Reduction in infarct size and enhanced recovery of systolic function after coronary thrombolysis with tissue-type plasminogen activator combined with β-adrenergic blockade with metoprolol

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ABSTRACT The effect of β-adrenergic blockade on the salvage and functional recovery of reperfused myocardium was investigated in anesthetized dogs. Immediately after thrombotic occlusion of the left anterior descending coronary artery, the cardioselective β-blocking agent metoprolol was given intravenously at a dose of 0.5 mg/kg infused over 10 min. One hour after the onset of occlusion, recanalization was initiated by intravenous infusion of recombinant human tissue-type plasminogen activator (rt-PA, 10 μg/kg/min for 30 min). Anatomic infarct size expressed as percent of the left ventricular mass (I/LV), global ejection fraction, and mean systolic shortening of the segmental radii (SS) of the infarcted area were measured either after 24 hr or 1 week in six groups of six dogs each: group I (rt-PA + metoprolol, evaluated at 24 hr), group II (rt-PA + metoprolol, evaluated at 1 week), group III (rt-PA alone, evaluated at 24 hr), group IV (rt-PA alone, evaluated at 1 week), group V (persistent occlusion, evaluated at 24 hr), and group VI (persistent occlusion, evaluated at 1 week). The smallest infarcts were found in reperfused dogs given metoprolol, but the differences from dogs receiving rt-PA alone were not statistically significant (I/LV, expressed as mean ± SEM: 5.5 ± 0.9% in group I, 6.7 ± 1.9% in group II, 15.4 ± 5.0% in group III, 11.4 ± 3.5% in group IV, 23.6 ± 2.5% in group V, and 26.9 ± 2.3% in group VI). At 24 hr a significant recovery of segmental systolic function of the infarcted area was observed only in reperfused dogs receiving metoprolol (SS: 7.29 ± 3.1% in group I, −0.27 ± 2.5% in group III, and −1.15 ± 1.5% in group V). This earlier recovery compensated for the further decrease in global ejection fraction observed after 24 hr in the other groups. After 1 week, no differences in global or segmental left ventricular systolic function were observed between dogs given rt-PA alone and those receiving rt-PA combined with metoprolol. We conclude that thrombolytic therapy combined with β-adrenergic blockade results in an earlier functional recovery of the infarcted area but without long-term increased improvement in global or regional left ventricular function at rest.


THE QUANTITY of myocardial tissue salvaged by coronary recanalization in laboratory animals is inversely related to the duration of the coronary occlusion, and maximal functional recovery is only obtained within 1 to 2 weeks after reperfusion.1-6 Experimental and clinical studies have shown that β-adrenergic blockade limits myocardial necrosis after coronary occlusion,7-19 and therefore might constitute a valuable adjunctive to reperfusion therapy.20,21 Early administration of timolol after coronary occlusion in dogs resulted in enhanced salvage by reperfusion, but without concomitant improvement in regional left ventricular function measured within 3 hr.20 Long-term ventricular function was not evaluated, however. Bush et al.21 demonstrated that reperfusion therapy combined with the calcium-entry blocker diltiazem and the β-blocker propranolol significantly reduced the extent of necrosis of reperfused myocardium and resulted in improved recovery of systolic function. However, neither diltiazem or propranolol alone enhanced long-term recovery.

In the present study we evaluated the effects of coronary thrombolysis with intravenous recombinant hu-
man tissue-type plasminogen activator (rt-PA),22, 23 given alone or in combination with β-adrenergic blockade, on the infarct size and on the time course and the extent of functional recovery of the reperfused myocardium in closed-chest dogs.

Methods

Instrumentation and administration of t-PA and metoprolol. Fifty-seven dogs weighing approximately 20 kg were anesthetized with 15 mg/kg sodium barbital, intubated, and placed on a Bird respirator. Catheters were inserted into the descending aorta, the left ventricle, and the pulmonary artery (Swan-Ganz thermodilution catheter) via the femoral arteries and veins.

Coronary thrombosis was induced by advancing a 3 to 5 mm long copper coil mounted on the tip of a guidewire via the carotid artery into the left anterior descending coronary artery distal to the first main diagonal branch, as previously described.24 Occlusive thrombosis occurred within 5 to 10 min and was confirmed angiographically in all dogs. In 17 dogs (groups I and II), metoprolol was then given intravenously at a rate of 1 mg/min for approximately 10 min, up to a total dose of 0.5 mg/kg. In 35 dogs (groups I, II, III, and IV), recanalization of the occluded coronary artery was attempted by administration of rt-PA (Genentech Inc., South San Francisco, CA). The material used in the initial phase of the study consisted of two-chain t-PA (lot G11021), whereas the second half of the study was carried out with single-chain rt-PA (lot G11035), but both materials were used with the same frequency in all experimental groups. After 1 hr of occlusion, rt-PA was infused intravenously at a rate of 10 μg/kg/min for 30 min. In five dogs in which this 30 min infusion did not induce coronary reperfusion, additional rt-PA was infused directly into the occluded coronary artery at the same rate for 30 min. In 22 dogs (groups V and VI) the copper coil in the coronary artery was left in place to produce persistent coronary occlusion. Blood samples were taken before and at the end of the 1 hr occlusion period for the determination of the plasma levels of fibrinogen, α2-antiplasmin, t-PA antigen,24 and metoprolol.25

In the reperfused dogs, the copper coils were removed at the end of the infusion of rt-PA. After angiographic control, all catheters were removed and the arteries and veins were carefully sutured. The animals were extubated and allowed to recover, and 50 mg of apriprindine (class IC antiarrhythmic drug with a plasma half-life of approximately 12 hr) and 2 g of piperacillin (extended-spectrum penicillin) were given intravenously. After 24 hr (groups I, III, and V) or 1 week (groups II, IV, and VI), the surviving dogs were reinstrumented as described above and reexamined as described below. All animals were then killed and their hearts were removed for the determination of infarct size. The experiments were continued until six dogs in each group had completed the study protocol.

Measurements. Left ventricular hemodynamics were repeatedly measured throughout the experiment. The electrocardiogram, left ventricular peak systolic and end-diastolic pressure, and aortic pressure were recorded on a multichannel ink-jet recorder (Mingograph, Siemens). The cardiac output was calculated by the thermodilution technique and the mean values of three consecutive measurements are reported.

Infarct size was measured after staining with triphenyltetrazolium chloride (TTC), as previously described.26 The ostia of the left and right coronary arteries were cannulated along with the left anterior descending coronary artery distal to the site of the thrombus. The area of the left anterior descending coronary artery was perfused with TTC, while the ostia were perfused at the same pressure with a mixture of Ringer’s solution and Evans blue. Ten minutes later, each heart was perfused with 2% glutaraldehyde for 3 min. In this way, viable tissue in the area of the left anterior descending coronary artery stains red, infarcted tissue is white, and the area of the circumflex and right coronary arteries is blue. The hearts were cut in 1 cm thick slices perpendicular to the apex-base axis, and the differently colored areas were measured by planimetry. Both the perfusion area of the left anterior descending coronary artery (area at risk) and the infarct size were expressed as a percentage of the left ventricular mass.

Global ejection fraction and regional wall motion were measured on the left ventricular angiograms. One milliliter per kilogram of contrast medium (Renografin 76%) was injected during diastole at a rate of 16 ml/sec into the left ventricle via a pigtail catheter with use of a Medrad Power Injector pump triggered by the R wave of the electrocardiogram. The injection mode and the position of the image intensifier and the x-ray tube were unchanged during the serial angiographic evaluations in the same animal.

Global ejection fraction and percentage systolic shortening (SS) of the segmental radii in the infarcted area were measured using a computer program, as previously described.27 Briefly, left ventricular cavity borders were outlined manually at end-diastole and end-systole. Global ejection fraction was calculated from the traced silhouettes according to the area-length method. For the evaluation of regional wall motion, a radial coordinate system based on the centerpoint of the long axis of the left ventricular end-diastolic silhouette was constructed. End-systolic and end-diastolic contours were superimposed and the silhouettes were automatically divided into 60 segmental fractions with 6 degree angles with the use of the Siemens Digitron II system. SS of each radius was calculated by the formula SS = 100 × (D - S)/D, where D is the end-diastolic and S the end-systolic length of the radius. The left anterior descending coronary artery was assumed to supply the territory between radii 6 and 41; radii were numbered clockwise from the center of the aortic valve, and this area corresponded to the angle between 36 and 246 degrees. To eliminate small deviations from normal motion unrelated to ischemia, only radii on the postocclusion angiogram with a reduction in SS greater than 50% or greater than 2 normal standard deviations were taken into account for further comparisons.28 Both calculations gave very similar results and therefore only the data obtained with the 50% reduction method are reported here. The number of segmental radii with a 50% or greater reduction in SS on the postocclusion angiogram averaged 22 per animal, without significant differences among the six groups.

Statistical analysis. Numerical results are given as the mean ± SEM. One-way analysis of variance was used for the evaluation of the statistical significance of differences between groups. Intragroup comparisons were evaluated with a two-factor (time and treatment) analysis of covariance. Tukey’s multiple-comparisons method was applied to determine the significance of the differences between means.29

Results

Mortality. Of a total of 57 dogs, 21 died before the end of the 24 hr or 1 week study period (37% mortality). The number of deaths in the six groups were: three of nine in group I (rt-PA + metoprolol, 24 hr evaluation), two of eight in group II (rt-PA + metoprolol, 1 week evaluation), three of nine in group III (rt-PA alone, 24 hr evaluation), three of nine in group IV (rt-PA alone, 1 week evaluation), two of eight in group V
(persistent occlusion, 24 hr evaluation), and eight of 14 in group VI (persistent occlusion, 1 week evaluation).

Thrombolysis. Coronary thrombolysis was achieved in all 35 dogs to which rt-PA was administered, starting 1 hr after occlusion. In five of the 35 dogs an intracoronary dose of rt-PA was required, however. Three of these dogs completed the study (one each from group II, III, and IV), while two died during the study period. For the total group of 35 animals, the mean time interval between the start of the infusion and onset of recanalization was 27 ± 1.8 min. In the 24 dogs that received rt-PA and completed the study, these time intervals were: 24 ± 3 min (group I), 30 ± 6 min (group II), 28 ± 6 min (group III), and 34 ± 6 min (group IV). These differences were not statistically significant. The infusion of rt-PA was not associated with systemic activation of the fibrinolytic system or with clinically evident bleeding. In the 24 dogs that received rt-PA and completed the study, fibrinogen levels before and after infusion were nearly identical (1.16 ± 0.12 and 1.11 ± 0.09 g/liter). Corresponding α2-antiplasmin levels (expressed as a percentage of pooled plasma) dropped significantly from 100 ± 4.7% to 84 ± 5.8% (t = 3.8, p < .005). The plateau level of t-PA antigen in plasma during rt-PA infusion was 0.77 ± 0.05 µg/ml.

Infarct size. The mean perfusion area of the left anterior descending coronary artery (area at risk) expressed as a percentage of the left ventricular mass was not significantly different among the six groups (table 1).

Infarct sizes expressed as a percentage of the left ventricular mass are represented in table 1 and in figure 1. The infarct size in reperfused dogs (groups I to IV) was significantly smaller than in the dogs with persistent coronary artery occlusion (groups V and VI). The smallest infarcts were found in groups I and II (dogs receiving rt-PA and metoprolol), although the differences between groups III and IV and groups I and II were not statistically significant. No significant difference between infarct size in the 24 hr and 1 week groups was found with any of the three treatments.

### TABLE 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Area at risk, infarct size, and global and segmental left ventricular systolic function</th>
<th>Global EF (%)</th>
<th>SS (%)</th>
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<td>Number</td>
<td>Treatment</td>
<td>Evaluation</td>
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<tr>
<td>I</td>
<td>24 hr</td>
<td>rt-PA, metoprolol</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1 wk</td>
<td>rt-PA, metoprolol</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>24 hr</td>
<td>rt-PA</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1 wk</td>
<td>rt-PA</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>24 hr</td>
<td>Persistent occlusion</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>1 wk</td>
<td>Persistent occlusion</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P/LV = perfusion area of the left anterior descending coronary artery expressed as a percentage of the left ventricular mass (area at risk); I/LV = infarct size expressed as a percentage of the left ventricular mass; EF = ejection fraction; SS = systolic shortening of segmental radii of the infarcted area; F = F ratio (analysis of variance/covariance); Preoccl = before coronary artery occlusion; Postoccl = immediately after coronary artery occlusion.

*Significantly different from the corresponding 24 hr or 1 week group with persistent occlusion. +Significantly different from the same treatment group evaluated after 24 hr. The brackets join values significantly different in the same group at two different evaluations (postoccl vs 24 hr/1 wk). *p < .001.

CIRCULATION
FIGURE 1. Anatomic infarct size expressed as a percentage of the left ventricular mass (open bars) and percent systolic shortening of the segmental radii in the infarcted area (hatched bars) in the different groups. Both at 24 hr and at 1 week, the smallest infarcts were observed in the dogs that received combined therapy with thrombolytic (rt-PA) and β-adrenergic–blocking (metoprolol) agents. This combined therapy resulted in a recovery of systolic function (at 24 hr) that was not observed in the other groups. However, no differences in segmental systolic function in the rt-PA alone and rt-PA combined with metoprolol groups were found at 1 week.

(persistent occlusion, rt-PA alone, and rt-PA combined with metoprolol).

Left ventricular global and segmental systolic function. Global ejection fraction and SS of the infarcted area before and immediately after coronary occlusion and at follow-up (24 hr or 1 week) are given in table 1.

No significant differences in global ejection fraction in the six groups was found before or immediately after coronary artery occlusion. Twenty-four hours after occlusion, global ejection fraction remained unchanged in group I, while a further decrease was observed in the other two groups (III and V). This further decrease in global ejection fraction during the first 24 hr after occlusion was statistically significant in group V (from 37.8 ± 3.4% to 22.2 ± 2.7%, p = .004) and of borderline significance in group III (from 31.2 ± 4.2% to 21.5 ± 4.3%, p = .074). Although global ejection fractions were higher at 1 week in all three treatment groups when compared with the values obtained immediately after occlusion, the increase was only statistically significant in the two groups of reperfused dogs (from 43.8 ± 1.5% to 55.8 ± 3.0%, p = .029, in group II; from 43.8 ± 4.0% to 56.8 ± 5.3%, p = .019, in group IV; but only from 45.8 ± 2.4% to 50.3 ± 2.3%, p = .397, in group VI). Global ejection fractions at 1 week were nearly identical in the groups receiving rt-PA alone (group IV) and that receiving rt-PA combined with metoprolol (group II) (table 1). The global ejection fraction at 1 week in group VI was smaller than that in groups II and IV, but this difference did not reach statistical significance, possibly due to the limited sample size (table 1). A significant improvement in global ejection fraction was observed after 1 week in all three treatment groups when compared with the corresponding 24 hr values.

SS of the infarcted area before and immediately after coronary artery occlusion was not different among the six groups. After 24 hr, a significant improvement in regional left ventricular function was observed only in group I (from −1.13 ± 2.9 to 7.29 ± 3.1%, p =
.037). After 1 week a significant recovery of systolic function in the infarcted area was observed in all reperfused animals (from 10.0 ± 1.6 to 24.5 ± 3.1% in group II and from 6.03 ± 2.8 to 24.0 ± 7.0% in group IV, p < .001 for both groups), but not in the dogs with persistent occlusion (from 3.90 ± 1.1 to 10.14 ± 2.0%, p = .117). No significant differences in segmental systolic function in the rt-PA group and that receiving rt-PA and metoprolol were found after 1 week. Infarct size and segmental systolic function at 24 hr and 1 week are illustrated in figure 1.

Left ventricular hemodynamics. Heart rate, left ventricular systolic pressure, end-diastolic pressure, and cardiac output at 24 hr and 1 week are listed in table 2. In all groups, the cardiac output and left ventricular systolic pressure were significantly higher and the heart rate significantly lower at 1 week than at 24 hr (see pooled results, table 2). Left ventricular end-diastolic pressures did not show significant differences among the groups, although the highest values were observed at 1 week in the dogs with persistent occlusion.

Plasma concentration of metoprolol. The mean plasma concentration of metoprolol at the end of the occlusion period in the 12 dogs (groups I and II) that received the drug and completed the study protocol was 48.0 ± 3.2 ng/ml.

Discussion

β-Adrenergic blockade in association with coronary reperfusion might constitute an attractive therapeutic regimen to augment salvage of ischemic myocardium. Indeed, in two recent experimental studies in dogs, a significantly greater reduction in ultimate necrosis was demonstrated, although both studies failed to show significantly better long-term recovery of contractile function in the combined treatment group.20, 21

Study design. In the present study the short-term (24 hr) and long-term (1 week) effects of coronary artery reperfusion with rt-PA or reperfusion in combination with β-adrenergic blockade with metoprolol on infarct size and global and segmental systolic function were evaluated.

A limited number of animals (six in each of six groups) were studied, with replacement of animals that died before completion of the study protocol. Although this design could have introduced a bias in the results due to the selection of surviving animals, the main conclusions of our study cannot have been influenced by variability in mortality in the different study groups. Indeed, with the exception of group VI (persistent occlusion, 1 week follow-up), the mortality rates in the groups were almost identical. The higher mortality in group VI is not unexpected in view of the longer follow-up and the greater infarct size found in the six surviving dogs in this group, which was probably even more extensive in the animals that died before the end of the study.

Infarct size. As anticipated, infarct sizes were significantly smaller in reperfused dogs than in dogs with persistent coronary artery occlusion. Although the smallest infarcts were found in dogs given rt-PA and metoprolol, the differences from dogs given rt-PA alone did not reach statistical significance. This finding contrasts with the results of the above-mentioned studies,20, 21 in which the differences in infarct sizes in the groups receiving reperfusion alone and those receiving reperfusion combined with β-adrenergic blockade were statistically significant. The lack of a statistically significant difference in our study may be attributable to the smaller number of dogs per group and the shorter coronary artery occlusion times. Also, differences in timing of the administration of the β-blocking agent and the type and extent of β-adrenergic–blocking activity might have played a role. In the present study the cardioselective β-adrenergic–blocking agent metoprolol25 was given at a fixed dose (0.5 mg/kg) within 15 min after complete coronary artery occlusion. This therapy resulted in therapeutic plasma concentrations of metoprolol at the end of the occlusion period, when thrombolytic therapy was initiated.

<table>
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<tr>
<th>Group</th>
<th>HR (bpm)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CO (l/min)</th>
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</table>

Brackets indicate significant difference (p < .05) between pooled results at 24 hr (I + III + V) and at 1 week (II + IV + VI).

HR = heart rate; LVSP = peak left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output.
Global and segmental left ventricular systolic function. Global and regional left ventricular function were evaluated by angiography, which allows a high spatial resolution and a more complete evaluation of wall motion that can be obtained with two-dimensional echocardiography or segment length measurements with ultrasonic crystals, which were used in previous studies.20, 21

The present study demonstrated that at 24 hr, segmental systolic function was partially restored only in reperfused dogs receiving metoprolol. In dogs with persistent occlusion or receiving reperfusion alone, no recovery of contractile function or even a slight dyskinesia of the infarcted area was observed. In the latter two groups, global ejection fraction at 24 hr had further decreased in comparison with the values obtained immediately after coronary artery occlusion. In the group receiving reperfusion combined with β-adrenergic blockade, global ejection fraction did not change during the first 24 hr. These data taken together suggest that, in the group with persistent occlusion or that receiving reperfusion alone, a decline in contractile function in nonischemic regions might have occurred during the first 24 hr. This indicates that in the group receiving rt-PA and metoprolol the decline in systolic function in the noninfarcted areas was less pronounced and/or neutralized by an earlier recovery of systolic function of the infarcted area, resulting in an unchanged global ejection fraction after 24 hr. A tendency toward a decrease in contractility in regions remote from the site of occlusion has indeed been demonstrated previously.30-32

At 1 week, a significant recovery of systolic function of the infarcted area occurred in all reperfused dogs. In dogs with persistent occlusion some improvement in global and regional function was also observed, although the differences were much smaller and were statistically nonsignificant. In all three treatment groups an improvement in left ventricular hemodynamics occurred after 1 week. Global ejection fraction and SS of the infarcted area at 1 week were nearly identical in the groups receiving reperfusion alone and reperfusion combined with β-adrenergic blockade. These data are in agreement with those of Bush et al., 21 who also failed to detect enhanced long-term recovery of segmental function after propranolol in combination with reperfusion.

Clinical implications. In the present experimental study in dogs we have attempted to simulate the clinical situation in patients with acute myocardial infarction as closely as possible, focusing on the following aspects: (1) use of a closed-chest model with thrombotic acute coronary artery occlusion, (2) injection of the β-blocking agent after coronary artery occlusion was established, and (3) use of intravenous infusion of rt-PA as thrombolytic therapy. Still, significant differences between our animal preparation and patients with atherosclerotic disease persist, including: (1) the absence of atherosclerotic disease in our animals (2) differences in architecture of the copper coil–induced clot and that of a constitutional thrombus in an atherosclerotic artery, and (3) differences in collateral blood flow in the myocardial tissue in dogs and man.

Nevertheless, previous studies have shown that the copper coil–induced thrombosis of the coronary artery is a very useful model for the investigation of the thrombolytic potency of rt-PA and also of the importance of early reperfusion on the metabolic function of the myocardium.24 These findings in dogs have been confirmed in a preliminary manner in patients33 and are presently being further explored in multicenter trials. Thus, although our present findings in dogs may not necessarily be extrapolated as such to patients, they do constitute a significant basis for further experimental investigation in man.

Our data indicate that an earlier recovery of systolic function of the infarcted area occurs after combined therapy with thrombolytic and β-adrenergic–blocking agents. Earlier recovery of systolic function, although moderate, might be very significant in patients with critically impaired left ventricular function. Indeed, the 15% decrease in cardiovascular mortality within 1 week observed after intravenous administration of the cardioselective β-adrenergic blocker atenolol to patients with suspected acute myocardial infarction (ISIS trial) was entirely attributable to a decreased mortality during the first 24 hr.34

The absence of long-term differences in global and segmental systolic function in animals subjected to reperfusion alone and those receiving reperfusion combined with β-adrenergic blockade suggests that possible enhancement of salvage of reperfused myocardium by early β-adrenergic blockade may remain undetected with a single assessment of left ventricular function at rest. Therefore, to demonstrate increased myocardial salvage and functional long-term benefit from a combined thrombolytic and cardioprotective therapy in patients with recent myocardial infarction, evaluation of global and regional left ventricular function during stress (e.g., inotropic stimulation, exercise, or pacing) might be required.

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