Effectiveness of Dipyridamole in Reducing the Size of Experimental Myocardial Infarction

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SUMMARY The role of vasodilators in reducing the extent of myocardial necrosis after acute coronary occlusion has been controversial. The present study was performed to evaluate the efficacy of dipyridamole in reducing infarct size either 8 or 24 hours after ligation of the left anterior descending (LAD) coronary artery in 12 dogs. On the basis of identical epicardial ST-segment elevations 15 minutes after coronary ligation, the dogs were divided equally into control or dipyridamole-treated (3 mg/kg) groups. Technetium-99m-glucoheptonate (TcGH) was injected intravenously 1 hour after coronary occlusion and myocardial imaging performed before autopsy. Blood pressure (BP), heart rate (HR), left ventricular end-diastolic pressure (LVEDP) and left ventriculography (VG) were recorded before and at regular intervals after LAD occlusion. Autopsy delineation of myocardial infarct size was determined by planimetry of myocardial slices stained with nitroblue tetrazolium (NBT) and in vivo infarct size was measured by planimetry of myocardial TcGH uptake in the right anterior oblique view.

During the infusion of dipyridamole, mean BP fell in the dipyridamole group from 102 ± 4 to 80 ± 6 mm Hg (p < 0.05) (mean ± SEM), HR decreased from 134 ± 5 to 122 ± 5 beats/min (p < 0.05), tension-time index decreased from 3120 ± 296 to 1839 ± 211 mm Hg-sec/min (p < 0.05) and LVEDP was unchanged, 7.7 ± 0.6 vs 7.9 ± 0.9 mm Hg (NS). VG analysis 1 hour after coronary occlusion revealed less decrease in regional ejection fraction in the anterior wall of dipyridamole-treated animals compared with the control group, -11 ± 3% vs -33 ± 5% (p < 0.01), while inferior wall ejection fraction increased in both groups, although more in dipyridamole-treated animals, 30 ± 3% vs 20 ± 5% (p < 0.05). The radionuclide uptake of TcGH was smaller in dipyridamole compared with control animals, 7.9 ± 0.9 vs 16.7 ± 1.0 cm² (p < 0.025), while autopsy-determined infarct weight (NBT technique) was also less, 7.7 ± 1.2 vs 17.6 ± 1.4 g (p < 0.025).

These results documented that dipyridamole can favorably alter the course of acute experimental myocardial infarction. The decrease in infarct size can be quantified in vivo and noninvasively by TcGH myocardial imaging and verified postmortem by the NBT histochemical staining technique.

FUNCTIONAL IMPAIRMENT,¹ serious ventricular arrhythmias² and even survival³ appear to be related to the extent of myocardial ischemic damage in patients with acute myocardial infarction. A vast clinical and experimental experience suggests that the balance between local myocardial oxygen supply and demand is a critical determinant of myocardial injury after acute coronary occlusion. Vasodilators, on the basis of hemodynamic effects, may favorably influence this balance, resulting in improved cardiac performance and reduced ischemic injury.⁴ Dipyridamole (Persantin), a potent vasodilator, has been shown to cause marked increases in coronary blood flow in the experimental animal.⁵ Whether such improvement in total coronary flow actually benefits the ischemic myocardium or results in further impairment by the process of “coronary steal” is uncertain.⁶ In addition, vasodilator-induced reduction in ventricular afterload might favorably influence ischemic myocardium by reducing left ventricular wall tension and lowering myocardial oxygen requirements. Conversely, a reduction in arterial pressure might compromise coronary blood flow and actually increase the extent of evolving myocardial necrosis. Finally, experimental studies have shown that dipyridamole also has a potent antithrombotic effect⁷ that theoretically might prevent or decrease extension of arterial thrombus and occlusion of collateral vessels surrounding an acute myocardial infarct. In this study, we tested the hypothesis that the net effect of dipyridamole is to protect ischemic myocardium and decrease eventual infarct size after experimental acute coronary occlusion.

Methods

Experiments were carried out in 12 adult mongrel dogs of both sexes that weighed 15–25 kg. They were anesthetized with sodium pentobarbital (30 mg/kg of body weight), auffed endotracheal tube was inserted and respiration maintained by a Harvard respirator. A #6F Lehman catheter was advanced in a retrograde fashion into the ascending aorta from the femoral artery and periodically advanced across the aortic valve into the left ventricle under direct fluoroscopic control to obtain left ventricular pressure recordings. Central aortic pressure and left ventricular end-diastolic pressure (LVEDP) were recorded before and at regular intervals after coronary occlusion with Statham P23 Db transducers and a multichannel Electronics for Medicine DR8 oscillographic recorder. Lead II of the standard ECG was monitored continuously. Tension-time index was derived by mul-
tipplying the product of the planimetered area of the systolic phase of the aortic pressure pulse by the systolic ejection time per minute.

Median sternotomy was performed and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was permanently occluded with a ligature at the junction of its proximal and middle thirds. A 36-unit cloth grid was moistened and molded to the shape of the epicardial surface of the heart and oriented along the interventricular groove in a standardized manner that was constant from dog to dog. A hand-held hollow metal electrode was gently applied to each of 36 sites to obtain epicardial electrogroms 15 minutes after coronary occlusion. The details of this technique have been previously described. Earlier investigations have validated a direct relationship between the magnitude of epicardial ST-segment elevation 15 minutes after coronary occlusion and the degree of myocardial creatine phosphokinase (CPK) reduction and histologic evidence for myocardial necrosis measured 24 hours after ligation. Unipolar epicardial electrocardiography was performed at one-tenth sensitivity (1 mmV-1 mV) and a permanent record made on a Hewlett Packard 7712 recorder. Both the number of sites with ST-segment elevation ≥ 2 mm (NST) and the sum of ST-segment elevation in all 36 epicardial sites (EST) were determined.

Analysis of epicardial ST-segment elevations was performed immediately after epicardial mapping and the following subdivisions were made: 1) Dogs with EST < 20 mm were excluded because our previous experience has shown that this level of injury is associated with insignificant myocardial necrosis; 2) dogs with EST 20–40 mm were considered to have moderate ischemic injury; and 3) dogs with EST > 40 mm were considered to have severe ischemic damage. Three dogs from each of subdivisions 2 and 3 were randomly assigned to either treatment (n = 6) or control (n = 6) groups.

After epicardial ST-segment mapping was analyzed (30 minutes after coronary ligation), the treatment group received dipyridamole, 3 mg/kg body weight, mixed in 5% dextrose in water to a total volume of 100 ml delivered over the next 45 minutes by constant intravenous infusion, while the control group received only 100 ml 5% dextrose in water. The chest was closed in layers 30 minutes after coronary occlusion with chest tube drainage connected to an underwater seal.

Left ventriculography was performed in the right anterior oblique (RAO) position after the manual injection of 10 ml Renografin-76 (meglumine diatrizoate) before and 1 hour after coronary ligation. The ventriculograms were recorded on 16-mm film with a single-plane cine fluorographic unit. Images representing consecutive end-diastole and end-systole were projected on a 9 × 12-inch screen and their outlines were traced. Each heart tracing was divided into anterior (A) and posterior (B) portions by a line drawn from the midpoint of the aortic valve to the left ventricular apex and the end-diastolic and end-systolic areas of A and B were determined planimetrically before and 1 hour after coronary occlusion as previously described. By comparing the change in areas from diastole to systole before and after coronary occlusion, a regional ejection fraction (anterior and inferior) was calculated and expressed as percent change in the respective areas A or B before and 1 hour after coronary ligation.

Reproducibility of this ventriculographic method was determined by measuring the end-diastolic and end-systolic areas of A and B in triplicate and finding a mean value before calculating a percent reduction in area. These measurements demonstrated a standard deviation of 3–10%. Furthermore, two observers traced the heart borders without knowing whether they were from control or dipyridamole-treated animals.

One hour after coronary occlusion, 20 mCi of 99mTc-glucophoneatonate (TcGH) were injected intravenously and images of the myocardial uptake of this radiopharmaceutical were obtained using a Picker Dyna Camera 2C scintillation camera with a low-energy, high-resolution collimator, 7 or 23 hours after injection. Half the treatment and control groups (three pairs) were sacrificed 8 hours after ligation while the remainder (three pairs) were sacrificed at 24 hours.

We feel that it is justified to group together these two subsets of dogs, sacrificed after 8 and 24 hours of coronary occlusion, because our own experience and the work of others indicate that experimental canine myocardial infarcts reach a maximum size after approximately 8 hours of permanent coronary occlusion and change very little thereafter. The following observations support this concept:

1) Studies of Reimer et al. indicate that 84% of the cells destined to die within a myocardial infarct have died 6 hours after coronary occlusion. Although they did not specifically study 8-hour-old infarcts, the trend was such that it is likely that the infarct was already completed by that time.

2) In a previous study in our laboratory to evaluate methods for the quantification of myocardial infarction in dogs, mean infarct size did not vary significantly whether the dogs were sacrificed at 8 hours or 24 hours after coronary occlusion.

3) Hillis et al. did not observe any reduction in infarct size when hyaluronidase was given 9 hours after coronary occlusion, but the same drug was effective in limiting infarct size when given at 20 minutes, 3 hours and 6 hours after coronary occlusion. This work suggests that 9 hours of permanent ischemia are sufficient to complete a myocardial infarct.

4) We have shown that scintigraphic infarct size determined in dogs by 99mTc-glucophoneatonate imaging is an accurate reflection of true infarct size as measured at autopsy. We recently extended these observations using serial 99mTc-glucophoneatonate imaging and showed that maximum scintigraphic infarct size is achieved by either 5 hours or 8 hours after coronary occlusion in the case of transmural and non-transmural infarcts, respectively (Jacobstein JG, Cahill PT, Alonso DR: unpublished data).
After the animals were sacrificed, their hearts were removed and sectioned perpendicular to the atrioventricular groove at 1-cm intervals from apex to base. The myocardial slices were imaged and immediately incubated in buffered nitroblue tetrazolium (NBT). Experimental myocardial infarction is clearly delineated by this method: A dark blue NBT precipitate is deposited on the normal myocardium while the infarct remains unstained. We recently confirmed the accuracy of the method by electron microscopy and showed that myocardium grossly unstained by NBT displays unequivocal ultrastructural evidence of necrosis. Kodachromes were taken of the heart slices stained by NBT and projected on tracing paper to life size and the perimeters of the infarct and entire slice were traced. Planimetry of the percent area occupied by the infarct in ventricular slices of known weight permitted calculation of the total weight of the infarct (fig. 1). Scintigraphic infarct size was established by planimetry of the cross-sectional area of isotope uptake in the RAO projection and corrected to life size (fig. 2). The RAO projection was chosen because it has been shown to correlate well with autopsy-determined infarct size. The accuracy of the described techniques in the evaluation of experimental infarct size has been previously documented.

In each case, individual infarct sizes were determined scintigraphically and pathologically by different observers who did not know whether a given animal was control or dipyridamole-treated. All data are expressed as mean ± SEM. Statistical correlations were carried out using the appropriate t test and a p value < 0.05 was considered significant.

Results

Analysis of epicardial ST-segment mapping showed that dipyridamole-treated and control groups had ini-
Effect of Dipyridamole on Infarct Size/Roberts et al.

Tially sustained comparable ischemic injury as reflected by the ST-segment elevation 15 minutes after coronary occlusion but before drug intervention. At this time, EST was 43.1 ± 1.7 mm and NST 12.1 ± 0.8 mm in dipyridamole-treated animals, compared with 42.6 ± 1.5 mm and 12.0 ± 0.7 mm, respectively, in control animals.

Baseline hemodynamic data were similar in dipyridamole and control groups, but differences were observed after coronary ligation (fig. 3). One hour after coronary occlusion, heart rate, mean aortic pressure and tension-time index were lower in the dipyridamole group than in the controls, 122 ± 7 beats/min vs 150 ± 8 beats/min (p < 0.05), 80 ± 6 mm Hg vs 100 ± 9 mm Hg (p < 0.05), and 1839 ± 211 mm Hg-sec/min vs 2756 ± 249 mm Hg-sec/min (p < 0.05), respectively, but LVEDP was similar between groups, 7.8 ± 0.9 in the dipyridamole group and 7.0 ± 0.9 in controls (NS). By 8 hours after ligation only a lower heart rate persisted in dipyridamole-treated animals compared with controls, 120 ± 8 beats/min vs 153 ± 5 beats/min (p < 0.05). At 24 hours after ligation the dogs not electively sacrificed at 8 hours had similar heart rate, mean aortic pressure and LVEDP.

Left ventriculograms taken in the RAO projection were evaluated before and 1 hour after coronary occlusion (fig. 4). Table 1 shows the percent reduction in area from end-diastole to end-systole for each dog. No differences in left ventricular wall motion were

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**Figure 3.** Comparison of hemodynamic changes in dipyridamole and control groups before and after coronary ligation. LVEDP = left ventricular end-diastolic pressure.

**Figure 4.** Changes in regional ventricular function as demonstrated by left ventriculography before and after left anterior descending coronary artery ligation. RAO = right anterior oblique.
Table 1. Effect of Coronary Occlusion on Regional Ejection Fraction Determined by Left Ventriculography

<table>
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<th>Percent reduction in area (cm²)</th>
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<tr>
<td></td>
<td>Area A</td>
<td>Area B</td>
<td></td>
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<tr>
<td></td>
<td>Pre-occlusion</td>
<td>1 hr after occlusion</td>
<td>Pre-occlusion</td>
</tr>
<tr>
<td>Control</td>
<td>1  59.5</td>
<td>25.8</td>
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<td></td>
<td>2  44.6</td>
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<tr>
<td></td>
<td>6  22.6</td>
<td>8.5</td>
<td>22.1</td>
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<tr>
<td>Dipyridamole</td>
<td>1  32.6</td>
<td>24.5</td>
<td>6</td>
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<td></td>
<td>2  43.0</td>
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<td>6  30.8</td>
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noted between dipyridamole and control groups before coronary occlusion in either anterior (area A) or inferior (area B) segments of the left ventricle. One hour after coronary occlusion, area A showed a decrease in regional ejection fraction in both groups compared with baseline values but less change was observed in the dipyridamole-treated dogs than in the control group (−11 ± 3% in comparison to −33 ± 5%, p < 0.01). In addition, area B showed no change from baseline in control animals, but an increase in ejection fraction was noted in dipyridamole-treated dogs, from 18 ± 5% to 30 ± 3% (p < 0.05). The difference in area B regional wall motion between groups 1 hour after coronary ligation was also marked (30 ± 3% in the dipyridamole group vs 20 ± 5% in controls, p < 0.05).

Figure 5 shows the scintigraphic appearance of myocardial infarcts in the RAO and anterior projections in two representative dogs. The RAO projection is better for scintigraphic quantification of infarct size, probably because the chest wall configuration in the dog makes myocardial images in the anterior projection more difficult to outline. The mean scintigraphic infarct size in the RAO projection was substantially smaller in dipyridamole-treated animals compared with controls (7.9 ± 0.9 cm² vs 16.7 ± 1.0 cm², p < 0.025). Similarly, the mean infarct weight determined at autopsy by the NBT technique also demonstrated smaller infarcts in dipyridamole-treated animals compared with controls (7.7 ± 1.2 g vs 17.6 ± 1.4 g, p < 0.025). These results are shown in figure 6.

Discussion

The present study assessed whether dipyridamole could reduce the extent of myocardial necrosis after acute coronary occlusion. The techniques used to determine the effectiveness of this vasodilator have been reported from our laboratory and found to be accurate. Epicardial electrocardiography has been used to predict the extent of subsequent myocardial injury as measured by tissue CPK depletion and con-
firmed by histology after experimental myocardial infarction.11, 12 Despite some disagreement over the specificity and quantitative value of this electrocardiographic indicator of myocardial damage,19 this method was used in the present experiment to assure that the magnitude of initial ischemic injury after coronary occlusion, but before therapeutic intervention, was similar between control and dipyridamole-treated dogs. Epicardial ST-segment elevations were identical between these groups, suggesting that their initial response to coronary occlusion reflected a comparable ischemic insult.

Myocardial infarct imaging has been reported to provide direct information in a noninvasive fashion concerning the presence or absence18, 20-23 and extent15, 18 of myocardial necrosis after acute coronary occlusion. Our recent experience with 99mTc-glucoheptonate showed a good positive correlation (r = 0.85, p < 0.01) between in vivo scintigraphic infarct size measured in the RAO view and autopsy-determined infarct weight in 28 dogs that survived anterior wall myocardial infarcts.15 Others have shown similar results with 99mTc-pyrophosphate.18, 24 Success in documenting a pharmacologic and mechanically induced reduction in the extent of myocardial necrosis after coronary ligation using 99mTc-glucoheptonate scintigraphy and other independent techniques has also been reported from our laboratory.26 In the present study, a 53% reduction in scintigraphically determined infarct size was observed in the dipyridamole group compared with control animals.

Left ventriculography has been used as a technique for evaluating ventricular function and localizing specific areas of abnormal wall motion in experimental coronary occlusion.26 Although a decrease in relative anterior wall motion was observed in both dipyridamole and control groups after coronary ligation, there was less depression in anterior wall ejection fraction in the treatment group. In addition, an increased regional ejection fraction occurred in the posterior portion of the left ventricle in dipyridamole-treated dogs after coronary ligation, while control dogs had no changes in this region remote from the central ischemic zone. These ventriculographic findings suggest a better maintenance of left ventricular performance in dipyridamole-treated dogs compared with controls, although changes in afterload and heart rate also contributed to the changes in left ventricular wall motion.

Postmortem examination of these canine hearts by the NBT method further substantiated a reduction in infarct size in the dipyridamole-treated group. This histochemical technique revealed that infarct size was 56% less than in controls. The close agreement between NBT and 99mTc-glucoheptonate procedures in documenting a reduction in infarct size (56% and 53%, respectively) corresponds to our previous data that shows that the scintigraphic cross-sectional area of radionuclide uptake correlates in a straight-line fashion with the autopsy-determined infarct size.10, 11, 20

The results of the present study indicate that in the dog, myocardial infarct size can be reduced by dipyridamole as shown by 99mTc-glucoheptonate and NBT techniques and that this is associated with a smaller degree of left ventricular functional impairment as documented by left ventriculography.

Myocardial ischemic injury appears to reflect the balance between myocardial oxygen supply, myocardial oxygen demand and substrate availability.11, 12, 27 Factors that augment oxygen demand, such as increased heart rate28 or increased contractility29 also increase the severity of ischemic tissue injury and increase the extent of infarction defined by myocardial CPK analysis and morphology. Conversely, factors that decrease oxygen demand, such as β-adrenergic blockade30 and intraaortic balloon counterpulsation,25, 31 reduce the amount of ischemic injury. Lowering the systolic blood pressure decreases myocardial oxygen requirements by diminishing left ventricular wall tension,29 and if coronary perfusion is not compromised, a decrease in myocardial ischemia can be expected. Interventions which increase myocardial oxygen supply, such as coronary artery bypass grafting,23 may also limit the extent of ischemic tissue damage. The role of vasoconstrictors in the treatment of myocardial ischemia has been considered detrimental,24 primarily because of an increase in afterload and probable coronary artery vasoconstriction, but recent evidence suggests that a reverse coronary steal phenomenon, associated with the use of vasopressors, may actually reduce myocardial ischemic injury under certain conditions.35 Vasodilators, by decreasing ventricular afterload and/or preload, reduce myocardial oxygen requirements and therefore have been considered important for limiting the extent of myocardial ischemia.4, 36

Several mechanisms can be proposed to explain the beneficial effects of dipyridamole, a potent vasodilator, on ischemic myocardium. The hemodynamic effects of dipyridamole have been previously reported in the normal anesthetized dog37 and in the canine after acute coronary occlusion.38 In the present study, dipyridamole caused an early decrease in mean arterial blood pressure and heart rate, while LVEDP remained unchanged. Similar laboratory investigations using sodium nitroprusside, another nonspecific vasodilator, have shown that such hemodynamic changes may be associated with improved global and regional myocardial performance, provided coronary blood flow is maintained.46 However, nitroprusside has also been shown to cause increased ischemic injury with decreased regional myocardial blood flow using different experimental techniques to quantify ischemic changes.45 The reduction in tension-time index associated with dipyridamole infusion in this experiment presumably decreased myocardial oxygen consumption.41 Nevertheless, sufficient reduction in blood pressure in the presence of acute myocardial ischemia can be hazardous, since myocardial oxygen supply is related to coronary perfusion pressure and systemic hypotension has been shown to increase the extent of ischemic injury under certain experimental conditions.42 The modest reduction in mean systemic
pressure associated with a controlled infusion of dipyridamole in the present study was not sufficient to adversely affect the final balance between myocardial oxygen supply and demand. In addition, the dipyridamole-induced reduction in afterload and heart rate associated with the presumed increase in total coronary blood flow were probably responsible for the ventriculographic findings of an increased ejection fraction in the nonischemic inferior portion of the left ventricle. We know of no data to suggest that dipyridamole has a positive inotropic action in either normal or ischemic myocardium.

It is well known that dipyridamole and other vasodilators reduce coronary resistance48 and increase total coronary blood flow in the experimental animal.4, 44 In the presence of acute myocardial ischemia, however, the relative distribution of coronary blood flow after the administration of vasodilators is still controversial. The effects of various vasodilators on the coronary vascular bed itself is not uniform. Diverse effects attributed to vasodilators have been shown on the degree of myocardial ischemia detected during acute and chronic experiments,45, 46 indicating that coronary vasodilators are pharmacologically a heterogeneous group of drugs. Vasodilators that act on proximal conductance vessels have been considered beneficial,47, 48 while those that act on peripheral resistance vessels may be detrimental46 because they may produce a redistribution of flow similar to that observed in the coronary steal phenomenon. An example of the former type of vasodilator is nitroglycerin, which has been shown to redistribute coronary blood flow toward the ischemia area of myocardium after coronary occlusion.49 If dipyridamole reduced resistance in normal vessels, whereas resistance in diseased vessels changed very little because of a previously maximal vasodilation, then a steal phenomenon could occur in which blood flow would be deflected from ischemic to nonischemic zones of the myocardium. Watanabe et al.38 presented evidence supporting such a mechanism in the presence of experimental coronary occlusion, showing that epicardial ST-segment injury increased after dipyridamole administration despite an increase in total coronary blood flow. On the other hand, Becker40 found that coronary steal occurred with dipyridamole infusion only when the coronary arteries that supplied collateral vessels to an area of infarction were significantly stenosed. In fact, Becker40 showed that dipyridamole improved collateral flow and lessened the extent of myocardial injury in the presence of single coronary artery ligation in the canine, when other coronary arteries were normal. Using a technique of 133Xenon clearance, Rees and Redding51 found that dipyridamole also increased coronary blood flow to ischemic myocardium by increasing anastomotic blood flow.

The net effect of vasodilators on regional perfusion during myocardial ischemia is therefore due to a complex interaction between their effects on normal, stenotic and collateral coronary vessels. In addition, peripheral vascular effects, such as reduction in systemic arterial and pulmonary vascular resistance, may alter afterload and preload, which in turn may affect the ischemic zone associated with a myocardial infarct. Although the vasodilator hypothesis is still subject to further investigation, our data and the preponderance of other studies involving regional flow measurements and simultaneous assessment of ventricular function and metabolism after experimental coronary occlusion favor improved regional perfusion to ischemic myocardium after vasodilator therapy, especially in the presence of coronary collateral vessels.4, 59, 62

Although the present study supports the effectiveness of dipyridamole in reducing the extent of acute myocardial ischemia, it does not reveal the relative contribution of several possible mechanisms of action to explain the reduction in infarct size attributed to dipyridamole. The hemodynamic effects of dipyridamole may be only a part of its beneficial action in reducing myocardial ischemic injury. Anti-coagulation has been proposed as a means of reducing or preventing extension of myocardial damage in myocardial infarction.50 Historically, definitive evidence of the clinical efficacy of anticoagulants has been questioned, but when large doses were tested in dogs subjected to coronary occlusion, heparin significantly modified the pathophysiologic and electrocardiographic pattern of myocardial injury.54 Dipyridamole, by reducing platelet adhesiveness, which has been observed in the canine51-53 and in man,55 might improve the relatively slow blood flow in collateral vessels surrounding an area of acute infarction and might also prevent propagation of thrombus after a proximal obstruction in a major epicardial coronary artery. Both of these effects could tend to limit the ultimate size of a myocardial infarct. Moschos et al.56 have shown that dipyridamole significantly reduces the extent of microcirculatory thrombosis in canine occlusion as determined by 51Cr-labeled platelet distribution and histologic examination. Whether the above microcirculatory changes attributed to dipyridamole actually contribute to the reduction in infarct size in this study is speculative.

In summary, dipyridamole has the potential to substantially decrease infarct size in experimental acute coronary occlusion. Using epicardial ST-segment mapping as the means of assuring comparable ischemic injury in control and treatment groups, several independent techniques, including left ventriculography, myocardial infarct imaging with 99mTc-glucoshoptonate, and myocardial histochemical staining with NBT confirm the effectiveness of dipyridamole in reducing infarct size. Further studies are necessary to delineate the exact mechanisms involved in dipyridamole-induced myocardial salvage after experimental acute coronary occlusion.

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References

44. Wendt VE, Sundermeyer SE, Denbakker PB, Bing RJ: Relationship between coronary blood flow, myocardial oxygen consumption and cardiac work as influenced by persantin. Am J Cardiol 9: 449, 1962
46. Winbury MM, Howe BB, Hefner MA: Effects of nitrates and other coronary dilators on large and small coronary vessels: an
Prognostic Value of a Single Exercise Test 3 Weeks after Uncomplicated Myocardial Infarction

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SUMMARY The prognostic value of exercise testing was assessed in 195 men, mean age 54 ± 8 years, 3 weeks after uncomplicated myocardial infarction. In the first 82 men, effort was terminated at a heart rate of 130 beats/min in the absence of limiting symptoms, exertional hypotension or ventricular tachycardia. In the last 113 men, heart rate was not used as an end point. No complications of exercise testing were noted. From 13 clinical and treadmill test characteristics, a stepwise multiple logistic regression program identified exercise-induced ST-segment depression (STi) ≥ 0.2 mV, angina pectoris and maximal work load < 4 multiples of resting energy expenditure (mets) as “risk factors” predictive of combined medical and surgical events (myocardial infarction, sudden death, cardiac arrest and coronary artery bypass surgery) in a subset of 92 patients followed 2 years or more. Clinical characteristics and exercise-induced ventricular ectopic activity were not predictive of such events. Life-table analysis in the entire population of 195 men confirmed the increased probability of combined medical and surgical events in patients with one or more “risk factors.” For medical events alone, STi ≥ 0.2 mV and maximal work load < 4 mets were predictive, whereas angina pectoris was not. STi ≥ 0.2 mV and exercise-induced angina pectoris were predictive of surgical events. We conclude that patients without evidence of congestive heart failure 3 weeks after uncomplicated myocardial infarction can safely undergo symptom-limited exercise testing. Valuable prognostic information is gained that is independent of selected clinical characteristics.

IDENTIFICATION of patients soon after myocardial infarction who are at relatively high risk for subsequent cardiac events offers two major benefits. High-risk patients could be identified for more aggressive medical or surgical therapy to reduce their morbidity and mortality. Patients at low risk could be spared needless invasive studies and unwarranted restriction of their physical activities.

Routine clinical methods are sufficient to identify certain subgroups of patients at increased risk for subsequent cardiac events after acute myocardial infarction. A history of congestive heart failure or shock in the coronary care unit, cardiomegaly on chest x-ray, audible third heart sound (S3) and a history of digitalis usage are all features of left ventricular dysfunction that have been associated with increased mortality during the year after myocardial infarction.14 In contrast, these abnormalities are absent in the majority of patients who survive myocardial infarction. Hypothetically, the risk of subsequent cardiac events in these clinically uncomplicated patients may be further stratified by treadmill exercise testing performed soon after the acute event.

The present study was designed to determine whether treadmill exercise testing, performed soon after uncomplicated infarction, further defines the risk of subsequent cardiac events and, if so, which specific exercise test characteristics are most predictive of such events in this population.
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