Improvement of regional myocardial metabolism after coronary thrombolysis induced with tissue-type plasminogen activator or streptokinase*


ABSTRACT To assess the effects on the heart itself of coronary thrombolysis induced with either tissue-type plasminogen activator (t-PA) or streptokinase (SK), we performed positron emission tomography with $^{11}$C-palmitate in 19 patients with initial transmural myocardial infarction immediately after admission and again within 48 to 72 hr after intracoronary administration of t-PA ($n = 2$) or SK ($n = 17$). Clots were persistent in eight patients treated with SK despite an average dose of 336,000 IU, sufficient to markedly deplete fibrinogen. In the absence of lysis, favorable tomographic changes did not occur. In contrast, in each of the 11 patients in whom lysis was induced (two with t-PA and nine with SK) myocardial accumulation of $^{11}$C-palmitate improved by an average of 29% in late compared with early studies ($p < .001$). Results were comparable in patients with anterior and those with inferior infarction. Thus clot lysis induced with either t-PA or SK led to improved regional myocardial metabolism.


THROMBOTIC CORONARY OCCLUSION is common early after the onset of transmural infarction. Restoration of coronary arterial patency with thrombolytic agents has been demonstrated convincingly.1-6 However, the extent to which the heart itself benefits is not yet clear.7 Improved global function,8 improved regional left ventricular function,9 and restoration of thallium-201 uptake10 are not necessarily seen consistently. Furthermore, these end points as well as altered symptoms, electrocardiograms, or myocardial enzyme release may be difficult to interpret in the setting of reperfusion.11 Accordingly, we studied patients by positron emission tomography with $^{11}$C-palmitate before and after administration of thrombolytic agents (generally 48 to 72 hr later) to clarify the extent to which thrombolysis benefits the heart itself.

Positron emission tomography delineates the regional distribution of short-lived, cyclotron-produced tracers of physiologic, metabolic substrates of the heart. We have previously shown that tomographically detectable accumulation of $^{11}$C-palmitate is homogeneous in normal myocardium and diminished in reversibly or irreversibly injured zones compromised by ischemia. In dogs subjected to coronary thrombolysis at selected intervals after experimental induction of coronary thrombosis, positron emission tomography can delineate restoration of myocardial uptake of $^{11}$C-palmitate after reperfusion in salvaged regions that remain viable.12-14 It also can define the temporal boundaries of the relatively brief interval of ischemia after which salvage of jeopardized myocardium can be accomplished.

Because the potential benefit of coronary thrombolysis depends in part on early implementation and because many patients in whom lysis is achieved may require surgery soon afterward to correct residual high-grade stenosis, certain properties of the activator to be used are particularly desirable.15 Ideally, it should be nonallergenic, clot-selective, and rapidly cleared or inactivated so that hemostasis can be restored promptly when invasive procedures are required. It should not induce a systemic fibrinogenolytic state (lytic state), which would predispose the patient to bleeding. Pro-
longed fibrinolysis with such an agent could be attained by prolonged infusion, inhibition of metabolism or clearance, or augmentation of endogenous release of activator.

Tissue-type plasminogen activator (t-PA) activates the fibrinolytic system by converting plasminogen to plasmin. Since it does not bind avidly to circulating plasminogen ($k_m = 65 \mu M$) but has a high affinity for fibrin ($k_s = 0.16 \mu M$), it does not convert plasminogen to plasmin in the circulation under physiologic conditions. However, it does convert plasminogen to plasmin at the fibrin surface of the clot, where the activator and plasminogen both bind. Any plasin that escapes into the circulation is inactivated rapidly by circulating $\alpha_2$-antiplasmin ($\tau/2 = 100$ msec). Recently, we demonstrated that purified human t-PA administered intravenously or via the intracoronary route to dogs with coronary thrombi elicited clot lysis promptly and without the marked depletion of circulating fibrinogen or plasminogen, accumulation of fibrin(ogen) degradation products, or consumption of circulating $\alpha_2$-antiplasmin that occurs with lysis induced by intravenous or intracoronary streptokinase (SK). We also showed that the material was capable of inducing coronary thrombolysis in patients. From a practical point of view, extensive clinical trials with t-PA will require widespread availability of biologically active material. Accordingly, we have recently evaluated the thrombolytic efficacy of human t-PA synthesized by recombinant DNA technology and found it to be effective after intravenous administration in dogs with experimental induced coronary thrombosis.

This study was performed to determine whether coronary thrombolysis with either t-PA or SK improves regional myocardial metabolism as delineated by positron emission tomography in patients with evolving myocardial infarction. A second objective was to determine whether lysis induced with the two activators differed with respect to concomitant induction of a systemic lytic state. In this initial study of the metabolic response of the heart to coronary thrombolysis, the intracoronary route was used for administration of both activators.

**Methods**

Each of the 19 patients studied was evaluated only after informed consent had been obtained in conformity with protocols approved by the Washington University Institutional Review Board. The following inclusion criteria applied: history of chest discomfort typical of myocardial ischemia persisting for at least 30 min, 1.5 mm ST segment deviation in at least two frontal plane or two precordial electrocardiographic leads, feasibility of initiating thrombolytic therapy within 18 hr after the onset of symptoms, and age under 70 years. Exclusion criteria included Q waves indicative of completed or remote infarction, major illness other than coronary disease, conventional contraindications to thrombolytic agents, or concomitant anticoagulation. Complete occlusion of an infarct-related vessel and myocardial infarction were documented in each case angiographically and by elevated plasma concentrations of MB creatine kinase.

The average interval between the onset of symptoms and administration of SK or t-PA was 7.3 hr. The range selected was broad because the temporal boundaries of possible effects of clot lysis on regional myocardial metabolism are not known.

Tomographic studies were performed after intravenous injection of 20 mCi of $^{11}C$-palmitate as previously described. Data needed for reconstructions of 14 parallel transverse sections of the heart, each approximately 1.6 cm thick, were acquired within an imaging interval of 20 min. Sagittal and coronal reconstructions from the same data were used to facilitate assessment of jeopardized zones in patients with evolving inferior infarction. The extent of the sum of reversible and irreversible myocardial injury was delineated with data obtained from the tomographic reconstructions of each transaxial, sagittal, and coronal section of the heart and with an interactive algorithm that takes into account both the distribution and magnitude of depression of accumulation of $^{11}C$-palmitate. In previous studies from our laboratory, results of repeat applications of the interactive algorithm by different observers correlated closely ($r = .93$), and repeat tomographic determinations from sequentially acquired sets of data from patients with infarction managed conventionally varied by an average of only 1% and within a range of less than 10%.

Right and left heart catheterization was performed percutaneously immediately after completion of the initial tomographic study. Cardiac output was measured by thermodilution. A stand-by bipolar pacing catheter was introduced into the right ventricle before left heart catheterization, which was performed with an angiographic pigtail catheter. Left ventriculograms were obtained in the right anterior oblique projection after left heart hemodynamics had been determined. Selective coronary arteriography was performed with conventional preshaped coronary catheters. The presumed "noninfarct" vessels were visualized first. After complete thrombotic occlusion had been documented, SK or t-PA was infused selectively in the doses indicated in table 1. Arteriography was repeated midway through the infusion and again after its completion. Seventeen patients were treated with SK; two were treated with t-PA (table 1). Ventriculography was repeated after thrombolysis, and repeat tomography was performed within 48 to 72 hr after the catheterization procedure.

Blood samples, treated with citrate to prevent coagulation, were obtained before, during, and after infusion of SK or t-PA, cooled to 0° to 4° C, and centrifuged immediately. One aliquot of the decanted plasma was mixed with 250 U/ml aprotinin to preclude proteolysis in vitro, frozen, and stored at −20° C before assay of fibrinogen and fibrinogen degradation products. Another aliquot was frozen with aprotinin for assays of overall activator activity by the fibrin plate method, plasminogen and $\alpha_2$-antiplasmin levels by an amidolytic method, and t-PA levels by radioimmunometric assay, all as previously described. t-PA from culture supernate of Bowes melanoma cells was isolated and purified as previously described and administered in conformity with our FDA-approved Investigational New Drug application. The doses selected (table 1) were extrapolated from our previous results with experimental animals. SK was purchased commercially (Hoechst and Roussel).

With the exception of administration of either t-PA or SK, treatment of all patients was conventional and included adminis-
TABLE 1

Results in 19 patients given activators of the fibrinolytic system

<table>
<thead>
<tr>
<th>Patients treated with SK</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Locus of MI</th>
<th>Locus of occlusion</th>
<th>Onset of symptoms to infusion (hr)</th>
<th>Dose (IU)</th>
<th>Onset of symptoms to peak CK (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With lysis (n = 9)</td>
<td>7 M, 2 F</td>
<td>56.9</td>
<td>AMI(n = 5)</td>
<td>LAD (n = 4)</td>
<td>5.4</td>
<td>355 × 10^3 ic</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>(42–75)</td>
<td></td>
<td>IMI (n = 4)</td>
<td>RCA (n = 4)</td>
<td>± 1.3 (SEM)</td>
<td>(range, 200–400 × 10^3)</td>
<td>± 2.8 (SEM)</td>
</tr>
<tr>
<td>Without lysis (n = 8)</td>
<td>6 M, 2 F</td>
<td>63.4</td>
<td>AMI (n = 4)</td>
<td>LAD (n = 3)</td>
<td>9.9</td>
<td>345 × 10^3 ic</td>
<td>22.6</td>
</tr>
<tr>
<td></td>
<td>(48–66)</td>
<td></td>
<td>IMI (n = 4)</td>
<td>RCA (n = 4)</td>
<td>± 2.8 (SEM)</td>
<td>(range, 200–400 × 10^3)</td>
<td>± 4.0 (SEM)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients treated with t-PA</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Locus of MI</th>
<th>Locus of occlusion</th>
<th>Onset of symptoms to infusion (hr)</th>
<th>Dose (IU)</th>
<th>Onset of symptoms to peak CK (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(both with lysis)</td>
<td>2 M</td>
<td>56</td>
<td>AMI (n = 2)</td>
<td>LAD (n = 2)</td>
<td>3.8 and 7.5</td>
<td>1.3 × 10^6 ic</td>
<td>12.9 and 16.3</td>
</tr>
<tr>
<td></td>
<td>(51–61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0 × 10^6 ic^</td>
<td></td>
</tr>
</tbody>
</table>

AMI, IMI = anterior or inferior transmural acute myocardial infarction; LAD = left anterior descending coronary artery; RCA = right coronary artery; Cx = circumflex coronary artery.

^After clot lysis had been demonstrated and the modest amount of t-PA available for this patient had been exhausted, SK was given at a dose selected to be equipotent for thrombolysis (250 × 10^3 IU ic) to permit comparison of effects of the two activators on the fibrinolytic system in the same subject.

fication of heparin after clot lysis. All patients in whom thrombolysis was achieved, i.e., both of the patients given t-PA and nine of the 17 patients treated with SK, were treated subsequently with heparin for 24 hr at a dose of approximately 1000 U/hr to maintain the partial thromboplastin time at approximately twofold the control level. No serious bleeding complications were encountered.

Changes after thrombolytic therapy were evaluated by paired t test. Since infarct size is log-normally rather than normally distributed, statistical comparisons of the tomographic estimates of the extent of myocardium compromised by ischemia before and after thrombolytic therapy were performed after logarithmic transformation of observed values as well as conventionally.

Results

Clot lysis. Clot lysis was successful in nine of the 17 patients treated with SK and in both patients given t-PA (table 1). In patients with lysis, MB creatine kinase time-activity curves peaked an average of 16.4 hr after the onset of symptoms in contrast to 22.6 hr in patients without lysis (p < .01). In the eight patients treated unsuccessfully with SK, depletion of circulating fibrinogen was marked (to values <50 mg/dl in each patient) and fibrinogen degradation products were as high (averaging 170 µg/ml) as those in patients treated with SK in whom lysis was indicated. Patients with and without lysis after administration of SK were indistinguishable with respect to the electrocardiographic locus of infarction, initial extent of ischemic injury estimated by positron emission tomography, and the dose of activator administered. Patients refractory to clot lysis tended to be those with a relatively long interval between the onset of symptoms and the onset of treatment.

Representative coronary angiograms (figure 1) from a patient in whom thrombolysis was induced with SK 5 hr after the onset of symptoms demonstrated restoration of patency of the initially occluded vessel. As is frequently the case, residual high-grade stenosis was evident.

Because this study involved initial experience with t-PA, it was not possible to standardize the dose of t-PA a priori. Both of the t-PA–treated patients exhibited clot lysis (in 30 and 51 min). In one patient SK was administered after clot lysis had been achieved with t-PA in an equipotent dose to permit comparison of the effects of the two activators on systemic fibrinolysis. Angiographic results from one are shown in figure 2. The angiographic findings after clot lysis were comparable to those seen generally when lysis was induced with SK.

All patients studied survived the episode of infarction. Nevertheless, residual, high-grade senosis after thrombolysis was evident generally (table 1). In three patients angina recurred within 4 days of thrombolysis. Each underwent coronary artery bypass surgery 4 to 6 days after lysis without complications. No major bleeding complications (defined as requiring blood transfusion) were encountered.

Fibrinogen depletion. As can be seen in table 2, SK led to fibrinogen depletion, a hallmark of fibrinogenolysis in the circulation and a systemic lytic state predisposing to bleeding. In contrast, t-PA did not elicit a systemic lytic state. Thus fibrinogen depletion did not occur after administration of t-PA alone (table 2). Fibrinogen degradation products did not increase,
α\(_2\)-antiplasmin was not consumed, and circulating plasminogen was not depleted (data not shown), confirming this impression. These clinical observations parallel those of previous studies with SK and t-PA in experimental animals, the general experience with SK given to patients,\(^{12,23}\) and initial experience with t-PA given to patients.\(^{16}\) Since bleeding at catheterization sites after treatment with SK may be due in part to effects of elevated fibrinogen degradation products interfering with the function of procoagulants, t-PA may be less likely to predispose patients to such episodes, although this remains to be proved.

**Ventricular function.** Effects of clot lysis on global and regional left ventricular performance were variable. Typically, improvement was modest or absent as shown by the end-systolic frames of the right anterior oblique left ventriculogram before and after thrombolysis (figure 3) from a patient in whom clot lysis was achieved with SK within 48 min after the onset of infusion and within 5 hr after the onset of symptoms.

**FIGURE 1.** Left coronary arteriogram (right anterior oblique [RAO] projection) before (left) and after thrombolysis (right) induced with SK. Before thrombolysis total proximal occlusion of the left anterior descending artery (LAD) is evident (arrow). After thrombolysis the distal LAD is well opacified. A high-grade residual stenosis (arrow) is evident at the site of the initial total occlusion.

**FIGURE 2.** Left coronary arteriogram (RAO) before (left) and after thrombolysis (right) induced with t-PA. Before thrombolysis total occlusion of the LAD just beyond the major septal perforating branch is evident (arrow). After thrombolysis the distal LAD is well opacified. Residual stenosis is evident at the site of the previous total occlusion.
TABLE 2
Indexes of systemic fibrinolysis

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Normal thrombin time (% patients)</th>
<th>Adequate fibrinogen (% patients)</th>
<th>FDPs positive with &gt;1:16 dilution (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK (with lysis)</td>
<td>100</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK (without lysis)</td>
<td>100</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-PA (n = 2)</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Maximal changes observed after infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK (with lysis)</td>
<td>9</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK (without lysis)</td>
<td>12</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-PA* (n = 2)</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

FDPs = fibrinogen degradation products.

*Ellis method; adequate values before infusion refer to ≥200 mg/dl.

*Measurements in the one patient who was given SK after t-PA were made before the infusion of SK.

Overall, left ventricular ejection fraction in patients in whom lysis was achieved did not change significantly (50.9 ± 3.6% before, 51.4 ± 4.1% after thrombolysis), although the trend was favorable.

**Positron emission tomography.** Clot lysis was accompanied in each case by improvement of regional myocardial metabolism. Such improvement may, of course, antecede improved regional wall motion, known to be delayed perhaps because of adenine nucleotide depletion during the interval of ischemia. Furthermore, its ultimate clinical significance cannot yet be ascertained definitely. Nevertheless, the favorable response is typical of that shown in experimental animals to correlate with enhanced myocardial viability and preserved ventricular performance. Tomographic reconstructions from a patient with evolving anterior infarction before and 48 hr after thrombolysis at the base, high ventricular level, midventricular level, and apex are shown in figure 4. After thrombolysis, improvement was evident and reflected by increased accumulation of 11C-palmitate in the jeopardized region. Improvement of regional accumulation of 11C-palmitate in the zone of supply of the initially occluded vessel was evident in every patient in whom lysis was achieved (figure 5) whether it was induced with SK or t-PA. The average improvement was restitution greater than 50% maximal ventricular counts in 29% of the jeopardized zone. Improvement was comparable in patients treated with each of the two activators. The percentage of improvement in patients with anterior infarction (27% average) was not significantly different from that in patients with inferior infarction (30%). Significant improvement in the extent of metabolic impairment caused by ischemia after thrombolysis was evident by comparison of nontransformed values and was confirmed by analysis based on logarithmic transformation of the observed data (p < .001, paired t test).

In contrast, among patients without lysis, late com-

**FIGURE 3.** End-systolic frames of the left ventriculogram (RAO) from the patient whose angiograms are depicted in figure 2 before (left) and after thrombolysis (right) induced with t-PA. End-diastolic configurations and dimensions were normal. Neither global nor regional contractile performance changed appreciably after thrombolysis.
pared with early tomographic reconstructions did not show favorable changes (figure 5). In these patients the tomographic estimate of ischemic injury averaged 51 ± 14 g-eq before and 53 ± 13 g-eq after attempted thrombolysis.

Discussion

It has been established in many studies that SK can elicit coronary thrombolysis.4, 5, 7-10 Our results indicate that when coronary thrombolysis is elicited with t-PA, lysis is clot selective and is not associated with the systemic lytic state (table 2) seen with either SK or urokinase.13, 15

Apparently beneficial effects of coronary thrombolysis include reduction of chest pain, resolution of ST segment elevation, and improved ventricular function.8, 11, 22 However, interpretation of these end points may be limited by several considerations. It is clear that lysis must be implemented early if it is to be maximally effective.12, 22 However, treatment of patients with suspected but not prospectively proven infarction may bias results in favor of or against the intervention when end points such as enzymatically estimated infarct size are used.11 The electrocardiogram may be misleading with respect to the ultimate extent of injury sustained after clot lysis because of accelerated changes. Improvement of global ventricular performance may reflect altered myocardial stiffness, changes in afterload, or changes in function of uncompromised regions as well as direct effects of reperfusion on myocardial viability.

The primary objective of this study was to determine whether or not coronary thrombolysis enhances accumulation of a tracer of metabolism in jeopardized myocardium. The positive results indicate that the intervention exerts salutary effects on the heart itself. Tomographic signs of improved metabolism are not attributable simply to restoration of flow. In dogs with prolonged ischemia, clot lysis sufficient to augment perfusion to near normal levels does not augment uptake of 11C-palmitate in non-viable myocardium in the zone of supply of the previously occluded vessel.13

Tomographically detectable improvement early after coronary thrombolysis may underestimate ultimate improvement. Restoration of ventricular function

FIGURE 4. Positron emission tomograms reflecting uptake of 11C-palmitate in four 1.5 cm thick transverse sections from the base, high ventricle, midventricle, and apex of the heart before (left) and after thrombolysis (right) induced with t-PA. Compromise of myocardial metabolism in the anterior left ventricular wall is visualized as a confluent, diminution of accumulation of 11C-palmitate before thrombolysis (arrow). The anterior left ventricular regions indicated by arrows in the tomograms after thrombolysis show increased accumulation of 11C-palmitate in jeopardized zones (arrows) in several sections.

FIGURE 5. A, Tomographic estimates of the magnitude of jeopardized myocardium before and after infusion of SK in patients in whom thrombolysis was not achieved. No significant change was evident. B, Tomographic estimates of the magnitude of jeopardized myocardium before and after successful thrombolysis induced with t-PA or SK. For the group as a whole, significant improvement (p < .001, paired t test) was evident. Furthermore, each patient exhibited a favorable change.
after complete or partial coronary occlusion followed by reperfusion is delayed,24,25 perhaps because of depletion of myocardial adenine nucleotide pools during the course of ischemia.26 Thus overall myocardial metabolism in jeopardized zones may continue to improve with time as does regional ventricular performance under some circumstances.

Coronary thrombolysis may abort or limit infarction, thereby providing the time needed for implementation of definitive procedures such as percutaneous transluminal angioplasty or coronary artery bypass grafting in patients with severe residual stenosis.27 Its ultimate value, of course, is likely to depend at least in part on the extent to which complications such as systemic bleeding can be avoided and the safety with which high doses of activator can be administered promptly.

These results indicate, in a preliminary fashion, that coronary thrombolysis elicited with t-PA can improve metabolism in jeopardized myocardium without inducing a systemic lytic state predisposing to bleeding, in contrast to the induction of a lytic state with SK or urokinase. Although rare, catastrophic cerebral, gastrointestinal, or retroperitoneal bleeding has been encountered with the latter two agents. Successful thrombolysis induced with t-PA is accompanied in patients, as it has been in experimental animals, by tomographic criteria of improved myocardial metabolism without depletion of circulating fibrinogen. Since the circulation time is so short with respect to the biological half-life of t-PA and since the binding affinity of t-PA for fibrin is so high, it is likely that intravenous doses required for clot lysis will be of the same order of magnitude as intracoronary doses. Because it is not prone to induce a systemic lytic state, t-PA probably can be administered more safely by any route than equipotent doses (defined by activity in the conventional fibrin plate assay) of SK or urokinase early after the onset of suspected infarction.

This study was not designed to define the long-term benefit or lack thereof of thrombolysis. Such assessments are likely to require large-scale, prospective clinical trials of randomized patients. Results of our study indicate, however, that coronary thrombolysis can exert salutary effects on the heart itself as well as on coronary arterial patency. They suggest also that thrombolysis with clot-selective activators can be accomplished without induction of a systemic lytic state and that it can therefore be coupled safely with early angioplasty or surgery to maintain myocardial viability and ventricular performance in patients with high-grade residual stenosis.

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