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Streptokinase thrombolysis in experimental coronary artery thrombosis: pattern of reflow and effect of a stenosis ¹

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We studied recanalization of an obstructed left circumflex coronary artery by streptokinase in open-chest anesthetized dogs. Thrombotic occlusion was induced by a 100 μ A anodal current selectively delivered to the intimal surface of the vessel. Intracoronary streptokinase (50,000 U) or saline was infused over a 50-min period beginning at either 30 min or 90 min after occlusion. Continuous recordings were made of antegrade circumflex flow and regional myocardial function, which was quantitated using sonomicrometer crystals in the regions of the left anterior descending and circumflex coronary arteries. In some experiments a fixed stenosis, having no effect on mean circumflex coronary artery blood flow, was placed at the site of subsequent thrombus formation. The presence of a stenosis decreased the weight of occlusive thrombi obtained from nonreperfused saline controls by 40% and increased the proportion of animals successfully reperfused by streptokinase from 13 to 76%. Streptokinase reduced thrombus mass by 44% in animals recanalized in the presence of the stenosis. On the average, reflow was established after 26 min of streptokinase infusion, was less in magnitude than pre-occlusion flow, and was unstable and intermittent, being marked by frequent reocclusions. Initiating treatment at 30 min or

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90 min post-occlusion did not influence characteristics of the reflow. Return of myocardial contractility in the ischemic bed was not detected during the immediate reperfusion period in the majority of these experiments.

(Key words: streptokinase; myocardial reperfusion; coronary stenosis)

Introduction

A number of recent clinical studies [1-3] have affirmed the effectiveness of streptokinase (STK) in reestablishing antegrade flow in acutely thrombosed coronary vessels. Nevertheless, several aspects of STK induced recanalization of both basic and applied scientific interest have proved difficult to approach experimentally in humans. The size of the thrombus removed during STK infusion is uncertain, as is the pattern and extent of antegrade flow return. Estimation of the duration and degree of occlusion, which are important factors to consider when assessing changes in myocardial function, are also inherently imprecise.

We have attempted to better delineate STK recanalization under carefully controlled conditions during acute thrombosis of canine coronary arteries *in vivo*. The model chosen employs a d.c. anodal current to selectively injure the intimal surface of the proximal left circumflex coronary artery (LCCA). The occlusive thrombi resulting from the intimal damage possess a morphology typical of arterial thrombi, a well-defined weight range and a susceptibility to inhibition by a variety of antiplatelet drugs [4,5]. This experimental model coupled with continuous monitoring of LCCA flow and regional LV function was used to determine the effectiveness of intracoronary STK in the absence and presence of a fixed stenosis.

Materials and Methods

Surgical preparation

Male, mongrel dogs (17-21 kg) were anesthetized with sodium pentobarbital (30 mg/kg, *i.v.*) and ventilated under positive pressure with room air using a Harvard respirator pump. All surgical procedures were performed by cauterization and blunt dissection to minimize bleeding during the subsequent administration of STK. Catheters were inserted into the carotid artery to record arterial pressure with a Statham P23DC pressure transducer and into the jugular vein for anesthetic supplementation. A left thoracotomy was performed at the 5th intercostal space and the heart was suspended in a pericardial cradle. A 1-2 cm section of the left circumflex coronary artery (LCCA) was isolated proximal to the obtuse diagonal branch and instrumented with an infusion cannula, a calibrated electromagnetic flow probe (Carolina Electronics, 3 or 3.5 mm *i.d.*) a stimulation electrode and a teflon screw occluder (Fig. 1). The stimulation electrode consisted of a 25-gauge hypodermic needle tip (3-4 mm) attached to a 30-gauge teflon-coated, silver-plated copper wire. The infusion cannula was constructed from a U-shaped 27-gauge hypodermic needle

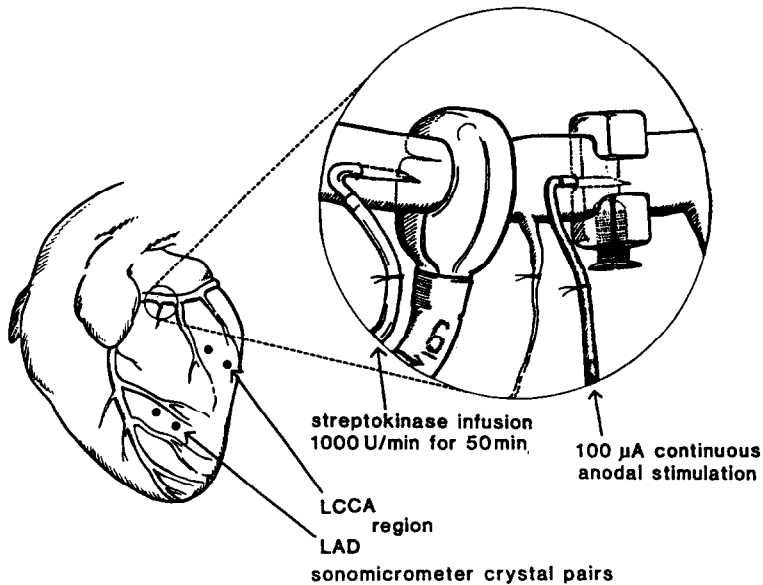


Fig. 1. Surgical preparation for thrombolysis studies. The proximal LCCA was dissected free and the following were affixed to the vessel as illustrated: infusion cannula, electromagnetic flow probe, stimulation electrode and screw occluder. Sonomicrometer crystal pairs placed to a midwall depth as described in Materials and Methods.

tip attached to Tygon tubing. The distance between the stimulation electrode and infusion cannula ranged from 2 to 8 mm; any intervening small LCCA branches were ligated.

Fig. 1 illustrates the positioning of the piezoelectric crystals (Norland Instruments, 3 mm diameter) which were placed 10 to 15 mm apart at a midmyocardial depth of 6 mm in the myocardial regions subserved by the left anterior descending (LAD) and LCCA. The dimension gauge crystals were connected to an oscilloscope sonomicrometer (Norland, NI-202) and were operated in radial mode at 800 kHz, achieving a resolution of 0.05 μ S. The distance between each crystal pair (regional segment length) was quantitated by multiplying the transit time (μ S) by the velocity of sound in myocardial tissue (1.58 mm/ μ S).

Continuous recordings of aortic pressure, lead II ECG, mean and pulsatile LCCA flow (Carolina Medical Electronics, Model 501 flowmeter, 0–30 or 0–100 ml/min range) and regional segment length were made on a Grass model 7 polygraph. Zero flow was determined by momentarily occluding the vessel distal to the flow probe and was confirmed during and upon termination of the experiment. The electromagnetic flow probe was calibrated initially using whole blood.

LCCA stimulation and streptokinase infusion

A fixed non-circumferential stenosis was produced at the point of electrode insertion in 22 of 35 preparations by adjustment of the screw occluder. This was a

TABLE 1

Effect of a stenosis on LCCA occlusion and the success of streptokinase in recanalization.

	Initial LCCA flow (ml/min)	Time to occlusion (min)	Number recanalated/ total (%)
<i>No stenosis</i>			
Saline (30 min post occlusion; <i>n</i> = 5)	27 ± 4	211 ± 26	0/5, 0%
Streptokinase (30 min post occlusion; <i>n</i> = 8)	28 ± 2	214 ± 30	1/8, 13%
<i>Stenosis</i>			
Saline (30 min post occlusion; <i>n</i> = 5)	30 ± 3	67 ± 13 *	0/5, 0%
Streptokinase (30 min post occlusion; <i>n</i> = 11)	29 ± 2	61 ± 10 *	8/11, 73%
Streptokinase (90 min post occlusion; <i>n</i> = 6)	28 ± 2	55 ± 8 *	5/6, 83%

Mean LCCA flow prior to electrical stimulation and the time from the onset of stimulation until flow decreased to and remained at zero for 30 min were compared among groups by one-way ANOVA and Duncan's test. Means for groups with a stenosis were less ($P < 0.05$) than those for groups without a stenosis. The proportion of animals successfully recanalated are also provided for each group.

relatively mild stenosis which resulted in an insignificant decrease in mean LCCA flow of $1.6 \pm 8.2\%$ (\pm SD). It did, however, decrease diastolic flow by an average of $19 \pm 4.5\%$ (\pm SD).

Within 30 min after surgical preparation, a 100- μ A d.c. current was applied to the intimal surface of the vessel and was continued until flow decreased to, and remained at, zero ml/min for 30 min. Constant d.c. current was delivered from a 9 V nickel-cadmium battery with the anode attached to the intracoronary electrode and the cathode placed in a subcutaneous site. Animals received a 50 μ l/min infusion of either 0.9% saline or STK (Hoechst-Roussel, 50 kU/2.5 ml saline at a rate of 1000 U/min) over a 50-min period starting at either 30 or 90 min after the initiation of thrombotic occlusion as indicated in Table 1. In some instances, another 50,000 U of STK was given at the end of the first infusion at twice the above rate for 25 min. Upon completing the infusion(s), the heart was arrested with KCl and the surgically isolated portion of the LCCA was clamped off proximally and distally and then removed. The isolated vessel segment was dissected longitudinally and any thrombus present at the site of injury was weighed immediately on an analytical balance.

The direct effect of STK upon coronary flow was examined in 3 separate preparations where STK was infused at 1000 U/min for 50 min without a stimulation wire or stenosis present.

Data calculations and statistical analyses

Segment length was calculated at end-diastole (LVED length) and at end-systole (LVES length) as demarcated by the peak of the QRS complex and the dichrotic

notch on the aortic pressure curve, respectively. Percent segment shortening was calculated by the formula $(\text{LVED length} - \text{LVES length}) \div \text{LVED length} \times 100\%$.

Equality of means between two groups was tested by the *t*-test. Multiple group comparisons were made by a one-factor or two-factor analysis of variance (ANOVA) with specific mean differences detected by Duncan's test. A value of $P < 0.05$, two-tailed, was considered significant. All values given in the text are expressed as mean \pm standard error of the mean (SEM).

Results

Effect of a stenosis on thrombogenesis and thrombolysis

Flows prior to electrical stimulation were comparable among all treatment groups as indicated in Table 1. The predominate effects of the stenosis in these experiments were upon the time required for an occlusive thrombus to form and the ability of STK to establish reperfusion. The average time to occlusion was decreased 72% overall by the stenosis, suggesting that either a greater stimulus for thrombus formation was elicited or that the size of the thrombus required to completely obstruct the vessel was decreased. The latter possibility is supported by the data in Fig. 2, which shows that occlusive thrombi in saline-treated controls were on the average 40% smaller in the presence than in the absence of a stenosis. These control animals provided an estimate of thrombus mass present at the site of injury and demonstrated that once flow was decreased to zero over 30 min, spontaneous reflow did not occur over the next 2 hr.

The number of animals from each treatment group which had measurable antegrade flow (> 3 ml/min) during STK infusion is also indicated in Table 1. Recanalization with STK was more effective with stenosed vessels and the resulting overall success rate of 76% was independent of whether infusion was begun 30 min

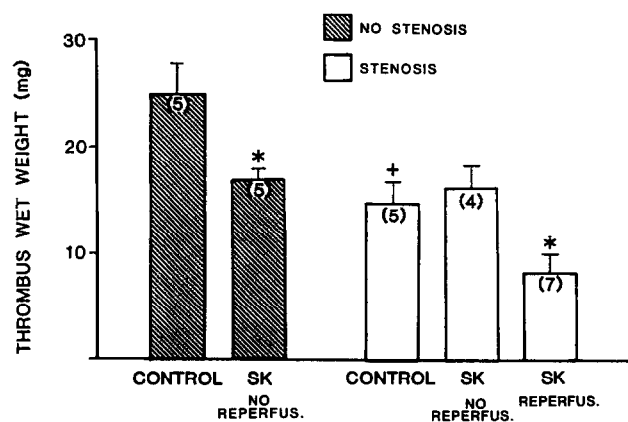


Fig. 2. Effect of a stenosis and streptokinase upon thrombus weight. Thrombi were isolated as described in Materials and Methods and weighed. Significant differences among the groups by one-way ANOVA were found with (+) less than control without stenosis at $P < 0.05$ and with (*) less than their respective controls at $P < 0.05$. Only one animal without a stenosis was reperfused; it had a thrombus weight of 17 mg.

or 90 min after thrombotic LCCA occlusion. Despite the relative inability of STK to induce reflow in animals lacking a stenosis, the average thrombus mass in these instances was diminished significantly by 30% relative to controls (Fig. 2). In STK-treated animals with a stenosis thrombus mass was reduced by 44% for the recanalized sub-group, while the non-reperfused sub-group failed to differ significantly from saline treated controls. Although reperfused vessels had smaller thrombi overall, residual thrombi weighing between 2–17 mg were observed in every instance at the termination of the infusion.

Flow characteristics after recanalization

Only one animal without a stenosis exhibited reflow and therefore flow-related data will be presented only from experiments where a stenosis was present. Fig. 3 consists of sample recordings from an experiment where STK elicited reflow at 16 min after the start of the infusion. This preparation was an exception in that pulsatile flow was restored; in all other cases the return of flow was non-pulsatile. Administering STK at 30 min compared to 90 min post-occlusion did not influence the reperfusion characteristics listed in Table 2 and, therefore, these data could be averaged together.

The overall magnitude of the initial return of flow (14 ± 1 ml/min, $n = 11$) and the maximum flow during reperfusion (22 ± 3 ml/min, $n = 11$) were usually less

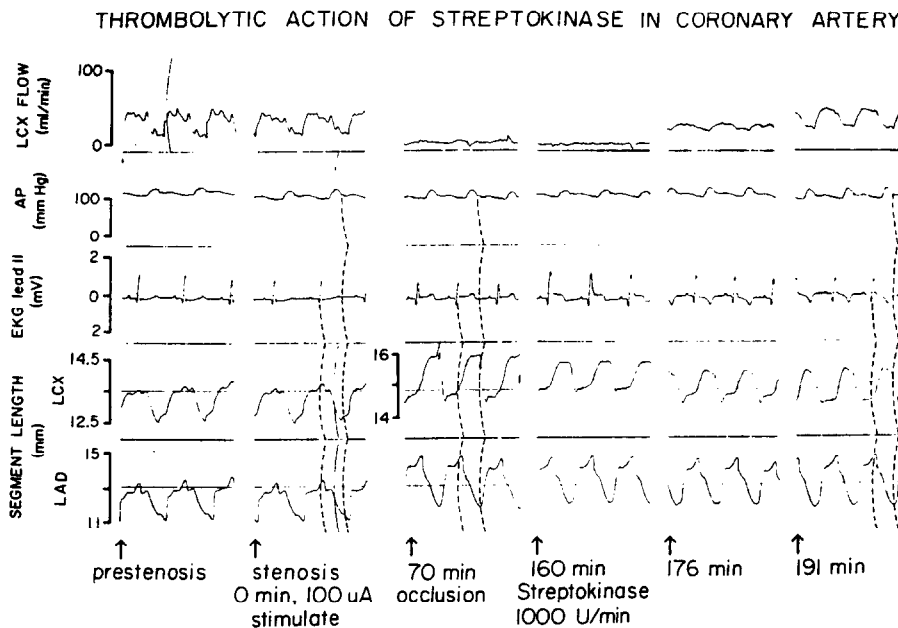


Fig. 3. Representative example of intracoronary streptokinase thrombolysis. The animal received 50,000 U of streptokinase beginning 90 min after occlusion. Flow was reestablished after 16,000 U were delivered (176 min) and was comparable to pre-occlusive flow after 31,000 U (191 min). Reocclusion (not shown) occurred by 200 min. Mean LCCA flow, also recorded in this experiment, was unaffected by the stenosis.

TABLE 2

Comparisons of reperfusion produced streptokinase infusions begun at 30 or 90 min post occlusion

Time to streptokinase infusion (min)	Time to reperfusion (min)	Initial flow upon reperfusion		Maximum flow upon reperfusion	
		ml/min	% Pre-occlusion	ml/min	% Pre-occlusion
30 ($n = 11$)	22 ± 3 ($n = 8$)	15 ± 1	53 ± 8	22 ± 3	76 ± 13
90 ($n = 6$)	28 ± 7 ($n = 5$)	13 ± 3	48 ± 11	21 ± 3	70 ± 10

Data are provided from only the experiments where reflow was established, even if momentarily. Comparisons by the *t*-test demonstrated no significant differences between the two groups.

than that existing prior to occlusion, indicating a lack of a reactive hyperemia. An overall average of 26 ± 6 min ($n = 11$) of STK infusion (26,000 U) was required to initiate reperfusion, although a considerable range of 5 min to 50 min was obtained for this parameter.

A very significant observation was the typical pattern of reflow which was obtained during STK infusion. The LCCA flows recorded during each successful reperfusion for animals receiving STK 30 min post-occlusion are summarized in Fig. 4. Essentially identical results were obtained with the five recanalized preparations receiving STK at 90 min post-occlusion. Flow was always unstable with sporadic fluctuations present during the entire period of STK infusion. Reocclusion of the vessel was observed in six of the eight preparations. To determine whether continued

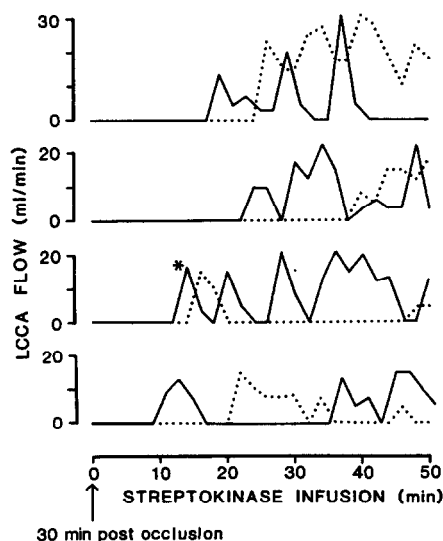


Fig. 4. Individual reperfusion patterns during streptokinase infusion. Changes in LCCA flow are presented for the 8 successfully reperfused animals in the group receiving streptokinase 30 min post occlusion. The maximum flows obtained over each 2-min period are plotted for each experiment as either a dotted or solid line for the sake of clarity.

or increased STK administration would be beneficial, three of these experiments were extended by infusing an additional 50,000 U STK over a 25-min period. No appreciable improvement in flow was detected in these instances and the intermittent pattern continued.

In the three experiments where STK was infused intracoronary in the absence of any thrombogenic stimuli (i.e., without electrical stimulation or stenosis), no effect on coronary flow was observed. Thus, STK itself was devoid of any significant coronary hemodynamic effect.

Cardiac function during thrombogenesis and thrombolysis

Sonomicrometer crystals were placed successfully in 24/35 of the animals included in the study. Representative changes in segmental shortening which occurred

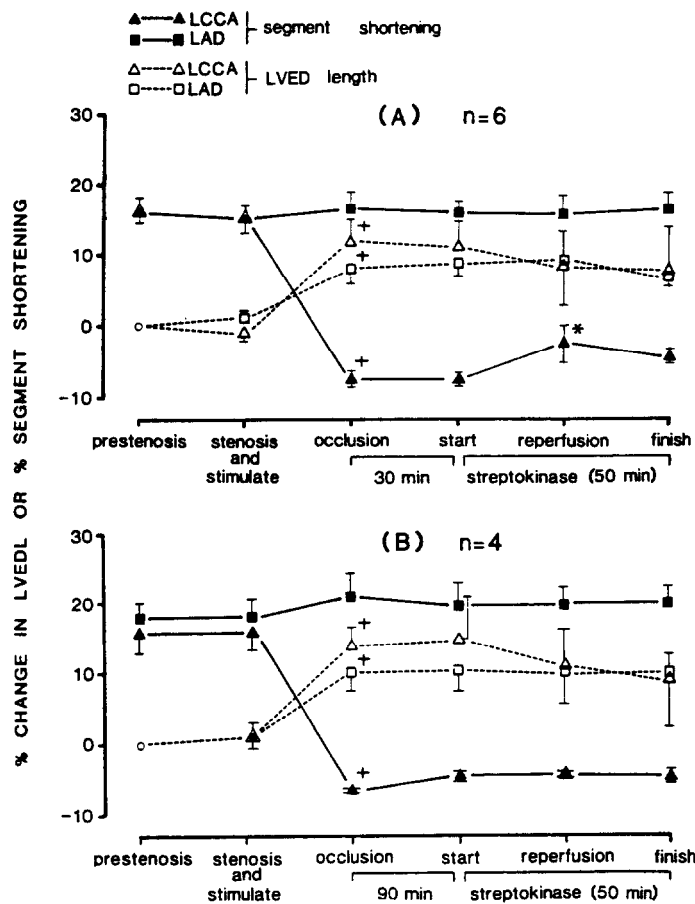


Fig. 5. Changes in regional cardiac function during thrombosis and thrombolysis. Percent segmental shortening and percent increase in LVEDL length are shown for animals treated at 30 min (a) or 90 min (b) post occlusion. Data points which were found to be significantly different from the preceding measurements by two-way ANOVA are indicated by (*) $P < 0.05$ and (+) $P < 0.01$.

in the LCCA and LAD perfusion beds upon thrombosis are shown in Fig. 3. Dyskinesia was evident when segmental length attained its greatest value at end-systole rather than end-diastole; in these cases, percent segmental shortening was less than zero. There were a total of 3 animals (11%) which retained contractile function in the LCCA region upon thrombotic occlusion of the LCCA, suggesting an effective collateralization of the coronary circulation in these instances.

The LV function data in Fig. 5 were derived from STK recanalized animals which demonstrated a loss of contraction in the LCCA region. Those animals receiving STK 30 min and 90 min post occlusion are shown separately; the corresponding times from occlusion until reflow began were 52 ± 3 min and 118 ± 7 min, respectively. None of the animals treated at the latter time point demonstrated any appreciable improvement in percent segmental shortening in the LCCA bed. STK infusion, at the earlier time, resulted in a small, but significant transient increase in segment shortening during the first few minutes of reperfusion. However, normal contractile function was not evident in this group since the average value was still less than zero.

Only one animal (Fig. 3), demonstrated positive segment shortening of 6% upon reperfusion which compared to a value of 15% prior to occlusion. Contractile function did not change significantly in the LAD region during the course of the experiments for any treatment group. LVED length, which was increased upon occlusion, was not significantly affected by STK in either group.

Discussion

Reduction of thrombus mass and recanalization

Streptokinase was relatively ineffective in reestablishing antegrade circumflex flow in the absence of a fixed stenosis even though it significantly reduced thrombus mass compared to saline treatment. It is possible that the size of the thrombus existing before the initiation of thrombolytic therapy was a crucial factor in determining the ability of intracoronary STK to recanalize the vessel. This hypothesis is supported by both the reduction in occlusive thrombus mass obtained when the partial obstruction was placed at the site of injury in saline-treated animals and the observation that STK elicited a proportionately greater (45% vs. 30%) decrease in thrombus weight in the presence of a stenosis. Furthermore, the percentage of experiments where at least intermittent flow could be restored by infusing 50,000 U STK was increased from 13 to 76% by the stenosis.

Despite its reduced size, a residual thrombus always was present at the site of electrode insertion whether or not flow was reestablished and no correlation was observed between the extent of reflow and the size of the remaining thrombus. Another interesting finding was the qualitative appearance of thrombi isolated from STK-treated animals which appeared to have a greater extent of red blood cell infiltration and were less firm than those removed from saline controls.

In other animal studies where lesions have been induced in large coronary arteries by copper coils [6,7] or electrical current [8], antegrade flow during STK induced

reperfusion was not monitored continuously. However, coronary flow was recorded continuously by Karshi et al. [9] who described a canine model of thrombosis induced by thrombin where a high degree stenosis was present on the affected vessel. Intracoronary STK (100,000 U in 200 ml over 50 min) was capable of reestablishing flow in this preparation which, after 60 min of infusion, approximated that before occlusion. Although these investigators did not indicate whether reflow was sporadic or increased in a smooth manner, reperfusion was maintained for up to 2 hr after completion of the STK infusion. These results are in contrast to ours in which a lower maximum flow and dramatic oscillations in flow were observed during reperfusion. The disparity can be reconciled by postulating that the injection of thrombin [9,10] or autologous thrombi [11] to produce occlusion may not inflict as severe a degree of injury to the vessel wall as does low intensity anodal current stimulation.

Infusion of STK alone may be incapable of preventing continued adhesion and aggregation of platelets to a sufficiently severe lesion, a process which is likely to proceed even after thrombus disruption. The continuing accumulation and removal of platelets could provide for the release of large vessel constricting substances such as thromboxane or serotonin, thereby inducing or accentuating flow decreases. In fact, the combination of a localized intimal injury superimposed upon a narrowed lumen is an important characteristic of our model. This is relevant to the majority of recanalized infarct patients in whom a persistent partial obstruction is present, although in these instances, the vessel injury is atherosclerotic in nature [12–14]. This physical deformation of the vessel may predispose to subsequent reocclusion which, although variable, has been reported to be as high as one-third of successful reperfusions [15,16].

Potential interventions during streptokinase thrombolysis

Meyer and co-workers [14] have suggested the use of balloon dilation in conjunction with STK treatment when the organic material of the stenosis, which may consist of residual thrombi, is of a sufficiently soft consistency. However, the recognition of methods aimed at physically removing an obstruction must be tempered by the potential disadvantages to such techniques. For example, the use of a guide wire on STK-resistant vessels has been criticized because of frequent reocclusions [13,17] which may be increased by aggravation of the lesion.

To achieve potentiation of thrombolysis and a greater success rate, some investigators have included plasmin (fibrinolysis) or plasminogen [6,7,18] with STK infusions. A synergistic action of plasminogen on STK has been demonstrated on thrombi in vitro [19] although arguments against the effectiveness of this combined therapy in vivo have been presented [3]. Heparin has been reported to be an effective agent in preventing reocclusion [20] and our preliminary results indicate that coadministration of heparin can enhance the extent and persistence of STK induced reflow. Heparin did not eliminate reocclusion in these studies [21] although procacyclin, a more effective antithrombotic agent, was beneficial in this regard.

Additional therapeutic interventions may be of advantage in limiting the injury of tissue resulting from the reperfusion process per se. Evidence for reperfusion injury in the clinical setting has been provided by Mathey et al. [22] who documented hemorrhagic infarcts upon necropsy in patients who were recanalized and in whom reflow was maintained until death. A number of recently developed experimental agents have been shown in animal models to increase the preservation of myocardium and to limit hemorrhagic infarction upon reperfusion without appreciably affecting cardiac oxygen supply or demand [23,24]. This type of intervention may become a logical extension of the therapeutic approach for the treatment of acute myocardial infarction.

Myocardial function during thrombolysis

The relative inability of STK to elicit a return of function when flow was restored after an average of 50 min (30 min STK group) to 110 min (90 min STK group) of occlusion is perhaps not surprising. According to previous studies 2–3 hr of ischemia requires 1–2 weeks for return of segmental function [25] while after 90 min of ischemia, regional function remains depressed for up to 72 hr [26]. Conflicting results have been obtained with shorter periods of ischemia. Banka et al. [27] detected improved segmental function within 5 min of reperfusion after 30 or 45 min, but not after 60 min, of occlusion. Kloner et al. [28] reported improved regional segment shortening within 1 to 60 min after 5 min, but not after ischemic periods of 15 min or longer. Other data suggest that any immediate return of contractility after brief occlusions is short lived and quickly deteriorates [29].

We administered STK as soon as possible once the occlusion was established in the hope of obtaining even a transient increase in contractility in the ischemic region. Although our model differs from those employed by others in that the loss and return of flow are gradual processes, avoidance of rapid occlusion and reperfusion did not appear to facilitate any return of regional function. It is possible that the amount of flow repayment was inadequate for the return of contractility. Alternatively, some of the midwall myocardial tissue, where segmental length was being measured, may have been irreversibly injured. This is perhaps more likely in the group receiving STK at 60 min than at 30 min post occlusion [30]. Due to the acute nature of our preparation, histochemical or histological examination of infarction was not accomplished.

The clinical literature in part also supports the contention that return of regional cardiac function is a delayed event [31–33] requiring from days to weeks. However, there is some variability among investigators on this matter and both a lack of improvement in global function after reperfusion [34] and an immediate decrease in akinetic segment length upon reperfusion [35] have been described. It is likely that much of this variability may represent technical differences in the assessment of myocardial performance. Since global indices may mask important changes in regional function, improved methods of measuring contraction in selected locations should be given emphasis.

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The Editorial Note to this article will be published in the next issue.