Effect of Nitroglycerin and Arterial Hypertension on Myocardial Blood Flow Following Acute Coronary Artery Occlusion in the Dog

ROBERT J. BACHE, M.D.

SUMMARY This study was designed to evaluate the effects of nitroglycerin and phenylephrine-induced arterial hypertension on regional myocardial blood flow in awake dogs with acute occlusion of the left circumflex coronary artery. Myocardial blood flow to four transmural layers from epicardium to endocardium was estimated with 7-9 micron radionuclide labeled microspheres in 1) the nonischemic myocardium, 2) the central ischemic zone, and 3) the border zone separating ischemic from normally perfused myocardium. Measurements were repeated 1) during infusion of nitroglycerin, 0.015 mg/kg/min, 2) during phenylephrine administered to increase arterial pressure 60 mm Hg above the control measurements, and 3) during combined nitroglycerin and phenylephrine administration. Both nitroglycerin and phenylephrine increased myocardial blood flow to the central ischemic area; nitroglycerin significantly decreased the resistance of the collateral vascular system, while the increased flow during phenylephrine administration was accounted for entirely by the increased arterial pressure with no change in collateral vascular resistance. The increased blood flow to the central ischemic zone during nitroglycerin administration was delivered preferentially to the subendocardium, while the increased blood flow during phenylephrine administration was directed exclusively to the subepicardium. Neither nitroglycerin nor phenylephrine significantly altered computed vascular resistance of the border zone, but because of the increased driving pressure, blood flow to the border zone was significantly increased during phenylephrine administration.

RECENT STUDIES in experimental animals have demonstrated that the epicardial ST-segment elevation which develops in response to acute coronary artery occlusion is ameliorated by administration of nitroglycerin or by elevation of aortic blood pressure with methoxamine or phenylephrine. The apparent reduction of myocardial ischemia by these maneuvers could result from augmentation of intercoronary collateral blood flow into the area of ischemic myocardium. Although nitroglycerin has been shown to dilate the large coronary collateral vessels which develop in response to chronic myocardial ischemia, the effect of nitroglycerin on the small, pre-existing coronary collateral vessels at the time of acute coronary artery occlusion has been equivocal. Thus, while Leignninger and associates, Becker, and Capurro and associates reported increased collateral blood flow into the area of ischemic myocardium following acute coronary occlusion in dogs, other workers have been unable to demonstrate such an increase in collateral inflow.

The effect of coronary perfusion pressure on intercoronary collateral flow was studied by Kattus and Gregg. Using measurements of retrograde flow from an acutely occluded coronary artery to estimate collateral blood flow in open-chest dogs, these workers demonstrated that coronary perfusion pressure is a principal determinant of intercoronary collateral flow. This suggests that following acute coronary artery occlusion reduction of the ST-segment elevation by arterial hypertension may result from increased collateral blood flow into the ischemic myocardium. Alternatively, it is possible that nitroglycerin and methoxamine or phenylephrine could affect ST-segment elevation by altering the transmural distribution of myocardial blood flow across the wall of the left ventricle. Consequently, the present study was carried out to measure the effect of nitroglycerin and phenylephrine-induced elevation of aortic pressure upon the volume and distribution of collateral blood flow distal to an acute coronary artery occlusion. These studies were performed in chronically instrumented, awake dogs to eliminate possible interfering effects associated with general anesthesia and acute surgical trauma.

Methods

Fifteen adult mongrel dogs weighing 20-31 kg were anesthetized with sodium thiamylal (20-30 mg/kg) and ventilated with a Harvard respirator. A left thoracotomy was performed in the fourth intercostal space. A heparin filled polyvinyl chloride catheter, outside diameter 3.0 mm, was inserted into the root of the aorta via the left internal thoracic artery. A similar catheter was inserted into the left atrial cavity via the atrial appendage and secured with a purse-string suture. The proximal 1.5 cm of the circumflex branch of the left coronary artery was dissected free and an inflatable cuff-type pneumatic occluder constructed in our laboratory of polyvinyl chloride tubing (outside diameter 2.7 mm) was placed around the artery. The catheters and occluder tube were tunneled dorsally into a subcutaneous pouch at the base of the neck but were not exteriorized to protect them from damage. The catheters and occluder tube were exteriorized through a 1 cm skin incision using 2% lidocaine infiltration anesthesia the morning before study.

Studies were carried out 9-20 days after the initial surgery. All animals were active and fully recovered from surgery without fever or other evidence of ill health. At the time of study, hematocrits ranged from 33 to 50% (mean = 42 ± 6%). Animals were trained to lie quietly on their right sides during study. The laboratory was dimly illuminated and kept free of noise or other activity which might disturb the dog. Aortic and left atrial pressures were measured using Statham P23Db pressure transducers. Lead II of a standard electrocardiogram was obtained. Data were
Coronary artery occlusions were performed by energizing an electric valve which connected the occluder tube to a compressed air source pressurized at 1,500 mm Hg. After all recording instruments were connected a 60-second coronary artery occlusion was produced while lead II of the electrocardiogram was monitored. All dogs exhibited ST-segment elevation as well as increased heart rate during occlusion, indicating proper functioning of the occluder. Subsequently, a 45 to 60 minute interval was allowed for the animal to adjust to the laboratory conditions. During this time, data were sampled continuously to insure that a control steady state had been achieved.

Measurements of regional myocardial blood flow were made using serial injections of microspheres 7-9 microns in diameter labeled with gamma emitting nuclides \(^{141}\text{Ce}, ^{51}\text{Cr}, ^{85}\text{Sr},\) and \(^{46}\text{Sc}.\) The microspheres were diluted in 10% low molecular weight dextran so that 1.0 ml (the volume injected) contained approximately \(3 \times 10^6\) microspheres. Serial injections of this quantity of microspheres resulted in no change in heart rate or arterial pressure in any of the dogs studied. Before injection the microspheres were thoroughly mixed by alternate agitation for at least fifteen minutes in an ultrasonic bath and a vortex agitator. During each intervention, 1.0 ml of microsphere suspension was injected into the left atrial catheter and flushed in with 3 ml of normal saline. All injections were made over a ten-second interval. Beginning simultaneously with each microsphere injection and continuing for 90 seconds, a reference sample of arterial blood was collected from the aortic catheter at a constant rate of 15 ml/min using a Harvard Model 1210 withdrawal pump. Each arterial blood reference sample was collected in six separate 15-sec aliquots which were counted individually to insure that all radioactivity had been cleared from the circulation within the sampling interval.

To evaluate regional blood flow during coronary artery occlusion, 1.0 ml of microsphere suspension was injected into the left atrial catheter five minutes after the onset of a left circumflex coronary artery occlusion. The occlusion was maintained for an additional 90 seconds to insure complete dispersion of microspheres, and the occluder was then completely deflated. A minimum of 45 minutes was allowed between coronary artery occlusions, and in all cases heart rate and arterial pressure had returned to within 5% of the pre-occlusion control level before each subsequent intervention was begun.

To study the effect of nitroglycerin on regional myocardial blood flow during coronary artery occlusion, nitroglycerin was administered intravenously as a bolus of 0.4 mg followed by an infusion of 0.015 mg/kg/min (average dosage was 0.43 mg/min). The left circumflex coronary artery was occluded five minutes after beginning the nitroglycerin infusion, and microspheres labeled with a different radionuclide were administered five minutes after the onset of the coronary artery occlusion as previously described. The nitroglycerin infusion was continued until release of the occlusion.

To evaluate the effect of arterial hypertension on regional myocardial perfusion during coronary occlusion, phenylephrine (0.02 mg/ml) was infused intravenously at a rate sufficient to maintain arterial blood pressure approximately 60 mm Hg above the control level. After steady state elevation of arterial pressure had been maintained for five minutes, the left circumflex coronary artery was again occluded, and microspheres labeled with a third radionuclide were injected five minutes after the onset of occlusion as before. Arterial pressure was maintained at a constant level until release of the occlusion.

Finally, to evaluate the combined effects of nitroglycerin and arterial hypertension, nitroglycerin was infused at a dosage of 0.015 mg/kg/min while phenylephrine was infused to maintain arterial pressure 60 mm Hg above the control level. After a five minute interval of steady state hypertension had been achieved during nitroglycerin infusion, a coronary artery occlusion was again performed and microspheres were injected after five minutes of occlusion.

Two dogs developed ventricular fibrillation during coronary occlusion while receiving phenylephrine, and were eliminated from the study. Both of these dogs had previously undergone the control 6.5 minute coronary artery occlusion without difficulty. In all animals the control occlusion was performed first. The remaining three interventions (nitroglycerin alone, phenylephrine alone, and nitroglycerin combined with phenylephrine) were performed in random sequence. To determine whether the sequence in which interventions were performed had any effect on the results, animals were subgrouped so that the response to phenylephrine was compared in animals which had previously received nitroglycerin and in animals in which phenylephrine was the initial intervention. Similarly, the effects of nitroglycerin were compared in subgroups of animals which had previously received phenylephrine and in which nitroglycerin was the initial intervention. In all instances, no significant difference was found between subgroups in which the drug under consideration was administered first or was administered subsequent to the other drug. It was assumed that the sequence of drug administration did not affect the results and all data were pooled.

After completion of study, the animal was anesthetized with sodium thiopental (20-30 mg/kg) and a left thoracotomy performed through the intercostal space below the previous incision. The left circumflex coronary artery was cannulated and 15 ml of Evans blue dye was injected at a pressure equal to mean aortic pressure to delineate the region of myocardium perfused by the circumflex artery. The heart was then removed and fixed in 10% buffered formalin. Following fixation, the atria, right ventricle, and large epicardial blood vessels were dissected from the left ventricle and discarded. Full thickness myocardial specimens were taken from the densely stained posterior left ventricular wall including the posterior papillary muscle to represent the central area of ischemia. Full thickness specimens were taken from the surrounding left ventricular wall representing the border zone separating the central ischemic area from normally perfused myocardium. A full thickness specimen of the anterior left ventricular wall, including the anterior papillary muscle, was removed to represent an area of normally perfused myocardium. Each myocardial specimen was then sectioned into four equal transmural layers from epicardial to endocardial surface, weighed, and placed in vials for counting. For the remainder of this paper, these layers will be referred to as layers 1 through 4, layer 1 being the most epicardial layer and layer 4 the most endocardial layer. The average myocardial sample weight was 1.261 ± 0.058 g with most samples weighing 1-2 g.
Myocardial and blood reference specimens were counted in a Beckman Model 167776 gamma spectrometer at window settings corresponding to the peak energies of each nuclide. The counts/minute recorded in each energy window were corrected for background activity and overlapping counts from the accompanying isotopes by a digital computer. Blood flow (ml/min) to each sample of myocardium (Qm) was computed using the formula: Qm = Qr x Cr/Cm where Qr is the reference blood flow rate (ml/min), Cr is counts per minute of each sample of myocardium, and Cm equals counts per minute of the reference blood sample. Blood flow to each myocardial specimen was divided by the specimen weight and expressed as ml/min/g of myocardium.

Heart rate, aortic and left atrial pressures were measured directly from the strip chart recordings. Coronary vascular resistance of the nonischemic myocardium, the border zone and the central ischemic zone was computed as: vascular resistance (mm Hg x min x g x ml⁻¹) = mean aortic pressure (mm Hg)/myocardial blood flow (ml x min⁻¹ x g⁻¹). The ratio of subendocardial to subepicardial blood flow (endo/epi) was obtained by dividing flow to layer 4 by the corresponding flow to layer 1. Data analysis was performed using Student's t-test for paired data.

### Results

Mean heart rate during resting control conditions was 89 ± (SE) 7 beats/min (range 58 to 120 beats/min), mean aortic pressure was 98 ± 4 mm Hg (range 75 to 125 mm Hg), and mean left atrial pressure was 3 ± 0.6 mm Hg (range 0 to 7 mm Hg). As shown in table 1, occlusion of the left circumflex coronary artery resulted in a significant increase in heart rate to 125 ± 4 beats/min (range 106 to 138 beats/min; P < 0.01) and a significant increase in left atrial pressure to 9 ± 1.4 mm Hg (range 7 to 19 mm Hg; P < 0.01) while aortic pressure was unchanged.

During unrestricted coronary inflow, administration of nitroglycerin resulted in significant decreases of mean aortic pressure (mean change −9 ± 3.4 mm Hg; P < 0.05) and left atrial pressure (mean change −3 ± 0.8 mm Hg; P < 0.01) while mean heart rate increased 27 ± 6.6 beats per minute (P < 0.01) (table 1). Coronary artery occlusion during nitroglycerin infusion resulted in no significant change of heart rate or mean aortic pressure, while left atrial pressure increased by 4 ± 0.6 mm Hg (P < 0.01).

Administration of phenylephrine to elevate mean arterial pressure to 151 ± 3 mm Hg (range 130 to 165 mm Hg) resulted in a significant decrease of heart rate and a significant increase of mean left atrial pressure (table 1). Coronary artery occlusion during phenylephrine infusion resulted in a significant increase in heart rate (mean change 24 ± 6 beats/min; P < 0.01) which was not significantly different from the increment in heart rate resulting from coronary artery occlusion during control conditions. During phenylephrine infusion, coronary artery occlusion resulted in a 16 ± 1.8 mm Hg increase in left atrial pressure (P < 0.01); this increase in left atrial pressure was significantly greater than the increment in left atrial pressure resulting from coronary artery occlusion during control conditions (P < 0.01).

When phenylephrine and nitroglycerin were infused simultaneously to elevate mean arterial pressure to 151 ± 4 mm Hg, heart rate and mean left atrial pressure were not significantly different from the values observed during phenylephrine infusion alone. Coronary artery occlusion during simultaneous nitroglycerin and phenylephrine infusion resulted in significant increases of heart rate and mean left atrial pressure; these increases in response to coronary artery occlusion were not significantly different from those observed during coronary occlusion with phenylephrine infusion alone.

Mean blood flow to the anterior nonischemic myocardium during coronary artery occlusion during control conditions was 1.23 ± 0.13 ml/min/g of myocardium (range 0.76 to 1.92 ml/min/g), and subendocardial flow significantly exceeded subepicardial flow (endo/epi = 1.33; table 2, fig. 1). Infusion of nitroglycerin resulted in a significant decrease in blood flow to the anterior nonischemic myocardium (mean change −22 ± 6%; P < 0.01), resulting in a significant increase in computed coronary vascular resistance (P < 0.05). Nitroglycerin did not significantly alter the transmural distribution of perfusion. Administration of phenylephrine did not significantly alter total anterior wall myocardial blood flow, but did result in significant transmural redistribution of blood flow toward the subendocardium (endo/epi = 1.71; P < 0.03). Computed mean vascular resistance to the anterior myocardium was significantly increased during phenylephrine infusion (P < 0.05) (table 3). Simultaneous administration of nitroglycerin and phenylephrine resulted in a 28 ± 11% mean increase in blood flow to the nonischemic myocardium (P < 0.01), without significant alteration of the transmural distribution of perfusion (endo/epi = 1.48).

Mean blood flow to the border zone was 0.32 ± 0.06 ml/min/g of myocardium during the control occlusion (range 0.17 to 0.62 ml/min/g), and flow to the four transmural layers did not vary significantly (table 2). Infusion of nitroglycerin resulted in no significant change in mean myocardial blood flow and no change in the transmural distribution of perfusion within the border zone during coronary artery occlusion. Elevation of arterial pressure by administration of phenylephrine resulted in a 28 ± 10% increase in mean myocardial blood flow compared with the control occlusion (P < 0.05), while simultaneous administration of nitroglycerin and phenylephrine resulted in a 63 ± 9%
TABLE 2. Mean Myocardial Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Normal zone</th>
<th>Border zone</th>
<th>Ischemic zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean myocardial</td>
<td>Endo/Epi</td>
<td>Mean myocardial</td>
</tr>
<tr>
<td></td>
<td>blood flow (ml/min/g)</td>
<td></td>
<td>blood flow (ml/min/g)</td>
</tr>
<tr>
<td>Control occlusion</td>
<td>1.23 ± 0.13</td>
<td>1.33†</td>
<td>0.32 ± 0.06</td>
</tr>
<tr>
<td>Occlusion +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitroglycerin</td>
<td>0.96 ± 0.13*</td>
<td>1.38†</td>
<td>0.32 ± 0.06</td>
</tr>
<tr>
<td>Occlusion +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenylephrine</td>
<td>1.30 ± 0.14</td>
<td>1.71†</td>
<td>0.41 ± 0.06*</td>
</tr>
<tr>
<td>Occlusion +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitroglycerin +</td>
<td>1.57 ± 0.25*</td>
<td>1.48†</td>
<td>0.52 ± 0.13*</td>
</tr>
<tr>
<td>phenylephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 in comparison with control occlusion.
†Endo/Epi ratios significantly different from 1.0 (P < 0.05).

increase in myocardial blood flow relative to the control occlusion (P < 0.01). Neither phenylephrine nor the combination of nitroglycerin and phenylephrine resulted in significant alteration of the transmural distribution of myocardial perfusion in the border zone, nor in computed vascular resistance (table 3).

Mean blood flow to the central area of ischemia during the control occlusion was 0.09 ± 0.02 ml/min/g (range 0.03 to 0.22 ml/min/g) (table 2). As shown in figure 2, during the control occlusion transmural blood flow in the central ischemic area decreased progressively from layer 1 to layer 4, resulting in an endo/epi ratio significantly less than unity (endo/epi 0.29; P < 0.01). Infusion of nitroglycerin resulted in a significant increase of mean myocardial blood flow to 0.13 ± 0.03 ml/min/g of myocardium (range 0.03 to 0.35 ml/min/g; P < 0.05), and a decrease in computed vascular resistance (P < 0.05). This increase in mean blood flow during nitroglycerin infusion resulted from significant increases in flow to transmural layers 2, 3 and 4 with no change in blood flow to layer 1, resulting in an increase in the endo/epi ratio to 0.47 (P < 0.05). Administration of phenylephrine resulted in a similar increase in mean myocardial blood flow (table 2). In contrast to nitroglycerin, however, phenylephrine caused a significant increase in blood flow to layer 1, with no significant increase in flow to the three deeper myocardial layers (fig. 2). This alteration of the transmural distribution of perfusion during phenylephrine administration resulted in a significant decrease of the endo/epi ratio to 0.22 (P < 0.01). Simultaneous administration of nitroglycerin and phenylephrine resulted in significant increases in myocardial blood flow to transmural layers 1, 2 and 4, as well as in mean myocardial blood flow (P < 0.05), with no significant change in the endo/epi ratio (fig. 2). The increase in mean myocardial blood flow to the ischemic zone during combined administration of nitroglycerin and phenylephrine (mean increase 0.10 ml/min/g) exactly equaled the sum of the increases observed during separate administration of nitroglycerin (mean increase 0.04 ml/min/g) plus phenylephrine (mean increase 0.06 ml/min/g) (table 2).

**Discussion**

Administration of nitroglycerin resulted in significant decreases of both arterial pressure and left ventricular diastolic pressure. During control conditions, nitroglycerin administration resulted in a significant increase in heart rate while in the presence of a coronary artery occlusion (when heart rate had already been increased by the occlusion), nitroglycerin did not further increase the heart rate. Both the decrease in systolic aortic pressure and the decrease in left ventricular diastolic pressure during nitroglycerin administration appeared to reflect decreased cardiac work and, presumably, decreased myocardial oxygen consumption. Since myocardial blood flow is generally closely coupled to oxygen consumption, it was not unexpected that blood flow to the normally perfused myocardium decreased significantly during administration of nitroglycerin. Although previous studies of experimental coronary artery occlusion in the dog have failed to demonstrate decreased blood flow to the nonischemic myocardium during nitro-

**Figure 1. Mean blood flow (ml/min/g) ± SE to four transmural layers of anterior nons ischemic myocardium during occlusion of the circumflex coronary artery. Data are reported during control conditions, during infusion of nitroglycerin (0.015 mg/kg/min), during administration of phenylephrine to increase mean arterial pressure to 153 ± 6 mm Hg, and during simultaneous administration of nitroglycerin and phenylephrine. *P < 0.05 in comparison with control measurements.**

**Table 3. Computed Mean Coronary Vascular Resistance (mm Hg · min · g · ml⁻¹)**

<table>
<thead>
<tr>
<th></th>
<th>Normal zone</th>
<th>Border zone</th>
<th>Ischemic zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control occlusion</td>
<td>76 ± 8</td>
<td>294 ± 55</td>
<td>1040 ± 188</td>
</tr>
<tr>
<td>Occlusion +</td>
<td>91 ± 14*</td>
<td>272 ± 64</td>
<td>669 ± 247*</td>
</tr>
<tr>
<td>nitroglycerin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion +</td>
<td>118 ± 23*</td>
<td>373 ± 36</td>
<td>1020 ± 284</td>
</tr>
<tr>
<td>phenylephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion +</td>
<td>94 ± 10*</td>
<td>283 ± 45</td>
<td>774 ± 267*</td>
</tr>
<tr>
<td>nitroglycerin +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenylephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 in comparison with control occlusion.
glycerin administration, \( \text{\textsuperscript{a}, \text{\textsuperscript{16}}} \) it is likely that this apparent disparity is in part related to differences in experimental preparation, since the previous studies were performed in anesthetized open-chest dogs, while the present study was carried out in intact awake animals. General anesthesia and acute thoracotomy have been shown to result in alterations of both regional and total myocardial blood flow, and in depression of the reactivity of the coronary vascular system.\( \text{\textsuperscript{17}, \text{\textsuperscript{18}}} \)

In the present study, coronary artery occlusions were maintained for only five minutes before blood flow measurements were performed, and repeated occlusions were performed to evaluate the effect of interventions upon myocardial perfusion. The five minute interval of coronary artery occlusion was chosen since 1) previous studies using the epicardial ST-segment mapping technique have demonstrated that ST-segment elevation stabilizes within five minutes after acute coronary artery occlusion,\( \text{\textsuperscript{1, \text{\textsuperscript{4}, \text{\textsuperscript{12}}}}} \) 2) repeated coronary artery occlusions have been demonstrated to result in similar degrees of ST-segment elevation measured five minutes after the onset of occlusion,\( \text{\textsuperscript{1, \text{\textsuperscript{4}, \text{\textsuperscript{12}}}}} \) and 3) following acute coronary artery occlusion in the dog collateral blood flow into the ischemic myocardium appears to stabilize within the first 5 min and then remain at a constant low level during the initial six hours of coronary occlusion.\( \text{\textsuperscript{19}} \) These data suggest that a uniform degree of myocardial ischemia may be produced repeatedly by application of repeated brief coronary artery occlusion. Nevertheless, it is possible that the interventions used in the present study would have different effects upon myocardial blood flow during coronary artery occlusions of longer duration.

Oclusion of the circumflex coronary artery resulted in an area of dense ischemia encompassing the posterior left ventricular wall and posterior papillary muscle in which blood flow was less than 10% of the normally perfused left ventricular myocardium. In agreement with previous studies, this limited arterial inflow (representing blood flow through intercoronary collateral channels) was delivered preferentially to the subepicardial myocardium, resulting in a perfusion gradient with flow decreasing from epicardium to endocardium.\( \text{\textsuperscript{9, \text{\textsuperscript{12}, \text{\textsuperscript{17}}}}} \) Administration of nitroglycerin increased total collateral inflow into the central ischemic zone. Since the resistance vessels within the ischemic zone would be expected to be maximally vasodilated by ischemia, and since mean arterial pressure was significantly decreased during nitroglycerin administration, the observed increase in total blood flow to the ischemic zone implies significant vasodilation of the intercoronary collateral system. Computation of vascular resistance into the ischemic zone takes into account both the resistance of the intercoronary collateral channels and the resistance residing in the coronary arteries from the aorta to the origin of the collateral vessels. It is therefore possible that part of the observed decrease in collateral vascular resistance resulted from dilation of the large coronary arteries; this postulate is consistent with the well-known vasodilator action of nitroglycerin on the epicardial arteries.\( \text{\textsuperscript{20}} \) In addition, Schaper\( \text{\textsuperscript{21}} \) has shown that the small intrinsic coronary collateral vessels contain a layer of smooth muscle and are therefore potentially capable of active vasomotion. It has been demonstrated that collateral vessels may not be vasodilated by regional myocardial ischemia, and thus may have potential for vasodilation by nitroglycerin even in the presence of regional ischemia.\( \text{\textsuperscript{22}} \) Finally, it is possible that the increase in blood flow to the ischemic zone in response to nitroglycerin could have resulted from reduction of extravascular myocardial compressive forces on the collateral vessels. Since the intercoronary collateral vasculature in the dog is principally epicardial, however, it is likely that the extravascular component of collateral resistance would be minimal.\( \text{\textsuperscript{21}} \)

In addition to increasing total inflow to the central ischemic zone, nitroglycerin resulted in significant transmural redistribution of perfusion with increased subendocardial blood flow. This may have been related to reduction of left ventricular diastolic pressure during nitroglycerin administration. In diastole a transmural gradient of intramyocardial tissue pressure exists, increasing from the level of intrathoracic pressure at the epicardial surface to left ventricular cavitary pressure at the endocardium.\( \text{\textsuperscript{23}} \) Although this modest gradient of tissue pressure would not be expected to significantly affect transmural myocardial perfusion at normal levels of coronary artery pressure, at the very low perfusion pressure distal to an acute coronary occlusion, the transmural gradient of tissue pressure could have an important effect on transmural perfusion. Alternatively, it is possible that nitroglycerin increased subendocardial blood flow by virtue of differing effects on various elements of the intramural coronary vasculature. Winbury et al.\( \text{\textsuperscript{24}} \) have suggested that the transmural penetrating arteries which conduct blood from the epicardial coronary arteries to the subendocardium behave similarly to epicardial arteries, i.e., they are not vasodilated by local ischemia but are responsive to nitroglycerin. In the presence of intense local myocardial ischemia when arteriolar resistance is minimal in both subepicardium and subendocardium, the additional series resistance offered by the penetrating arteries could significantly impede subendocardial perfusion. In this situation, nitroglycerin-induced vasodilation of the penetrating arteries would reduce the total vascular resistance for perfusion of the subendocardium.

Arterial hypertension produced by administration of phenylephrine resulted in no change in blood flow to the nonischemic myocardium, and consequently a significant increase in computed mean coronary vascular resistance. This finding is in agreement with the previous demonstration of coronary vasoconstriction in response to intravenous or in-
tracoronary administration of norepinephrine or phenylephrine. \(^{20}\) Despite the absence of change in mean coronary inflow, phenylephrine resulted in a significant transmural redistribution of perfusion within the normally perfused myocardium, with increased blood flow to the subendocardium while subepicardial flow was decreased. Zuberbuhler and Bohr\(^{20}\) have demonstrated differences in the sensitivity of large and small coronary arteries to alpha-agonists. It is possible that similar differences in sensitivity to phenylephrine may exist across the wall of the left ventricle, with greater sensitivity of the subepicardial vessels to phenylephrine.

Infusion of phenylephrine resulted in a mean increase in coronary blood flow to the central ischemic zone which was similar in magnitude to that produced by nitroglycerin. Unlike nitroglycerin, however, the increased inflow during phenylephrine infusion was delivered preferentially to the subepicardium, resulting in further reduction of the endo/epi ratio in the central ischemic zone. This redistribution of collateral inflow may have been related to the increased left ventricular diastolic pressure during phenylephrine administration, which would be expected to cause selective compression of the subendocardial vasculature to result in preferential blood flow into the more superficial myocardial layers. Total collateral vascular resistance to the ischemic zone was not altered during phenylephrine infusion, so the increase in collateral flow could be explained entirely by increased aortic driving pressure. The failure of collateral vascular resistance to increase during phenylephrine infusion suggests lack of prominent alpha-receptor activity in the collateral vessels. Nevertheless, it might be expected that increasing intravascular distending pressure would have resulted in a passive decrease in collateral vascular resistance. The fact that collateral resistance did not decrease during increased aortic pressure may indicate some degree of vasoconstriction during phenylephrine administration.

In the present study, the left ventricular wall was deliberately divided to examine blood flow to the border zone separating normally perfused from ischemic myocardium. This region of myocardium which included the boundary between stained and unstained myocardium when the circumflex coronary artery was injected with Evans blue dye demonstrated blood flow rates intermediate between the central ischemic zone and normally perfused myocardium. This zone of apparent intermediate blood flow may in part be artifactual, however, representing an arithmetic mean of adjacent myocardial areas having normal and severely impaired perfusion. Thus, changes in blood flow to tissue samples encompassing the ischemic border cannot be used to predict the effect of interventions on the location of the actual boundary between ischemic and normally perfused myocardium. For example, although blood flow to the border zone did not change during nitroglycerin infusion, this could be explained by decreased flow to the normally perfused portion of myocardium in parallel with increased flow to the ischemic area. In contrast to this, during phenylephrine infusion (with or without nitroglycerin), when blood flow to both normally perfused and ischemic myocardium increased significantly, border zone flow also increased. Thus, changes in blood flow to the border zone tissue specimens could be accounted for by the sum of simultaneous changes in flow to normally perfused and ischemic myocardium with no change in the relative proportions of normally perfused and underperfused tissue.

References

Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog.

R J Bache

Circulation. 1978;57:557-562
doi: 10.1161/01.CIR.57.3.557

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/57/3/557

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/