Selective enhancement of function of stunned myocardium by increased flow

Lloyd D. Stahl, M.D., Thomas R. Aversano, M.D., and Lewis C. Becker, M.D.

ABSTRACT Although augmentation of flow does not improve the performance of normal myocardium, the hyperemic response after brief coronary occlusion is associated with transient hyperfunction in the previously ischemic region. In this study we assessed the effect of vasodilator-enhanced coronary blood flow on the systolic function of posts ischemic stunned myocardium. In 18 open-chest, anesthetized dogs the anterior descending artery was occluded for 5 min, followed by a 10 min period of reflow, repeated 12 times with a final 90 min recovery period. After the recovery period, either 0.06 mg/min dipyridamole (n = 6), 1 mg/min papaverine (n = 6), or 1.5 μg/kg/min nitroglycerin (n = 6) was infused intravenously for 15 min. Regional myocardial blood flow, which had returned to normal before administration of vasodilator, was increased 150% above baseline by dipyridamole and 80% by papaverine, but was unchanged by nitroglycerin. Segmental shortening decreased after repeated occlusions: from 17.5% to 9.5% in the group later treated with dipyridamole, from 18.6% to 6.7% in the papaverine group, and from 19.2% to 1.9% in the nitroglycerin group (p < .005 for all groups). Segmental shortening increased to 8.8% after dipyridamole, 13.6% after papaverine, and 5.1% after nitroglycerin (p < .05 for all groups), although the load-independent end-systolic pressure-length relationship (ESPLR) showed a significant shift to the left, reflecting enhanced performance, only after dipyridamole and papaverine. For all dogs combined, the percent improvement in ESPLR was correlated with the percent increase in flow (R = -.73, p < .001). Performance was unchanged in the control region despite similar augmentation of flow. This study demonstrates that the function of posts ischemic myocardium can be selectively enhanced by augmentation of coronary blood flow to levels greater than normal.

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UNDER PHYSIOLOGIC CONDITIONS coronary blood flow is closely coupled to myocardial metabolic demands by a number of important mediators of autoregulation, including oxygen, carbon dioxide, and vasodilator metabolites such as adenosine. Changes in myocardial performance associated with alterations in myocardial oxygen demand result in proportional changes in coronary blood flow. Flow itself, however, does not appear to be an independent determinant of function if oxygen supply is adequate. Supranormal flow induced by intracoronary or systemic administration of vasodilators is not associated with an increase in function above baseline levels.1-4

In stunned myocardium, however, the situation may be different. Brief periods of ischemia insufficient to produce necrosis cause a prolonged depression of function after reperfusion, even when flow is returned to normal. Pagani et al.5 demonstrated that after a short period of ischemia the myocardium exhibits a transient augmentation of function during the reactive hyperemic phase of reperfusion. This hyperfunction could be prevented only by the restriction of coronary blood flow to baseline levels in the reperfusion period, thereby eliminating reactive hyperemia. When the coronary flow restriction was removed as long as 3 to 5 min after the initial reperfusion, the delayed reactive hyperemia produced a similar transient hyperfunction. The transient nature of the flow increase, and the changing hemodynamic conditions and oxygen requirements in the immediate posts ischemic period, make it difficult to be certain that this increased flow during reactive hyperemia directly caused the increase in function.

To better delineate the effect of coronary blood flow on function in stunned myocardium, this study was undertaken using the canine preparation of repeated brief coronary occlusions. We have previously shown
this preparation to produce prolonged deterioration in regional systolic function without histochemical or ultrastructural evidence of myocardial necrosis. During steady-state conditions, after creation of post-ischemic dysfunction and return of flow to baseline levels, myocardial function was assessed in stunned and normal regions as coronary blood flow was increased by three vasodilators with different mechanisms and sites of action: dipyridamole, papaverine, and nitroglycerin.

Methods

Animal preparation. Twenty mongrel dogs of both sexes (20 to 26 kg) were anesthetized with intravenous sodium thiamylal (12.5 mg/kg) and intramuscular α-chloralose (100 mg/kg) in urethane, intubated, and ventilated with room air at a constant volume with a piston respirator. After a left lateral thoracotomy was performed on each, the lungs were retracted and the heart was exposed through a pericardiotomy. Pairs of 5 mmHg cylindrical piezoelectric crystals (0.06 inch outside diameter, 0.06 inch length, 0.015 inch thick; Vermitron, Columbus, OH) were implanted in the myocardium served by the anterior descending coronary artery and the anterolateral-basal region within the circumflex artery territory. The crystals were implanted in the midwall of the left ventricle, 10 to 15 mm apart, and were oriented parallel to the minor axis. Segment lengths were measured with a pulse transit sonomicrometer (model Sono-1-XB; James Davis Consultants). Left ventricular pressure, and its first derivative with respect to time, left ventricular dP/dt, were measured with a catheter-tip pressure transducer (Millar) that was inserted through an implanted silicone rubber left atrial catheter and advanced across the mitral valve. Aortic pressure was measured with a Statham P23-10 transducer (Gould Statham, Inc.). Catheters were placed in the descending aorta for measurement of blood pressure and withdrawal of microsphere reference samples, in the left atrium for microsphere injections, and in the femoral vein for infusion of drugs and fluids. Pressures, segment lengths, and lead II of the electrocardiogram were recorded continuously on a direct-writing recorder (Gould Brush 200).

Experimental protocol. A pneumatic occluder was placed around the left anterior descending coronary artery just distal to the first diagonal branch. Stun was induced by 12 occlusions of 5 minutes duration alternating with 10 minutes recovery periods, followed by a 90 minutes recovery period. After this recovery period, six dogs received 0.06 mg/min iv dipyridamole, six dogs received 1.5 μg/kg/min iv nitroglycerin, and six dogs received 1 mg/min iv papaverine. All drug infusions were maintained for 15 minutes by continuous infusion through the femoral vein. Drug concentrations and rates of infusion were determined in prior pilot studies in which the doses were titrated to the maximum that produced less than a 10% decrease in both peak left ventricular pressure and mean aortic pressure. Two dogs were excluded from the study because of ventricular fibrillation (one after the first occlusion and one after the second).

Blood flow to stunned and normal myocardium was determined with the use of radioactive microspheres (15 μm diameter, New England Nuclear Co) labeled with 124I, 125I, 103Ru, 60Nb, or 46Sc and injected into the left atrium. Three to five million microspheres were injected after a 3 minute mechanical agitation, while reference arterial samples were withdrawn at a constant rate of 2.16 ml/min by a calibrated pump. Blood flow was calculated from the radioactivity in tissue and reference blood samples determined in a well-type gamma scintillation counter (Packard model 5986) by standard methods after correction for overlap of the different radionuclide energy peaks. In each dog, flows to stunned and normal zones represented measurements in single tissue blocks weighing 1 to 3 g, divided into endocardial and epicardial halves, and encompassing each crystal pair. Flows were measured at baseline, 80 min after the last ischemic episode, and 10 min after the start of the drug infusion.

Hemodynamic and ultrasonic crystal measurements were made at end-expiration during the following periods: the baseline state, at the end of each reflow period, 90 min after the first occlusion, and 15 min after the start of the drug infusion. After this experimental protocol, the animals were killed by intra-atrial injection of potassium chloride. The hearts were cut into five to six short-axis slices from apex to base, each of which was incubated at 37°C in tritiated hydrochloride for 20 min and photographed in color. The site of each ultrasonic crystal pair was marked with a needle for photography. After this, the site of each crystal pair was excised, weighed, and counted for radioactivity for measurement of blood flow. The fresh tissue and photographs were both inspected to identify unstained areas, which represented myocardial necrosis.

Analysis of function. Signals from the ultrasonic crystals, left ventricular pressure, and left ventricular dP/dt were routed to a microcomputer (North-Star Horizon) at selected times during the experiment, digitized at 150 Hz by a Taccor 12-bit analog-to-digital converter, and recorded on floppy disk for later computerized analysis. The end-systolic segment length was measured 20 msec before peak negative left ventricular dP/dt; end-diastolic length was measured just before the onset of positive left ventricular dP/dt. Percent systolic segmental shortening was calculated as segmental shortening (end-diastolic minus end-systolic length) divided by end-diastolic segment length times 100, and represented the average of at least 5 heartbeats.

Previous studies have shown that the end-systolic pressure-length relationship (ESPLR) is a relatively load-independent measure of regional performance. Data for calculating the ESPLR were obtained as left ventricular pressure rose during a gradual manual occlusion of the descending thoracic aorta. Data on left ventricular pressure and ultrasonic crystal segmental length were collected over a 7 sec period just before and during the rise in left ventricular pressure. For each cardiac cycle, instantaneous left ventricular pressure and length data were used to calculate the slope (Ees) and the length-axis intercept (L0), respectively, of the ESPLR as defined by: $Ees = \frac{P}{L0}$, where $Ees$ is slope of the ESPLR; $P = LV$ pressure at end-systole; $L0 = \text{segmental length at end-systole}$; $P = \text{length-axis intercept of the ESPLR}$. For each cardiac cycle the left ventricular pressure-length point that maximized the value of $Ees$ was taken as the end-systolic pressure-length point. End-systolic pressure-length points from each beat were then used to determine the best least squares linear regression from which the parameters Ees and L0 were calculated to define the ESPLR. Iterations were repeated until both Ees and L0 were constant.

While Ees and L0 define the ESPLR, it should be noted that L0 was calculated from data collected over a relatively narrow range of end-systolic left ventricular pressures (usually between 90 and 160 mm Hg). Thus, to estimate L0, an extrapolation of at least 90 mm Hg was required. As an alternative, the ESPLR can be defined by a slope and a calculated end-systolic length at any end-systolic pressure. Since the pressure-length data were collected at above 100 mm Hg end-systolic pressure, we used the calculated end-systolic length at a left ventricular pressure of 100 mm Hg (L100) as the length-axis intercept.

Data analysis. Data are presented as the mean ± SD. Sequential measurements were compared by a repeated-measures analysis of variance (ANOVA) and significant differences be-
between any two groups were sought with a Newman-Keuls multiple-range test. Differences in the ESPLR were defined by comparing the sequential EEs and the end-systolic length at a left ventricular pressure of 100 mm Hg by ANOVA.

Results

Hemodynamic changes after repetitive brief coronary occlusions. As shown in table 1, peak left ventricular pressure and mean aortic pressure tended to increase from baseline to the end of the 90 min recovery period after repetitive brief coronary occlusions, while heart rate did not change significantly. Left ventricular end-diastolic pressure increased during coronary occlusion but returned to normal during reperfusion so that baseline and recovery values were not significantly different.

Systolic shortening after repetitive brief coronary occlusions. Segments within the ischemic region generally demonstrated systolic lengthening during coronary occlusion, with transient recovery immediately after reperfusion. After 10 min of reflow, however, systolic shortening was significantly reduced relative to baseline values. With repeated 5 min occlusion/10 min reflow cycles, postischemic dysfunction became cumulative and no significant recovery occurred during the 90 min after the final ischemic period. Mean systolic shortening decreased from 17.5 ± 5.3% at baseline to 0.9 ± 4.9% 90 min after the last ischemic period in dogs subsequently treated with dipyridamole from 18.6 ± 5.6% to 6.7 ± 7.2% in the dogs treated with papaverine, and from 19.2 ± 6.1% to −1.9 ± 6.2% in the dogs treated with nitroglycerin (p < .005 in each group). There was no difference between the systolic shortening measured 60 and 90 min after the last ischemic period within any group. The segmental dysfunction was characterized by early systolic lengthening occurring during isovolumetric contraction followed by late shortening extending into early diastole. Considerable variability in stunning was seen from animal to animal (figure 1). End-diastolic length in the stunned region increased after the repetitive ischemic episodes and did not recover during the

TABLE 1

Hemodynamics after repetitive occlusions and during infusion of vasodilators

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>90 Min after ischemia</th>
<th>With vasodilator</th>
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<tr>
<td>Peak LV pressure</td>
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<td>(mm Hg)</td>
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<tr>
<td>DP group</td>
<td>105 ± 20</td>
<td>122 ± 16^a</td>
<td>121 ± 16</td>
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<tr>
<td>PAP group</td>
<td>123 ± 13</td>
<td>130 ± 13</td>
<td>129 ± 15</td>
</tr>
<tr>
<td>TNG group</td>
<td>120 ± 16</td>
<td>131 ± 7</td>
<td>120 ± 6^b</td>
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<tr>
<td>Mean aortic pressure</td>
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<tr>
<td>(mm Hg)</td>
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<tr>
<td>DP group</td>
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<td>96 ± 17</td>
<td>92 ± 21</td>
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<tr>
<td>PAP group</td>
<td>100 ± 14</td>
<td>106 ± 13</td>
<td>102 ± 13^b</td>
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<tr>
<td>TNG group</td>
<td>96 ± 13</td>
<td>107 ± 7^a</td>
<td>96 ± 6^b</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>(beats/min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DP group</td>
<td>127 ± 14</td>
<td>137 ± 16</td>
<td>132 ± 16^b</td>
</tr>
<tr>
<td>PAP group</td>
<td>122 ± 17</td>
<td>113 ± 20</td>
<td>122 ± 22^b</td>
</tr>
<tr>
<td>TNG group</td>
<td>136 ± 28</td>
<td>140 ± 29</td>
<td>135 ± 28</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

DP = dipyridamole; LV = left ventricular; PAP = papaverine; TNG = nitroglycerin.

^a p < .05 compared with baseline; ^b p < .05 compared with posts ischemic value.

FIGURE 1. Percent systolic shortening in stunned and control segments at baseline, 90 min after the final ischemic period, and 15 min after the initiation of the infusion of dipyridamole (A and B), papaverine (C and D), or nitroglycerin (E and F). The marked decrease in shortening in the stunned segments after the repeated occlusions was stable during the final 30 min of recovery and was partially reversed by the infusion of vasodilators.
90 min recovery period. End-diastolic length increased from 12.8 ± 3.5 mm at baseline to 14.0 ± 3.4 mm after 90 min of recovery in the dipyridamole group (p < .05), from 12.1 ± 1.6 to 13.7 ± 1.7 mm in the nitroglycerin group (p < .05), and from 14.2 ± 2.7 to 14.6 ± 3.0 mm in the papaverine group (p = NS).

The control region showed a statistically insignificant decrease in segmental shortening, with mean values of 15.0 ± 5.2% at baseline vs 13.0 ± 1.8% at the end of the 90 min recovery in dogs later given dipyridamole, values of 14.0 ± 5.5% vs 10.8 ± 3.2% in the dogs given papaverine, and values of 15.1 ± 7.9% vs 13.0 ± 9.9% in the dogs given nitroglycerin (figure 1).

**ESPLR after brief coronary occlusions.** The ESPLR in stunned regions showed a marked and significant shift to the right after repetitive brief coronary occlusions in all dogs, indicating decreased regional performance. The lines depicted in figure 2 were constructed from the mean values for L100 (the calculated segmental length at a left ventricular pressure of 100 mm Hg) and L150 (the calculated segmental length at a left ventricular pressure of 150 mm Hg) at baseline and 90 min after the final ischemic period.

In the control region there was no significant shift in the ESPLR from baseline to the end of the 90 min recovery period.

**Regional myocardial blood flow after repetitive brief coronary occlusions.** Regional myocardial blood flow was measured at baseline, during the first coronary occlusion, and 80 min after the last occlusion (table 2). Mean flows at baseline were similar in the three groups. During occlusions, ischemic zone flow decreased markedly to less than 10% of baseline values. There was no significant change in flow during occlusion in the nonischemic region. After the recovery period endocardial blood flow was similar to that at baseline in both the reperfused and control regions, while epicardial blood flow was slightly but significantly (p < .05) greater than baseline in both regions of animals that subsequently received dipyridamole or papaverine.

**Effects of infusion of dipyridamole.** Dipyridamole, 0.06 mg/min, was continuously infused intravenously for 15 min after the 90 min recovery period. There was no significant change in either peak left ventricular pressure or mean aortic pressure (table 1). Heart rate decreased from 137 ± 16 to 132 ± 16 beats/min (p =

![FIGURE 2](http://circ.ahajournals.org/DownloadedFrom/903x903/fig2.png)
No change in left ventricular end-diastolic pressure was noted.

Segmental shortening in the stunned region increased significantly during the infusion of dipyridamolene from 0.9 ± 4.9% to 8.8 ± 2.6% (p < .02; figure 1). This was associated with a corresponding significant shift in the ESPLR to the left, indicating improved regional performance, albeit not back to baseline levels (figure 2). End-diastolic length did not change significantly (14.0 ± 3.5 vs 13.8 ± 3.7 mm after dipyridamolene). The control segments showed a slight and insignificant increase in fractional systolic shortening during dipyridamolene (13.0 ± 1.8% to 15.6 ± 1.1%), with no change in the ESPLR (figures 1 and 2).

Myocardial blood flow increased significantly after 10 min of infusion of dipyridamolene in both the stunned and control regions (table 2). The increase was significantly less in the epicardial segment in both regions (240% endocardium vs 180% epicardium in the stunned region, 240% endocardium vs 220% epicardium in the control region, p < .05), and the increase in the epicardial segment of the postischemic region was less than that seen in the control region (p < .05).

**Effects of infusion of papaverine.** Papaverine, 1 mg/min, was continuously infused intravenously for 15 min after the 90 min recovery period. Peak left ventricular pressure did not change, although mean aortic pressure fell significantly (p < .05), reflecting a 6% fall in aortic diastolic pressure. No change in left ventricular end-diastolic pressure was seen. Heart rate increased from 113 ± 20 to 122 ± 22 beats/min during administration of papaverine (p < .05; table 1).

Segmental shortening in the stunned region increased during the infusion of papaverine from 6.7 ± 7.2% to 13.6 ± 9.6% (p < .02; figure 1). The end-diastolic segmental lengths were unchanged by the drug (14.6 ± 3.0 vs 14.5 ± 2.8 mm). The ESPLR showed a significant shift to the left after papaverine, indicating improved, although not baseline, performance (figure 2). Control segments demonstrated a significant increase in systolic shortening (10.8 ± 3.2% vs 12.7 ± 4.1%, p = .05), but the ESPLR was unchanged (figures 1 and 2). This reflects the afterload dependence of systolic shortening as a measure of cardiac performance. Myocardial blood flow increased, approximately 60% during the infusion of papaverine in both stunned and control regions (p < .005). Although epicardial flows were higher, there was no significant difference in the magnitude of the papaverine-induced flow increase between stunned and control regions or between endocardial and epicardial layers (table 2).

**Effects of infusion of nitroglycerin.** Nitroglycerin, 1.5 µg/kg/min, was continuously infused intravenously for 15 min after the 90 min recovery period. Nitroglycerin produced an 8% drop in peak left ventricular pressure (p < .05) and a 10% decrease in mean aortic pressure (p < .05; table 1). Heart rate and left ventricular end-diastolic pressure were unchanged.

Segmental shortening in the stunned region increased significantly during nitroglycerin from −1.9 ± 6.2% to 5.1 ± 5.5% (p < .05). The end-diastolic segmental length in the stunned region was unchanged (13.7 ± 1.7 vs 13.9 ± 1.7 mm). In the control region there was a slight although insignificant increase in shortening from 13.0 ± 9.9% to 13.5 ± 8.5% (figure 1). The ESPLR was unchanged in both the stunned and control regions (figure 2).
Myocardial blood flow during the infusion of nitroglycerin was not statistically significantly different compared with that at the end of the 90 min recovery period (table 2).

Relationship between augmented flow and improved function. To define a relationship between flow and function in the stunned region, the change in the length-axis intercept (L100) was used as a load-independent measure of regional function. The percent increase in flow induced by infusion of a vasodilator ([flow after vasodilator (Qvd) - flow before vasodilator (Q stun)]/Q stun) was compared with the percent shift in the L100 ([L100 before vasodilator (L100 stun) - L100 after vasodilator (L100 vd)]/L100 stun), and the percent recovery of function ([L100 stun - L100 vd]/L100 stun - L100 at baseline]). The percent increase in transmural flow and the percent shift in L100 (figure 3, A) showed a significant linear relationship (R = −.73, p < .001) with an intercept near the origin. A similar relationship was noted if the increase in endocardial flow (R = −.65, p < .005), or epicardial flow (R = −.71, p < .001) was used. The percent recovery of function also showed a significant linear relationship to the percent increase in transmural flow (R = −.68, p < .005; figure 3, B), endocardial flow (R = −.63, p < .005), and epicardial flow (R = −.62, p < .01).

Myocardial necrosis. No areas of necrosis were observed on visual inspection of the triphenyltetrazolium chloride-stained left ventricular slices from any of the 18 animals.

Discussion

The major finding of this study was that enhanced flow after infusions of dipyridamole and papaverine was associated with a significant increase in fractional systolic shortening and a shift in the ESPLR to the left in stunned segments, indicative of a load-independent improvement in contractile state. This effect was selective for the stunned region since improved performance was not found in the control segments. Nitroglycerin, which did not increase myocardial blood flow, did increase regional segmental shortening in the stunned segments. We believe that this effect was mediated by a reduction in afterload, since the ESPLR was unchanged.

The end-systolic pressure-thickness relationship and ESPLR have been shown to be sensitive, relatively load-independent indexes of regional contractile state, and the use of the ESPLR was important to the interpretation of the results of this study, in which systemic infusions of vasodilators produced significant changes in loading conditions..conf. 10 Miller et al.9 and Aversano et al.10 showed that administration of the inotropic agent dobutamine produced a shift of the ESPLR to the left with an accompanying increase in slope. Propranolol produced a rightward shift in the ESPLR with a significant decrease in the slope and an increase in the length-axis intercept. In our study, as would have been predicted, repeated coronary occlusions caused a shift of the ESPLR to the right, indicating decreased performance. Infusions of both dipyridamole and papaverine were associated with a significant leftward shift in the ESPLR, although baseline values were not reached. In the nitroglycerin experiment a 33% recovery of baseline segmental shortening was obtained with an 8% fall.

FIGURE 3. A. The percent increase in flow in the stunned region ([flow after vasodilator - flow before vasodilator]/flow before vasodilator) is significantly related to the percent shift in the length-axis intercept, L100 ([L100 before vasodilator - L100 after vasodilator]/L100 before vasodilator). A similar relationship is shown in B between the percent increase in flow and the percent recovery of function ([L100 before vasodilator - L100 after]/L100 before vasodilator - L100 at baseline]). Diamonds represent nitroglycerin data, triangles represent papaverine data, and circles represent dipyridamole data.
in peak left ventricular pressure and a 10% drop in mean aortic pressure. However, the line defining the ESPLR for the stunned segments was unchanged, supporting the interpretation that there was no real increase in regional performance with nitroglycerin, and that the increased shortening was a result of a decrease in afterload. In the control regions there was an increase in systolic shortening during infusions of all three vasodilators (this reached statistical significance only during papaverine infusion), although in all cases the ESPLR remained unchanged.

As shown in figure 4 for one of the dipyridamole experiments, the configuration and the length-axis intercept of the pressure-length loops were markedly altered during coronary occlusion. The configuration of the pressure-length loop was still distorted at the end of the 90 min recovery period. Dipyridamole not only shifted the length-axis intercept to the left, but also altered the shape of the pressure-length loop toward a more normal configuration. The area of the pressure-length loop, which has been used as an index of regional ventricular work, was greatly increased by dipyridamole, because paradoxical segment motion during isovolumetric contraction was virtually eliminated.

The vasodilators used in this study were chosen because of their different sites and modes of action. Dipyridamole, derived from a class of compounds whose structures consist of two condensed pyrimidine rings, has been known to be a potent coronary arteriolar dilator for many years. Many observations have linked the action of dipyridamole to the metabolism of adenosine by showing an increased plasma half-life of adenosine through inhibition of erythrocyte uptake. Dipyridamole potentiates many responses to adenosine and adenine nucleotides, such as coronary vasodilatation and atrioventricular node blockade, and inhibits ADP-induced platelet aggregation. Numerous studies have shown that adenosine produces no effect, or even a slight negative inotropic effect, on myocardial contractility as measured by peak dP/dt, the time from onset of left ventricular contraction to peak dP/dt, and the left ventricular tension-time index. Dipyridamole itself has not been shown to have any inotropic effects, and we noted no effect: control region systolic shortening and ESPLR were unchanged.

Papaverine increases cyclic AMP through inhibition

![END-SYSTOLIC PRESSURE-LENGTH RELATIONSHIP](image)

**FIGURE 4.** Four representative pressure-length loops obtained from the stunned segment of one animal at baseline (A), during LAD occlusion of the left anterior descending artery (B), 90 min after the final ischemic period (C), and 15 min after the infusion of dipyridamole (D). The line representing the ESPLR at baseline (solid line) and 90 min after ischemia (short dash) were drawn on subsequent panels to demonstrate the rightward shift after repeated occlusions and the leftward shift after dipyridamole infusion. Note the increase in the area of the loops after dipyridamole.
of cyclic AMP phosphodiesterase activity and it is a potent nonspecific direct smooth muscle relaxant. Its effects are seen predominantly in the larger blood vessels, although it also decreases resistance through its action on arterioles. The effect of papaverine on myocardial contractility is unclear. Several studies in isolated papillary muscles and isolated perfused hearts have shown that papaverine augments the inotropic response to catecholamines,15-17 while others have noted an increase in intracellular cyclic AMP without an influence on the contractile state.18 Endoh and Schumann15 found a variable and dose-related response in rabbit isolated papillary muscle. They noted an enhanced inotropic response to β-adrenergic stimulation at low doses, while at higher doses a negative inotropic response was seen, which was believed to be secondary to a calcium antagonistic effect. Ferrari19 has reported that papaverine affects membrane excitation, excitation-contraction coupling, and cell metabolism in smooth muscle. In our study papaverine produced a decrease in left ventricular afterload with an accompanying increase in the fractional shortening of the control region, but the ESPLR was unchanged in the control region. Therefore, the improvement in function seen in the postischemic region with papaverine and demonstrated by a significant shift of the ESPLR to the left is unlikely to be due to any direct inotropic effect of papaverine.

Nitroglycerin's effect on total coronary blood flow is transient and variable, and its clinical efficacy is based on dilatation of the epicardial conductance vessels, which produces improved collateral flow, and its ability to improve the loading conditions on the heart.2 In our study nitroglycerin had the greatest effect on aortic diastolic pressure, and therefore on coronary perfusion pressure. Coronary blood flow was not increased, and the endocardial/epicardial blood flow ratio was not altered.

The concept that increased flow can ameliorate the dysfunction of stunned myocardium is a new one, although the mechanism(s) responsible remain unknown. One possibility is that increased flow may be associated with an increase in blood volume within the ventricular wall, leading to myofiber stretching and an increase in contractile force through the Frank-Starling mechanism. If such a mechanism were operative, however, an increase in end-diastolic segmental dimensions should have occurred. No changes were found in end-diastolic segmental length, although wall thickness was not measured. Another possibility is that, despite our efforts to correct for loading changes with the ESPLR, the improved function observed after dipyridamole and papaverine was still due to reduced afterload. The ESPLR, while controlling for external loading, does not take into account internal loading changes resulting from alterations in left ventricular shape. Relatively small changes in blood pressure could have greater effects on the shape of stunned than on the shape of normal segments. Against this shape hypothesis, however, is the lack of change in end-diastolic segmental length in either the stunned or normal segments during the infusion of vasodilators, and the fact that a greater reduction in blood pressure occurred after nitroglycerin than after dipyridamole or papaverine, even though the latter agents were the ones associated with improved performance and increased blood flow.

A final possible explanation for the selective increase in the function of stunned myocardium during increased coronary flow may be related to a vasodilator effect on the microvasculature. The repeated short ischemic periods with reperfusion could have caused a heterogeneous pattern of microvascular injury, perhaps mediated by oxygen free radicals,20,21 with microvascular spasm or endothelial disruption, or with plugging by platelets or leukocytes. Hori et al.22 demonstrated an impairment in segmental shortening after repeated regional embolization with microspheres despite an increase in resting coronary blood flow, although peak flow during reactive hyperemia decreased. The enhanced coronary blood flow in Hori's study and the "normal" flow after repeated occlusions in our study may represent similar models of microvascular occlusion, local adenosine release, and subsequent dilatation and recruitment of adjacent capillary beds. Therefore, although microsphere analysis revealed normal endocardial and slightly enhanced epicardial flows in the stunned region, this does not rule out the possibility that a heterogeneity of flow may exist on a microvascular level that could result in impaired overall function. Both nitroglycerin and propranolol have been shown, with microspectrophotometric techniques, to improve microregional uniformity of oxygenation.23,24 In our preparation the small-vessel dilatation produced by dipyridamole and papaverine could have overcome the microvascular effects of repeated occlusions, especially in the endocardium, leading to improved oxygen supply/consumption ratios and improved overall regional function.

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