.05). During a 100 beats/min increase in heart rate induced by electrical pacing, CSA increased by 30.4 ± 6.3% from 6.13 ± 1.73 mm² and MCF increased by 40 ± 10% from 30 ± 2.9 ml/min. With flow held constant, when heart rate increased by 100 beats/min, large coronary CSA increased significantly (P < 0.05) (12 ± 1.1% from 6.28 ± 1.70 mm²).

Discussion

The major finding in this investigation is that large coronary arteries dilate following brief periods of coronary artery occlusion and myocardial ischemia. We called this effect on the large coronary arteries "reactive dilation." In comparison with reactive hyperemia, it was characterized by a delayed onset (6 vs. 60 sec) and delayed dissipation (50 vs. 150 sec). Prior studies in anesthetized, open-chest preparations have examined the effects of brief periods of coronary artery occlusion and myocardial ischemia and have found no effect on the large coronary arteries (Winbury et al., 1969; Fam and McGregor, 1969; Takeda et al., 1977). It is conceivable that the differences in either preparations (conscious vs. anesthetized) or technique (direct vs. indirect assessment of large coronary artery dimensions) can account for the apparent discrepancy. In our study, using the ultrasonic dimension technique in three anesthetized dogs prepared with an open chest, release of a 15-second coronary artery occlusion did not result in reactive dilation. In further support of the idea that the difference can be attributed to anesthesia and recent surgery (Altura and Altura, 1975; Vatner and Braunwald, 1975) is a recent study by Gould and Kelley (1982), who observed reactive dilation of coronary arteries in conscious dogs using the ultrasonic dimension technique in three preparations (conscious vs. anesthetized) or technique (direct vs. indirect assessment of large coronary artery dimensions) can account for the apparent discrepancy. In our study, using the ultrasonic dimension technique in three anesthetized dogs prepared with an open chest, release of a 15-second coronary artery occlusion did not result in reactive dilation. In further support of the idea that the difference can be attributed to anesthesia and recent surgery (Altura and Altura, 1975; Vatner and Braunwald, 1975) is a recent study by Gould and Kelley (1982), who observed reactive dilation of coronary arteries in conscious dogs using a different technique, i.e., quantitative angiography. However, in that study, the responses were not quantified, nor was the mechanism identified.

An important feature of the current investigation was to discern the mechanism of the reactive dilation. To test the possibility that the reactive dilation may be reflexly mediated, we compared responses before and after combined α- and β-adrenergic blockade and after ganglionic blockade. We observed that the reactive dilation was not blunted by these interventions and conclude that it is not due to an autonomic reflex.

Prostaglandins have also been proposed as a potential mediator responsible for reactive hyperemia (Alexander et al., 1975). However, this hypothesis has not been substantiated (Owen et al., 1975; Hintze and Kaley, 1977). In our study, indomethacin had no effect on either the peak effect, duration, or integrated area of either the reactive dilation or the reactive hyperemia, making prostaglandin mechanisms an unlikely mediator.

Berne and co-workers have proposed that adenosine is the mediator of metabolic changes in the coronary circulation (Rubio et al., 1969; Berne and Rubio, 1979) and of reactive hyperemia. However, prior studies have observed only 20–44% of the reactive hyperemic response attenuated by aminophylline (Curnish et al., 1969; Wadsworth, 1972; Schutz et al., 1977; Saito et al., 1981). In other studies, aminophylline had no significant effect on reactive hyperemia (Juhran et al., 1971; Bittar and Pauly, 1971). In our experiments, aminophylline completely eliminated the vasodilation of large coronary arteries in response to injected adenosine, but reduced the reactive hyperemia by only 19% and diminished the reactive dilation in response to a brief coronary artery occlusion by only a small, nonsignificant amount. Thus, it would be difficult to ascribe a metabolic mechanism mediated by adenosine as responsible for the reactive dilation.

Finally, a mechanism secondary to the rapid and large increase in coronary blood flow was considered. The first series of experiments demonstrated increasing reactive dilation with increasing duration of coronary artery occlusion. Increasing reactive hyperemia with increasing duration of occlusion was also noted, but has also been described previously for the response of coronary resistance vessels (Katz and Lindner, 1936; Coffman and Gregg, 1960; Gregg and Fisher, 1965; Olsson, 1975; Berne and Rubio, 1979). Second, the fact that proximal as well as distal occlusions induced similar reactive dilation indicates that an absolute reduction in distending pressure (Bayliss, 1902) during the occlusion was not essential, since, with the distal occlusion, the smooth muscle in the coronary artery in the area of the ultrasonic transducer did not relax, and appears to have actually been stretched. However, the pressure may have fallen upon release during the peak reactive hyperemia, since, by Bernoulli's equation, a decrease in pressure would be predicted with an increase in flow velocity. This could be the mechanism of the myogenic relaxation and consequent dilation. A similar mechanism was proposed by Ingebrigsten and Leraand (1970), Lie et al. (1970), and Gerova et al. (1980). Previous studies in which a large AV shunt was opened in the femoral circulation showed a dramatic increase in large arterial dimensions which was flow dependent (Lie et al., 1970; Ingebrigsten and Leraand, 1970). This large arterial dilation was independent of α- or β-adrenergic mechanisms, cholinergic mechanisms, or histaminergic mechanisms (Lie et al., 1970). Furthermore, the femoral arteries remained dilated as long as flow was increased (Ingebrigsten and Leraand, 1970). In the coronary circulation, Gerova et al. (1980) found large coronary artery dilation when flow increased dramatically with opening of an AV shunt.

To test the hypothesis that the reactive dilation observed in the current investigation was secondary to the marked increase in flow that occurred during
reactive hyperemia, we maintained flow constant with an hydraulic occluder (at preocclusion levels) during cardiac pacing, during an injection of adenosine, and also after release of a 15-second coronary artery occlusion. Following, coronary artery occlusion, no reactive dilation was observed (Fig. 6), when coronary blood flow was held constant with an occluder placed either proximal or distal to the implanted dimension crystals. However, under these same conditions of constant flow, adenosine still increased cross-sectional area, although by a reduced amount (13 ± 2.6%). Similarly, when heart rate increased by pacing, large coronary CSA still increased by 12 ± 1.1%, which was significant, but less than observed when flow was unrestricted. Thus, although a flow-dependent mechanism might explain the increase in large coronary dimension after release of a brief coronary occlusion, this mechanism cannot totally explain the large coronary vessel dilation accompanying the injection of adenosine or an increase in myocardial metabolic demand (Macho et al., 1981). Furthermore, it is also conceivable that by holding flow constant upon release of the coronary occlusion, a mechanism involving ascending vasodilation could have been impaired (Hilton, 1959; Duling and Berne, 1970). However, our studies with pharmacological blockade would suggest that the ascending dilation did not involve autonomic, adrenergic, purinergic, or prostaglandin mechanisms.

In summary, large coronary arteries undergo substantial active vasodilation following brief periods of coronary artery occlusion and myocardial ischemia. The time course of this reactive dilation is distinctly different from time course of the accompanying reactive hyperemia. The reactive dilation can be eliminated by preventing the increase in coronary blood flow following coronary artery occlusion.

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INDEX TERMS: Reactive hyperemia • Coronary diameters • Coronary blood flow • Aminophylline • Indomethacin • Myogenic mechanism
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Circ Res. 1984;54:50-57
doi: 10.1161/01.RES.54.1.50

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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