Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions

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ABSTRACT We tested the hypothesis that lesion rethrombosis after streptokinase reperfusion is related to luminal size of the residual stenosis. Two independent techniques of analyzing coronary angiograms, quantitative coronary angiography and computer-based videodensitometry, were used to estimate the size of the residual lumen immediately after discontinuation of streptokinase. These techniques were selected because they provide independent estimates of cross-sectional area of a lesion with high degrees of reproducibility and minimal observer variability. Twenty-four patients who had undergone successful reperfusion with streptokinase were studied. Seven patients had lesion rethrombosis documented either on a repeat angiogram, at autopsy, or, in one case, by the fact that the patient had an acute transmural infarction resulting in death. Vessel patency was documented by repeat coronary angiography 8 to 14 days after initial streptokinase reperfusion in the other 17 patients. As assessed by quantitative coronary angiography, seven of 13 patients (54%) with minimal luminal cross-sectional areas of less than 0.4 mm² had rethrombosis. None of the 11 patients with lumens greater than 0.4 mm² had rethrombosis. In the 17 patients with vessels that remained patent the size of the residual lesion at repeat catheterization was compared with its size immediately after reperfusion with streptokinase. Over the intervening 8 to 14 day interval, an average percentage increase in minimal cross-sectional area of 116 ± 34% was observed. In seven patients minimal luminal cross-sectional area more than doubled. Integrated optical density, an index of the severity of coronary stenosis derived from computer-based videodensitometry, was also useful in identifying a subgroup of patients at high risk for rethrombosis of lesion. Sixteen patients were identified as having integrated optical densities less than 2.5, and seven (44%) of these had rethrombosis of their lesions. Among the eight patients with integrated optical densities greater than 2.5, none had rethrombosis. These results show that rethrombosis of the vessel is in part related to the size of the residual lesion immediately after reperfusion with streptokinase. Vessels with residual stenotic cross-sectional areas less than 0.4 mm² are at high risk for rethrombosis whereas vessels with minimal cross-sectional areas of greater than 0.4 mm² are unlikely to develop rethrombosis. Furthermore, residual size of the lumen may change significantly during the 8 to 14 days after reperfusion. These changes may be due to remodeling of a ruptured atherosclerotic plaque, resolution of persistent coronary spasm, or lysis of persistent thrombi.


AFTER REPERFUSION WITH STREPTOKINASE residual high-grade stenoses are frequently present at the site of the previous obstruction. Decisions regarding the definitive care of these patients are based in part on the appearance of these lesions. In particular, treatment by emergency coronary artery bypass grafting or percutaneous transluminal angioplasty is often considered because these high-grade residual stenoses are thought to predispose the patient to rethrombosis and possible infarct extension.

In contrast to this line of reasoning, several anatomic studies have shown that a substantial percentage of lesions associated with vessel thrombosis and acute myocardial infarction are moderate in severity. The complexity of this issue is further compounded by the fact that there are at least three reasons why the appearance of lesions immediately after streptokinase reperfusion may not reflect the eventual geometry of the lesion several days or weeks later. These reasons in-
clude the following: (1) unlysed thrombi may be asso-
ciated with the stenosis, (2) there may be coronary
spasm at the site of the stenosis that is resistant to
traditional vasodiatory therapy, and (3) there may be
acute plaque rupture that may ‘‘remodel’’ over a peri-
od of days or weeks. Thus it is possible that, although
lesions appear severe immediately after reperfusion,
lesion geometry may change during the postreperfu-
sion period and thus decisions regarding ultimate care
of these patients should not in all cases be based solely
on the appearance of lesions immediately after reperfu-
sion with streptokinase.

This study was performed (1) to examine changes in
size of lesions that occur during the 8 to 14 days after
reperfusion with streptokinase, and (2) to determine if
certain characteristics of lesion geometry predict re-
 thrombosis. To accomplish this latter goal, two inde-
pendent methods of analysis were used: quantitative
coronary angiography and computer-based videoden-
sitometry.

Methods

Selection of patients. From Nov. 10, 1981 to April 3, 1983,
77 consecutive patients who were seen at the University of Iowa
Hospitals after the clinical onset of acute myocardial infarction
were entered into the study. Criteria for admission into the study
were as follows: (1) history of prolonged (greater than 20 min)
chest pain consistent with acute myocardial infarction; (2) onset
of chest pain within 9 hr preceding presentation to the cardiac
catheterization laboratory; (3) age less than 80 years, (4) no
prior history or evidence of infarction in the myocardial region
currently involved in the acute event; (5) electrocardiographic
findings suggesting acute transmural myocardial infarction, de-
dined as at least 1 mm ST segment elevation (80 msec after the 1
point) in two or more leads that reflect characteristics of the
infarcting wall (inferior: leads II, III, and aVF; anterior: I, aVL,
and V_{-}V_{a} ); (6) persistent ST segment elevation after admin-
istration of sublingual nitroglycerin (0.4 mg), (7) no recent (with-
in 14 days) history of a cerebrovascular event, major trauma, or
surgical procedure.

Informed written consent was obtained before the cather-
ization procedure from all patients and/or an immediate family
member if the patient’s condition precluded written consent.
The study protocol was approved by the Human Use Review
Committee at the University of Iowa. No patient was excluded
because of hemodynamic instability.

Of the 77 consecutive patients from which the study group
was derived, 12 had high-grade stenoses without total occlusion
and 31 had total occlusions that failed to reperfuse. The remain-
ing 34 patients had total occlusions that reperfused after admin-
istration of streptokinase. Of these, 24 patients had coronary
angiograms that were adequate for analysis by quantitative
coronary angiography. These 24 patients served as the study
group.

Administration of streptokinase. Cardiac catheterization
was performed by the percutaneous femoral Seldinger approach
with indwelling arterial and venous sleeves. Immediately after
vascular access, 5000 units of intravenous heparin was admin-
istered. Arterial pressure was monitored throughout the proce-
dure. Selective coronary arteriographic examination of the ves-
sels supplying the noninfarcted myocardial wall was performed
initially and subsequently selective coronary arteriographic ex-
amination of the vessel supplying the infarcted wall was per-
formed. If total coronary occlusion was identified in the vessel
supplying the infarcting region, 10 mg of sublingual nifedipine
and 300 to 400 μg of intracoronary nitroglycerin were adminis-
tered and another coronary arteriogram was recorded 1 to 2 min
later to exclude the possibility of coronary artery spasm. If
coronary occlusion persisted, an initial intracoronary bolus of
10,000 to 20,000 U of streptokinase was given, followed by a
continuous infusion of 2000 U/min. Patients were given repeat
boluses of 10,000 to 20,000 U of streptokinase every 15 min if
reperfusion did not occur.

Streptokinase was infused for a minimum of 45 min in all
patients and was continued for at least 30 min after initial reper-
fusion. Among the patients with successful reperfusion the aver-
gage time of streptokinase infusion was 62.2 ± 3.6 min
(range 45 to 135 min) and the total dose of streptokinase aver-
egaged 177,000 ± 13,000 U. After stopping streptokinase infu-
sion paired orthogonal views of the residual stenosis were ob-
tained that were subsequently analyzed by quantitative coronary
angiography.

Postreperfusion therapy. After catheterization all patients
were admitted to the coronary care unit for invasive hemody-
namic monitoring for a minimum of 18 hr. The arterial and
venous sleeves placed at the time of this initial catheterization
procedure were not removed until approximately 18 hr later.
Continuous intravenous heparin therapy was instituted at the
time of the cardiac catheterization procedure and was continued
throughout the remainder of the period of hospitalization, the
goal being to maintain a partial thromboplastin time greater than
60 sec. Heparin was discontinued when the arterial and venous
sleeves were removed the day after administration of streptoki-
rase. The total time that heparin therapy was interrupted did not
exceed 1 hr. We attempted to treat all patients with either topi-
cal, oral, or intravenous nitrates and 10 to 20 mg of nifedipine
by mouth every 8 hr. However, five patients were intolerant of
long-acting nitrates and two patients were intolerant of nifedi-
pine. These patients had either severe headache secondary to
these drugs or developed significant hypotension when given
nitroglycerin or nifedipine.

Follow-up cardiac catheterization. All patients who sur-
ived underwent repeat coronary angiography 8 to 14 days
(mean, 10.2 ± 0.7 days) after initial streptokinase reperfusion.
Each patient was pretreated with sublingual nitroglycerin (0.4
mg) and subcutaneous atropine (0.4 mg) before repeat coronary
angiography. As nearly as possible, the repeat coronary angi-
ogram included paired views from projections similar to those
obtained from the initial catheterization.

Quantitative coronary angiography. This technique has
been described previously. Briefly, the lesion was analyzed
from two orthogonal views. Each of these views was projected
on a large screen marked with rectilinear coordinates and was
carefully traced with as much of the adjacent vessel as could
be seen in either view. The portion of the catheter near its tip was
also traced. The position of the catheter and the vessel in each
view was noted on the rectilinear grid and subsequently entered
into a computer. The tracing of the lesion and the catheter tip
were then digitized on a digitizing tablet that interfaced with the
computer.

The x-ray magnification and pin cushion distortion charac-
teristics of the x-ray equipment used in these studies were prede-
termined and stored in the computer. With this information each
of the digitized views was corrected for x-ray magnification and
distortion. The centerline of the vessel and the lesion in each
view were matched by the computer. Thus, a three-dimensional
reconstruction of the vessel and the lesion was created. The
computer then calculated the cross-sectional area of the apparently normal portion of the vessel, the minimal cross-sectional area of the residual lumen, minimal luminal diameter in both the right anterior oblique (RAO) and left anterior oblique (LAO) views, percent diameter stenosis in both views, and percent area stenosis obtained from the paired views. For each lesion three paired frames were analyzed and the average values for percent area stenosis and minimal luminal cross-sectional area were determined. The data presented represent this average for each lesion. In addition, the view in which the lumen appeared to be most narrowed (either the RAO or the LAO) was selected and the average minimal luminal diameter was determined from these three frames.

**Computer-assisted videodensitometry.** This technique has been described previously. A specially constructed film-to-video conversion device was used to digitize individual cine frames. This device consisted of a conventional cine film transport device coupled through selectable optical lenses to a high-quality vidicon camera (Cohu model 8000). Optical magnifications of 1, 3, 7, or 7.0 could be selected. For use at the highest magnifications, the position of the transport stage could be adjusted to allow the operator to select the portion of the frame to be digitized. Cine frames were digitized with a De Anza 8500 image-array processor attached to our PDP 11/34 minicomputer. In designing this film digitizing system we took special care to ensure that the illumination and camera sensitivity were uniform across the field of view.

Before digitizing cine frames, the sensitivity of the vidicon camera was adjusted to prevent saturation in the brightest portions of the image. At this camera setting a calibration curve relating mean gray level (digitized value) and optical density was calculated with a Kodak gray-level step wedge with 21 levels and entered into the computer. All images were digitized at the same camera setting. One of the frames used for quantitative coronary angiography (in the angiographic view in which the vessel was most nearly parallel to the image intensifier) was identified and digitized. All images were digitized at a magnification of 3.7 into a 512 × 512 pixel matrix with an 8-bit (256 levels) gray-level resolution. The digitized data were displayed on a video monitor and an operator-interactive program was used to evaluate density profiles perpendicular to the axis of the vessel at the point of maximal apparent narrowing. The operator indicated the number of lines (rows of pixels) that would be used to calculate the density profile. A curve of gray level vs position along the profile was plotted along with the first derivative of this curve. Using the plotted profile as an aid, the operator identified on the image the left and right borders of the vessel as well as the borders of background regions on both sides of the vessel. The average background gray level on each side of the vessel was computed. The density profile within the vessel was then background corrected by linearly interpolating between the backgrounds on either side of the vessel. The gray-level profile was converted to an optical density profile with the previously determined calibration curve. The optical density for each pixel within the vessel was corrected for the optical density of the background and summed over all pixels within the vessel. We term this value integrated optical density. Assuming that the Lambert-Beer law adequately describes the image-formation process, the integrated optical density is an estimate of the cross-sectional area of the vessel lumen.

**Statistical methods.** Results are expressed as mean ± SEM. Paired t tests were used to compare changes in cross-sectional areas or percentages of stenosis between the initial and follow-up coronary angiograms. Unpaired t tests and chi-square analyses were used to compare the clinical and angiographic parameter values in patients with rethrombosis and those with lesions that remained patent.

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**THERAPY AND PREVENTION—THROMBOLYSIS**

**Results**

The clinical outcomes of the 24 patients in whom reperfusion was successful and with suitable films for analysis were as follows. Seventeen of the 24 had reperfused vessels that were patent at the time of recatheterization. In 16 of these 17, the clinical course was uneventful in the period between the two catheterizations. One of these 17 patients developed unstable angina and underwent repeat catheterization 4 days after reperfusion. Among the other seven, five had rethrombosis that was documented by coronary angiography. In four of these five, an episode of recurrent chest pain occurred at least 24 hr after reperfusion with streptokinase. In the four patients without chest pain, associated with ST segment elevation that suggested recurrent myocardial infarction. In only one of these five patients was rethrombosis documented at recatheterization as an asymptomatic event. Two patients died after an episode of chest pain and changes on the electrocardiograms of both suggested recurrent infarction and deteriorating hemodynamics. In one of these patients rethrombosis was documented at autopsy, but in the other an autopsy was not performed. The terminal events leading to the latter patient’s death, however, included recurrent chest pain, hypotension, ST segment changes that suggested acute myocardial infarction, and progressive hemodynamic deterioration. In this patient rethrombosis was suspected but not proved.

**Quantitative characteristics of lesions that rethrombosed after reperfusion with streptokinase**

**Clinical data.** The clinical data for patients with lesions that rethrombosed and lesions that remained patent are listed in table 1. There were no differences with respect to age or sex between these two groups. Hemodynamic characteristics immediately after streptoki-
nase reperfusion were similar between groups. Long-acting nitroglycerin was administered to both groups of patients, but five of the 17 patients with lesions that remained patent were intolerant of long-acting nitrates. All of the patients in whom the lesions rethrombosed were given long-acting nitrates. This difference between the groups approached but did not achieve statistical significance (p = .10). Similar numbers in each group could not tolerate nifedipine. Parameters of anticoagulation were similar between the groups.

Quantitative coronary angiography. Among the seven patients with rethrombosis, the residual minimal cross-sectional area after administration of streptokinase was 0.3 ± 0.03 mm², which is significantly less than the average minimal cross-sectional area of lesions that remained patent (0.9 ± 0.14 mm²; p < .05). The distribution of minimal cross-sectional areas in patients with rethrombosis vs in patients in whom lesions remained patent is shown in figure 1. Seven of 12 vessels with minimal cross-sectional areas less than 0.4 mm² had rethrombosis. In contrast, none of the 12 patients with lesions with minimal cross-sectional areas greater than 0.4 mm² had rethrombosis (p < .005).

Percent area stenosis was also useful in identifying a subgroup of patients at high risk for rethrombosis (figure 2). All vessels that rethrombosed had area stenoses of greater than 90%. Seven of the 17 vessels (41%) that remained patent had percent area stenoses in excess of 90%. Thus, seven of 14 patients with residual lesions causing more than 90% area stenosis had rethrombosis while none of the 10 with lesions causing less than 90% area stenosis had lesion rethrombosis (p < .01).

The residual diameter of the lumen averaged 0.8 ± 0.07 mm in patients in whom lesions remained patent and 0.4 ± 0.04 mm in those in whom they rethrombosed (p < .01). Of the 14 patients with lesions with residual luminal diameters of less than 0.6 mm, seven had rethrombosis. In contrast, all vessels remained patent in the 10 patients with residual minimal luminal diameters greater than 0.6 mm (p < .05).

Video densitometry. The distribution of integrated optical densities for lesions that rethrombosed vs lesions that remained patent is shown in figure 3. Among the 16 patients with lesions with integrated optical densities less than 2.5, seven had rethrombosis. All of the eight lesions with integrated optical densities greater than 2.5 remained patent (p < .05). The relationship between the integrated optical density and the minimal cross-sectional area, as determined by quantitative coronary angiography, is shown in figure 4. The subgroups identified by each technique as being at high risk for rethrombosis were similar. Thus, 12 of 16 patients (75%) with vessels with optical densities less than 2.5 had minimal cross-sectional areas less than 0.4 mm² as determined by quantitative coronary angiography.

Comparison of initial and repeat coronary angiograms. All surviving patients underwent repeat coronary angiography between 8 and 14 days after initial catheterization. The residual minimal luminal cross-sectional areas of stenosis determined after streptokinase are compared with those observed at recatheterization in figure 5, A. For the entire group, the average increase

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**FIGURE 1.** The distribution of minimal cross-sectional areas in patients with lesions that rethrombosed vs in those with lesions that remained patent. Seven of 12 patients with minimal cross-sectional areas less than 0.4 mm² had rethrombosis. In contrast, none of 12 patients with minimal cross-sectional areas greater than 0.4 mm² had rethrombosis. This difference was significant by chi-square analysis (p < .005).

**FIGURE 2.** Percent area stenosis as calculated by quantitative coronary angiography for patients with rethrombosis and for those with lesions that remained patent. Seven of 14 patients with residual lesions of stenosis of greater than 90% area had rethrombosis while none of the 10 with stenosis of less than 90% area had rethrombosis (p < .01).
in minimal cross-sectional area was 116 ± 34%, which was highly significant (p < .01) when compared with zero (no change). In seven patients minimal luminal cross-sectional area more than doubled and similar changes in percent area stenosis were observed (figure 5, B). The average absolute change in minimal cross-sectional area was 0.5 ± 0.2 mm². The ability to measure this difference is well within the accuracy of quantitative coronary angiography.⁶, ⁶⁰

Figure 6 provides a striking example of change in size of lesion in one patient during the interval between the initial and follow-up coronary angiograms. This patient presented with an anterior myocardial infarction and underwent coronary angiography within 5 hr of the onset of chest pain. Angiography revealed a totally occluded left anterior descending coronary artery and a total of 140,000 U of intracoronary streptokinase was administered. After discontinuation of streptokinase the residual lumen had a minimal cross-sectional area of 0.9 mm² and a percent area of stenosis of 83%. Upon repeat angiography the cross-sectional area had increased to 2.9 mm² and the percentage area of stenosis had decreased to 58%. This represents a threefold increase in minimal luminal cross-sectional area.

Discussion

The principal findings of this study are twofold. (1) A major determinant of vessel rethrombosis after reperfusion with streptokinase is the cross-sectional area of the residual stenosis of the lumen. This was confirmed by results obtained with two independent methods of analyzing coronary angiograms. When measured by computerized quantitative coronary angiography, this critical residual lesion size is less than 0.4 mm. (2) The appearance of a lesion immediately after reperfusion with streptokinase may not reflect the eventual size of the underlying fixed lesion. In particular, there can be substantial increases in minimal cross-sectional area of the lumen and decreases in percent stenosis during the 8 to 14 days after reperfusion.

Reasons for the relationship between minimal cross-sectional area and rethrombosis. In the coronary bed,⁹ as in

FIGURE 3. Integrated optical densities derived from computer-assisted videodensitometry for lesions that rethrombosed versus lesions that remained patent. All of eight lesions with integrated optical densities greater than 2.5 remained patent; seven of 16 lesions with integrated optical densities less than 2.5 (44%) rethrombosed (p < .05).

FIGURE 4. The relationship between integrated optical density derived from computer-assisted videodensitometry and minimal cross-sectional area determined by quantitative coronary angiography. The dotted lines indicate the retrospectively identified values that seemed to distinguish lesions that remained patent from lesions that rethrombosed for each of these parameters. Each of these techniques identified a similar subgroup of patients at high risk for lesion rethrombosis. The correlation between these two measurements of the residual luminal size was significant (p < .01).

FIGURE 5. A, Minimal cross-sectional area of a lesion determined by quantitative coronary angiography immediately after reperfusion compared with cross-sectional area found at recatheterization. The average percent increase in minimal cross-sectional area was 116 ± 34%. B, Percent area stenosis immediately after reperfusion compared with that found at recatheterization.
other circulations, the pressure loss across a stenotic region increases in an exponential fashion as the severity of the stenosis increases. These pressure losses result in a diminished driving pressure for flow distal to the stenosis and, if severe enough, may result in stagnation and eventual rethrombosis regardless of the adequacy of anticoagulation. Recent work by Schwartz et al., Santemore and Walinsky, and Kirkeide et al. suggests that high-grade stenoses may collapse when the arteriolar bed distal to the stenosis vasodilates. This phenomenon may contribute to stagnation of flow and may be associated with vessel rethrombosis.

Work by Folts et al. has shown that cyclic reductions in coronary flow, presumably due to platelet thrombi, may occur when experimental stenoses are induced in dogs. Among several important conditions that need to be present for this phenomenon to occur, the stenosis must be severe. It is conceivable that the markedly reduced minimal luminal cross-sectional areas in rethrombosed vessels predisposed them to more platelet aggregation than in the vessels with larger residual lumina. Importantly, the mass of platelets and thrombin necessary to precipitate rethrombosis would be significantly less in vessels with smaller residual minimal luminal cross-sectional areas.

**Reasons for the late change in minimal cross-sectional area of the lesion after reperfusion with streptokinase.** At least three mechanisms may play roles in late changes in size of stenosis after reperfusion with streptokinase. All of these relate to phenomena that prevent the vessel from opening to its fullest extent after streptokinase.

The first of these is acute plaque rupture, which undergoes remodeling during the ensuing 8 to 14 days. Several postmortem studies have shown that acute plaque rupture is a common predisposing event associated with acute coronary occlusion. The ruptured plaque serves as a nidus for platelet and thrombin adhesion. After streptokinase the ruptured plaque persists and may require several days for reendothelialization and resorption of associated hemorrhage.

Second, vasospasm superimposed upon the residual stenosis may be present despite therapy with intracoronary nitroglycerin and sublingual nifedipine. In contrast to traditional dogma regarding fixed stenoses, Brown et al. have shown that some coronary stenoses are responsive to vasoactive stimuli. This seems to be particularly true of eccentric lesions in which some portion of the circumference of the stenotic segment is not diseased.

An important factor that may predispose to persistent spasm after streptokinase reperfusion is related to endothelial damage that may result from underlying plaque rupture or be a consequence of vascular ischemia. In this regard, Ku has shown that the endothelium is particularly sensitive to ischemia. Loss of endo-

**FIGURE 6.** Example of the late change in lesion size that occurs after reperfusion with streptokinase. *Left,* RAO angiogram of a stenosis of the left anterior descending coronary artery immediately after infusion of streptokinase was discontinued. *Right,* The patient underwent recatheterization 12 days later and minimal cross-sectional area of the lesion increased from 0.88 mm² to 2.9 mm² during the interval.
Integrity produces dothelium and clin may of response vasodilating substance intense vasoconstriction may be removed kinase. basement membrane. Kinase responses to serotonin and platelets are enhanced in the absence of endothelium. Importantly, endothelial denudation may predispose to platelet adhesion to underlying collagen and basement membrane.

A third factor that may contribute to late changes in luminal size are unlysed thrombi that persist after administration of seemingly adequate doses of streptokinase. Endogenous thrombolyisins may continue to remove any persistent thrombi over the ensuing days after reperfusion with streptokinase. In this situation, larger initial doses of streptokinase might result in more complete opening of the stenosis and reduce the late change. This possibility is in part supported by separate analysis of a subgroup of eight patients treated late in this series who received a higher total dose of streptokinase (240,000 ± 16,700 vs 140,000 ± 9000 U for the earlier patients). In this high-dose subgroup, the minimal luminal cross-sectional area was 1.0 ± 0.3 mm² immediately after streptokinase compared with 0.6 ± 0.1 mm² in the remaining patients (p < .05). Among the vessels that remained patent, the average increase in minimal cross-sectional area during the 8 to 14 days after streptokinase was 40 ± 23% (range −16 to +124%) in this high-dose subgroup compared with 127 ± 47% in the remaining patients (p < .05). The incidence of rethrombosis was not different between these two subgroups, being three in eight (38%) in the high-dose subgroup and four in 16 (25%) in the remaining patients.

Possible influence of the dose of streptokinase used on results of the study. The dose (177,000 ± 13,000 U) and the schedule of administration of streptokinase in this study are similar to those used by several groups, but slightly lower than those used by others. As mentioned above, higher doses of streptokinase may have diminished the late change in lesion size. However, in four of the five patients who received higher doses of streptokinase, late changes in lesion size continued to be observed. In addition, patients with high-grade lesions (minimal cross-sectional areas < 0.4 mm²) continued to exhibit rethrombosis even when given doses of streptokinase in excess of 240,000 U.

The success rate for streptokinase therapy in this series is somewhat less than that reported by others. The reason for this is unclear, but we do not believe it is related to the dose of streptokinase administered. Patients in whom reperfusion failed received an average dose of 209,000 ± 11,000 U. All of these patients had prolonged bleeding times, diminished fibrinogen levels, and elevated fibrin degradation products after streptokinase. It is unlikely that our lower success rate affected the observations made in patients in whom reperfusion was initially successful.

Advantages of the experimental design. There are several important advantages to the approaches we used to analyze the geometry of stenotic lesion in these patients. First, in all patients who survived, vessel patency was documented by repeat coronary angiography. In only one of the two patients who died was rethrombosis not documented at autopsy. In this patient, the clinical events associated with death were very suggestive of acute transmural infarction, probably due to rethrombosis.

Second, the initial coronary angiograms were analyzed by two independent techniques. Quantitative coronary angiography provides an estimate of minimal cross-sectional area of lesions and percent area of stenosis. The small observer variability and accuracy of this technique makes it possible to discern subtle differences in size of the lumen that are not apparent on casual inspection of the coronary angiogram. It is unlikely that more traditional methods of analysis of these angiograms would have revealed these differences in size of the lesion.

Computer-assisted videodensitometry was also used to evaluate size of the lesion after reperfusion with streptokinase. The value derived with this technique, integrated optical density, should reflect the quantity of radiopaque material in the lumen after contrast injection and thus is a reflection of cross-sectional area of the lesion. The group of patients with severe reductions in integrated optical density corresponded well with that of patients with extreme reductions in minimal cross-sectional area. These subgroups also contained the patients who had rethrombosis. Thus, the findings obtained with the two different techniques both confirm the notion that severe reduction in minimal cross-sectional area is a predisposing factor to rethrombosis.

Potential criticisms and limitations. In this study we found that both percent stenosis and minimal cross-
sectional area were useful in identifying a subgroup of patients at high risk for rethrombosis. However, there are limitations inherent in each of these measurements when applied to human coronary atherosclerosis.

The use of minimal cross-sectional area to describe the severity of a stenosis is dependent on the cross-sectional area of that vessel segment without superimposed disease. All of the stenoses analyzed were in proximal major coronary vessels and the minimal cross-sectional areas associated with rethrombosis may have been different in more distal portions of the circulation. The major disadvantage of the use of percent stenosis for this purpose is that diffuse coronary narrowing is often present. Thus, a superimposed lesion that appears as a moderate degree of stenosis may produce a severe decrease in luminal area.

Both patients in the group with rethrombosis and those in the group with lesions that remained patent had occasional partial thromboplastin times of less than 50 sec. These episodes were not clearly temporally related to clinical evidence of rethrombosis. Whether or not lesion rethrombosis was related to inadequate anticoagulation is unknown. The adequacy of anticoagulation, however, as judged by the average partial thromboplastin time or the number of partial thromboplastin times under 50 sec, was not different between the two groups of patients (table 1).

Presently, neither quantitative coronary angiography nor computer-assisted videodensitometry is widely used to aid in interpretation of the coronary angiogram. This is in large part related to the expense and complexity of the necessary equipment and the additional time required. While these factors represent important limitations at present, there exists a substantial body of literature suggesting that the traditional analysis of coronary angiograms is inadequate, even for determining significance of coronary stenoses. Accurate measurements of the size of individual lesions are impossible without methods such as those used in this study. Based on the results of this study and similar work, it would appear that absolute measurements of size of stenotic lesions may contribute significantly to our understanding of coronary artery disease. Furthermore, if a method were available that would allow accurate measurement of size of stenosis to be easily obtained during cardiac catheterization, patient care would potentially be enhanced.

In summary, these studies demonstrate that after reperfusion with streptokinase the incidence of rethrombosis is dependent on the residual size of the lesion. Rethrombosis occurred in approximately one-half of the patients with residual luminal cross-section-
al areas less than 0.4 mm². Such patients may be candidates for either emergency transluminal angioplasty or coronary artery bypass grafting. In patients with residual cross-sectional areas greater than 0.4 mm², rethrombosis did not occur. Among patients with vessels that did not rethrombose, substantial increases in luminal size was observed during the 8 to 14 days after streptokinase. Based on this information, patients with luminal cross-sectional areas greater than 0.4 mm² can probably be treated medically and decisions regarding either coronary artery bypass grafting or percutaneous transluminal angioplasty should probably be based on the appearance of lesions at recatheterization 8 to 14 days after streptokinase infusion.

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