# Coronary Thrombolysis with Intravenous Streptokinase in the Anesthetized Dog: A Dose-Response Study

GREGORY A. KOPIA, LINDA J. KOPACIEWICZ and ROBERT R. RUFFOLO, JR.

*Department of Pharmacology, Smith Kline & French Laboratories, Swedeland, Pennsylvania*

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## ABSTRACT

In order to study the *in vivo* coronary thrombolytic dose-response effectiveness of i.v. streptokinase, pentobarbital-anesthetized, open chest dogs were instrumented for the measurement of lead II ECG, systemic arterial blood pressure, left ventricular developed pressure, left ventricular end-diastolic pressure, left ventricular *dP/dt* and left anterior descending (LAD) coronary artery blood flow. In some animals, two pairs of ultrasonic dimension gauges were positioned in 1) an area of the left ventricle which would become ischemic after thrombotic occlusion of the LAD and 2) a reference area which would remain unaffected by LAD occlusion. After making an occlusive thrombus by injecting thrombin (50–200 U) and calcium chloride (50–100 $\mu$mol) into a cannulated and mechanically occluded side-branch of an isolated segment of the mid- to distal LAD, animals were given either streptokinase (5,000, 10,000, 20,000 or 40,000 U of bolus, followed by 500, 1000, 2000 or 4000 U/min of infusion, respectively) or saline, i.v. At the termination of the experiment, thrombus wet weight and, in some animals, infarct size (measured by tetrazolium staining) were determined. In control animals, thrombus wet weight was 26.7 ± 5.4 mg (*n* = 8) and infarct size, as a percentage of the total left ventricle, was 30.1 ± 4.7% (*n* = 6).

Spontaneous reperfusion (return of LAD blood flow) was not observed in control animals that received saline. Intravenous administration of streptokinase produced a dose-dependent increase in the percentage of animals reperfusing, and a dose-dependent decrease in both thrombus wet weight and the time to reperfusion. Animals failing to reperfuse with streptokinase had smaller infarcts than saline-treated control animals (19.5 ± 2.9%, *n* = 12 *vs.* 30.1 ± 4.7%, *n* = 6, P < .05), and reperfusion with streptokinase produced yet a further decrease in infarct size (to 12.0 ± 2.6%, *n* = 10, P < .05 from saline). Myocardial function (percentage of wall thickening) decreased during LAD occlusion (P < .05) and remained depressed despite reperfusion with streptokinase. Left ventricular end-diastolic pressure increased after LAD occlusion and was the only hemodynamic parameter that changed significantly in response to LAD occlusion. This increase in left ventricular end-diastolic pressure was not affected by streptokinase treatment. We conclude that streptokinase is an effective thrombolytic agent when given by the i.v. route in this canine model of coronary thrombosis, and that the thrombolytic efficacy of streptokinase is highly dependent upon the administered dose.

Recently, major emphasis has been placed on the role of coronary thrombolysis and thrombolytic agents in the effective treatment of acute myocardial infarction (Rentrop *et al.*, 1981). The streptococcal protein, streptokinase, when complexed with plasminogen, forms an enzyme complex that converts circulating plasminogen to plasmin, which in turn degrades thrombus-bound fibrin, thus leading to thrombus dissolution (Christensen and MacLeod, 1945). Similarly, tissue-type plasminogen activator, a naturally occurring protein that increases the binding affinity of circulating plasminogen for thrombus-bound fibrin, converts plasminogen to plasmin, which is a powerful protease that degrades the fibrin structure of the thrombus (Bachmann and Kruithof, 1984). Although tissue-type plasminogen activator is still under clinical investigation (Collen *et al.*, 1984; Flameng *et al.*, 1985; Tiefenbrunn *et al.*, 1985), steptokinase has been used extensively in the management of acute myocar-

dial infarction precipitated by thrombus-induced coronary artery occlusion (Rentrop *et al.*, 1981; Ganz *et al.*, 1981; Cowley *et al.*, 1981, 1983; Raizner *et al.*, 1985). Currently, intracoronary administration of streptokinase is the approved therapy for thrombus-induced coronary occlusion, although i.v. administration of streptokinase has been used successfully to produce acute coronary thrombolysis (Eigler *et al.*, 1984; Marder and Francis, 1984; Valentine *et al.*, 1985). However, despite its widespread use, little information is available concerning the thrombolytic and pharmacologic dose-response effectiveness of streptokinase. Our goal in the present study is therefore to utilize an *in vivo* animal model to examine the coronary thrombolytic efficacy of a range of doses of streptokinase, and to determine the relationship that exists between streptokinase dose and the various hemodynamic parameters that are affected by acute coronary thrombosis. In addition, residual thrombus weight, left ventricular infarct size and a number of indices of left ventricular function were assessed. This study, therefore,

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**ABBREVIATIONS:** LAD, left anterior descending; ANOVA, analysis of variance.

describes 1) an effective method for the production of a thrombus in the coronary artery of an anesthetized dog, and 2) the dose-dependent thrombolytic efficacy of streptokinase. We believe this study represents the first complete evaluation of the dose-response relationship of streptokinase.

## Methods

**General considerations.** The method used for production of an intracoronary thrombus is a modification of the technique of Karsch *et al.* (1983) and Warltier *et al.* (1984). Dogs (18–25 kg) were anesthetized with sodium pentobarbital (35 mg/kg i.v.); the animals were intubated and respired with room air at a rate of 1C to 12 breaths/min and a tidal volume of 30 ml/kg. Systemic arterial blood pressure was monitored *via* a cannulated femoral artery, and i.v. administration of drugs was made *via* a cannulated femoral vein. Small stainless steel needle electrodes were placed in the right forelimb and the left hindlimb for the recording of lead II ECG.

The chest was opened at the 5th intercostal space and the heart was exposed and suspended in a pericardial cradle. A 6 French Millar Microtip catheter was advanced into the left ventricle cavity through the isolated left carotid artery for the measurement of left ventricular developed pressure, left ventricular end-diastolic pressure and left ventricular $dP/dt$. In some animals, pairs of ultrasonic dimension gauges were placed in 1) an area of the myocardium which would become ischemic upon occlusion of the LAD, and 2) an area near the base of the heart within the perfusion region of the left circumflex coronary artery which would remain well perfused despite LAD occlusion. One member of each pair of dimension gauges was implanted in the subendocardium, whereas the other was sutured to the epicardial surface of the heart directly over the subendocardial gauge, and each set of gauges was connected to a Triton model 120 sonomicrometer. In this manner, changes in the thickness of the intervening myocardial wall could be measured. Dimension measurements were considered to be valid only if the degree of wall thickening exceeded 12% (*i.e.*, end-systolic wall thickness had to exceed end-diastolic wall thickness by 12%).

A 1- to 2-cm section of the LAD coronary artery was isolated and a small distal left or right ventricular branch of the LAD was cannulated. Silk snare ligatures were placed at both ends of the isolated section of the LAD so that one ligature was just distal to the cannulated side-branch and was separated from the other ligature by approximately 1 cm. An electromagnetic flow probe (Carolina Medical Electronics, Inc;, King, NC) was placed at the most proximal end of the isolated LAD for measuring coronary artery blood flow (fig. 1).

All measured cardiovascular parameters were recorded on either a Grass model 7D Polygraph or a Gould Brush 200 Series Recorder.

**Preparation of coronary thrombus.** After a 30-min stabilization period, high speed (100 mm/sec) control recordings of the physiologic parameters were obtained, and a thrombus was created in the LAD by securing the distal snare ligature and injecting, sequentially, thrombin (50–200 U) and then calcium chloride (50–200 μM) mixed with whole blood, which, all together, did not exceed a total volume of 0.3 ml. The proximal snare ligature was secured before injection of the last 50 μl of solution so as to create a slight ballooning of the artery. Five minutes after the proximal ligature was secured, this same ligature was released, and after an additional 5 to 10 min, the distal ligature was released. If coronary blood flow was present, the above procedure was repeated with an equal or greater amount of thrombin, and the LAD was reoccluded until there was no coronary blood flow upon release of both ligatures. The successful creation of a LAD thrombus generally required approximately 30 min, after which the thrombus was allowed to "cure" for an additional 30 min.

**Experimental protocol.** Animals with intact LAD thrombi were randomly treated with either an i.v. saline infusion (1 ml/min) or a bolus injection of streptokinase (5,000, 10,000, 20,000 or 40,000 U) followed by a constant i.v. infusion (500, 1,000, 2,000, 4,000 U/min, respectively). Infusions were terminated shortly after maximum reflow
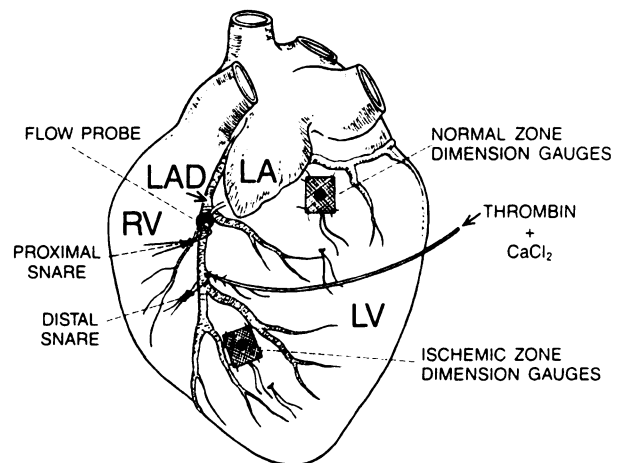
## INSTRUMENTATION



**Fig. 1.** Surgical preparation of the heart. A 1- to 2-cm section of the LAD was isolated and prepared with a proximal and distal snare occluder. An electromagnetic flow probe was placed just rostral to the proximal occluder and a small LAD branch was cannulated just rostral to the distal occluder. Wall thickness measurements were made in the distal LAD distribution area and in an area supplied by the left circumflex coronary artery.

was measured in the previously occluded LAD, or at 90 min, whichever came first. Animals were maintained for at least 30 min after termination of the infusion. High speed tracings were taken before LAD occlusion, before the administration of streptokinase, at 30, 60 and 90 min of the streptokinase infusion, and at 30 min after termination of the streptokinase infusion. At the termination of the experiment, the hearts were removed and the LAD was opened longitudinally and residual thrombus was removed and weighed. At this time, the position of the ultrasonic dimension gauges was verified. Also, in some animals, infarct size was determined by slicing the heart in bread loaf fashion (0.8–1.0 cm sections) from the apex to the level of the proximal snare ligature, and the slices were placed in 1% (w/v) triphenyltetrazolium chloride in 20 mM phosphate buffer warmed to 37°C. Triphenyltetrazolium chloride combines with intracellular dehydrogenase enzymes to produce a brick-red color. Infarcted and necrotic myocardial cells are depleted of dehydrogenase enzymes and appear as either brown or white. The size of the infarcted myocardium was then determined by cutting the unstained tissue apart from the nonstained tissue, and weighing both. Infarct size is then expressed as a percentage of the involved left ventricle.

**Drugs.** Streptokinase (Kabikinase, KabiVitrum AB, Stockholm, Sweden) was prepared fresh each day by dissolving 600,000 IU (1 vial) of the lyophilized powder in 40 ml of 0.9% saline for a final concentration of 15,000 U/ml. All bolus and infusion volumes were then calculated based on this concentration. Thrombin (Sigma Chemical Co., St. Louis, MO) was obtained in separate vials (100–5000 U/vial) and was dissolved in sufficient deionized water so that the amount injected (50–200 U) was contained in 0.1 ml. All drugs were kept refrigerated until used.

**Statistical analysis.** Changes in hemodynamics and myocardial wall thickness over time within an individual treatment group were analyzed by two-way ANOVA, whereas differences between individual treatments at the same time point were assessed by one-way ANOVA. Data on infarct size, thrombus weight and time to reperfusion were all analyzed by one-way ANOVA. For both analyses, differences between individual means were determined by Dunnett's test. For all statistical comparisons, the null hypothesis was rejected only when the probability of the calculated statistic was less than .05.

## Results

**Coronary artery thrombosis and thrombolysis with streptokinase.** Injection of thrombin and calcium chloride into a mechanically occluded segment of the LAD produces an occlusive coronary artery thrombus which remains in place after the mechanical occlusion is removed. In the control animals, the LAD thrombus did not spontaneously dissolve. In 8 of 10 control animals given 90-min saline infusions, thrombus wet weight was 26.7 ± 5.5 mg. Arteries from the two remaining animals were used for histological examination. Infarct size determined in six animals by the tetrazolium staining method was 30.1 ± 4.7% of the left ventricle.

Bolus i.v. injection of streptokinase followed by infusion of streptokinase produced a dose-dependent increase in the number of animals showing a return of LAD blood flow (fig. 2). After i.v. administration of 5000 U of streptokinase followed by a 500 U/min infusion, 1 of 7 animals (14.3%) demonstrated a return of LAD coronary artery blood flow after 30 min of drug administration. Conversely, all 8 animals (100%) receiving the highest bolus dose of 40,000 U of streptokinase followed by an infusion of 4000 U/min, recannalized as assessed by a return of LAD blood flow at an average time of 33.6 ± 7.2 min after administration of streptokinase. Intermediate doses of streptokinase produced an intermediate thrombolytic effect (4 of 10 animals recannalized at 10,000 U of bolus + 1000 U/min, and 5 of 7 animals recannalized at 20,000 U of bolus + 2000 U/min infusion). In addition to the dose-dependent thrombolytic effect of streptokinase on the number of animals recannalizing, both the time to reperfusion and the size of the residual LAD thrombus decreased with increasing doses of streptokinase (figs. 3 and 4).

**Infarct size.** Infarct size was measured in a total of 28



**Fig. 3.** Effect of increasing doses of streptokinase on the time to reperfusion. Only one animal reperfused at the 5000 U of bolus + 500 U/min dose after 38 min of streptokinase infusion and therefore could not be included in the figure. Increasing doses of streptokinase resulted in a decrease in the average time to the return of flow. * $P < .05$ from the 10,000 U of bolus + 1,000 U/min dose by ANOVA and Dunnett's test.
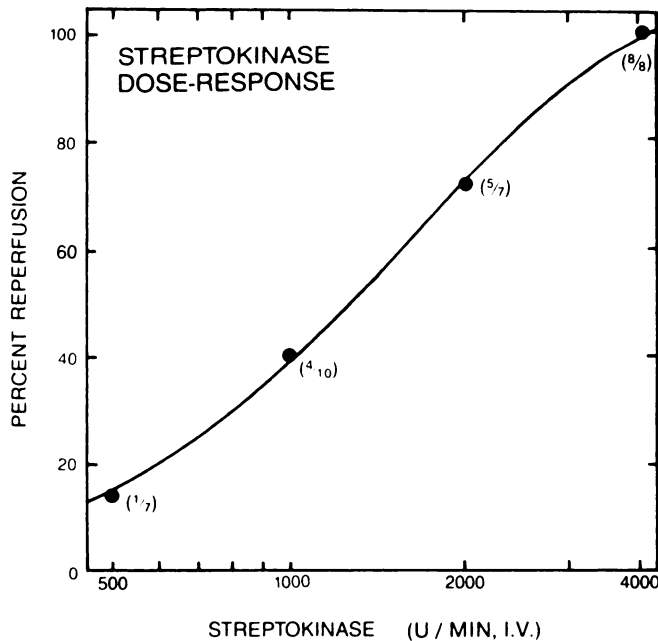


**Fig. 2.** Dose-response relationship between the infused dose of streptokinase and the percentage of animals in which coronary artery reperfusion occurred. Each infusion was preceded by an i.v. bolus dose 10-fold greater than the infused dose. The points were fitted to the equation MAXIMUM/$(1 + ED_{50}/X)^{slope}$, which resulted in the following least-squares line of best fit: $120.6/(1 + 1570.6/X)^{1.7}$. This is a significant regression ($P < .05$) by ANOVA. ( ), reperfusion animals/total number of animals.
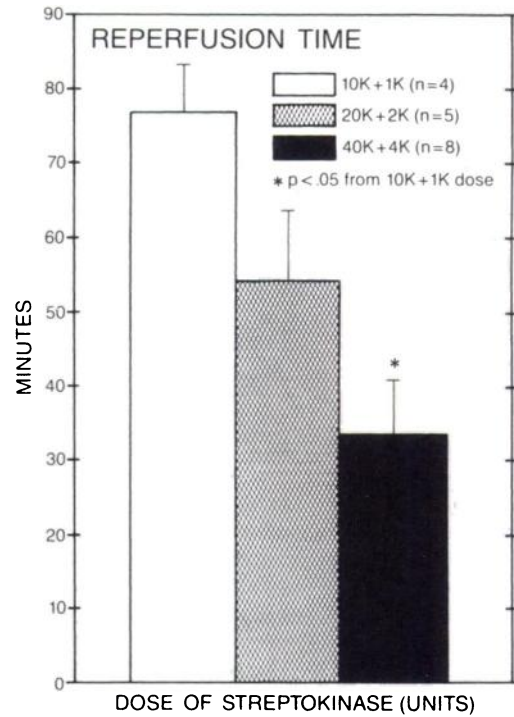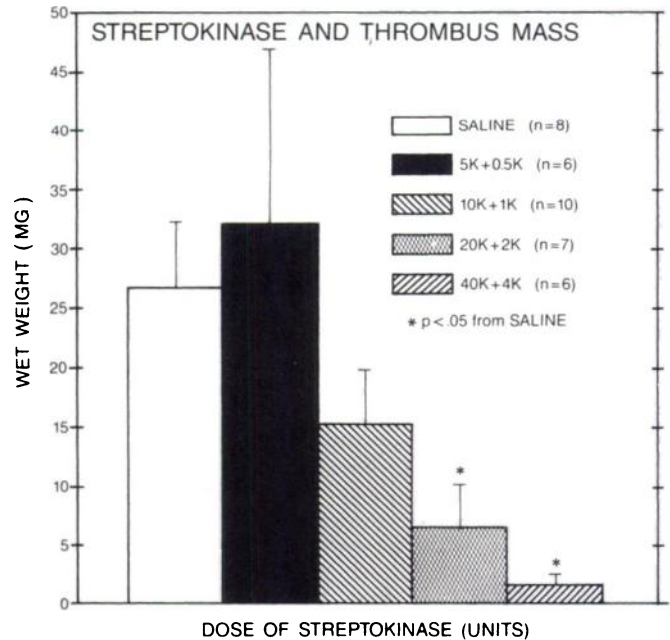


**Fig. 4.** Effect of increasing doses of streptokinase on residual thrombus mass. Thrombus mass decreased as the dose of streptokinase increased. * $P < .05$ from saline by one-way ANOVA and Dunnett's test.

animals; animals were grouped according to whether they received saline ($n = 6$) or streptokinase ($n = 22$), and within the streptokinase group, they were further subdivided based on whether the animals showed evidence of LAD reperfusion ($n = 10$) or no reperfusion ($n = 12$). In saline-treated animals, infarct

size represented 30.1 ± 4.7% of the left ventricle (fig. 5). In those animals treated with streptokinase and which *failed* to reperfuse the LAD, infarct size was decreased to 19.5 ± 2.9% of the left ventricle, which represents a 35% reduction when compared to saline. Animals in which reperfusion occurred after streptokinase, regardless of dose, had an average infarct size of 12.0 ± 2.6% of the left ventricle, a 60% reduction in infarct size compared with saline (fig. 5). Differences in infarct size between saline-treated and nonrecannalized, streptokinase-treated animals could not be attributed to differences in occlusion time (206.5 ± 11.7 min *versus*. 185.8 ± 4.2 min, respectively, P > .05 by one-way ANOVA and Dunnett's test). However, the streptokinase-reperfusion group had a significantly shorter duration of ischemia when compared to the saline animals (108.3 ± 9.5 min. p < .05 from saline).

**Hemodynamics.** In control animals, left ventricular end-diastolic pressure increased significantly after occlusion of the LAD and remained elevated for the duration of the experiment (fig. 6). This hemodynamic change also occurs in human subjects after acute myocardial infarction. No other hemodynamic parameter was altered significantly by occlusion of the LAD (fig. 6). In addition, administration of streptokinase had no effect on any of the hemodynamic parameters within the experimental observation period, regardless of the dose of strep-
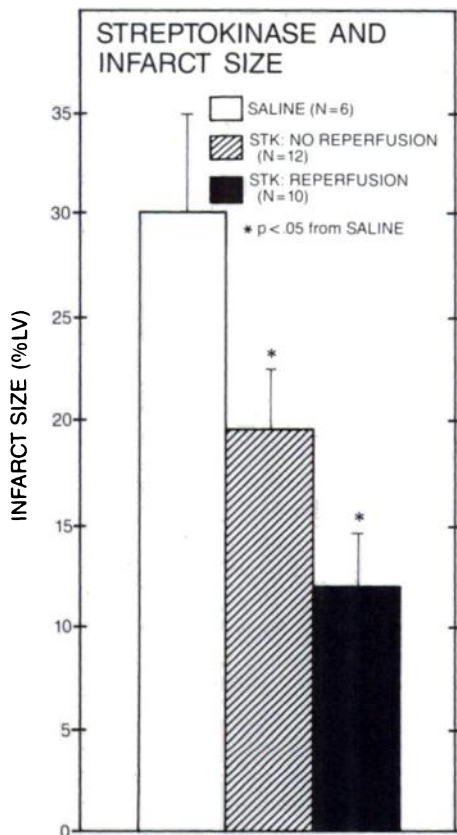
**Fig. 5.** Effect of streptokinase on myocardial infarct size. Animals were grouped according to whether they received saline (open bar), streptokinase and failed to reperfuse (hatched bar) or streptokinase and demonstrated a return of LAD blood flow (solid bar). Streptokinase reduced infarct size in animals despite no return of blood flow and produced a further decrease in infarct size in animals in which recannalization had occurred. * P < .05 from SALINE. Respective total left ventricular masses are: SALINE, 69.9 ± 8.1 g; STK: NO REPERFUSION, 64.2 ± 3.6 g; STK: REPERFUSION, 53.0 ± 3.4 g. These values are not different by one-way ANOVA.
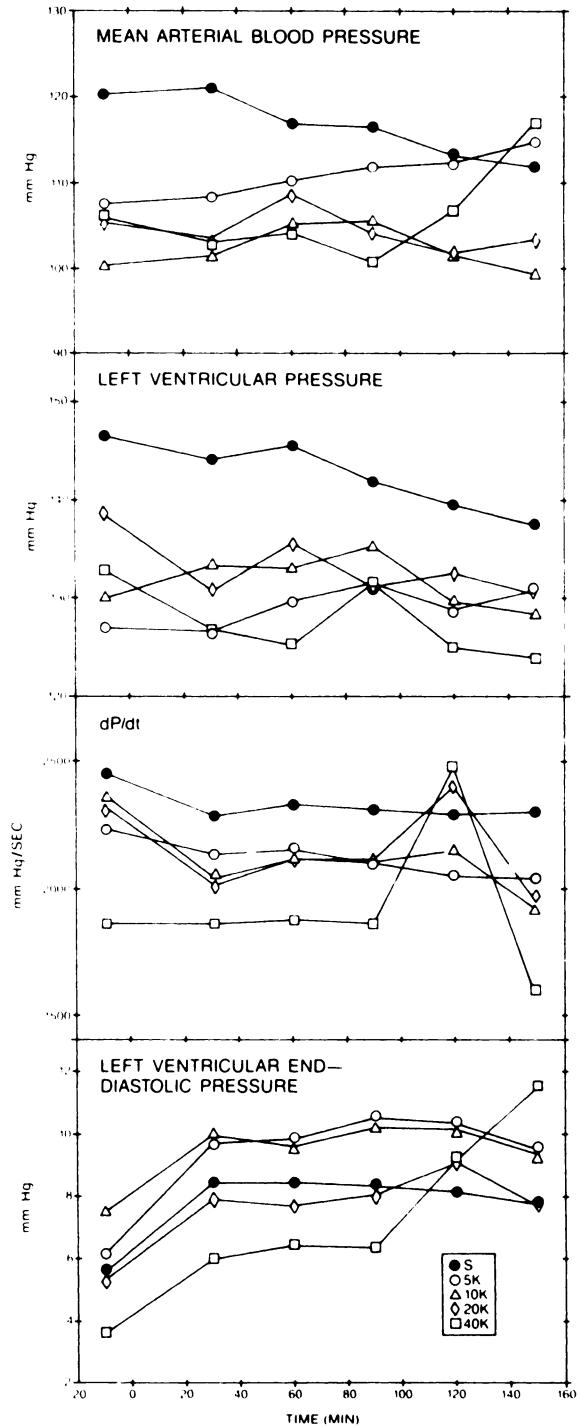
**Fig. 6.** Time course of hemodynamic changes after thrombotic LAD coronary artery occlusion and treatment with streptokinase. Zero time represents the point of initial thrombus formation and streptokinase administration was begun at 30 min. There were no significant differences between treatment groups at any time point for any parameter (P > .05 by one-way ANOVA and Dunnett's test). However, over time left ventricular end-diastolic pressure increased significantly in all treatment groups (at the point of LAD occlusion) and remained elevated for the entire experimental period (P < .05 by two-way ANOVA and Dunnett's test). No other measured parameter changed significantly over time. Standard error bars and asterisks were omitted for clarity.

tokinase infused or whether reperfusion occurred. Again, these results are also consistent with the clinical use of streptokinase.

**Myocardial function.** Myocardial wall dimension measurements from the nonischemic area of the myocardium were recorded successfully in 15 animals and from the ischemic zone in 17 animals, 5 of which demonstrated reperfusion after treatment with streptokinase. Animals were thus grouped according to whether or not LAD reperfusion occurred. Control systolic myocardial wall thickening in nonischemic myocardium was 19.9 ± 1.5% of end-diastolic wall thickness ($n$ = 15) and decreased only slightly by 120 to 150 min after LAD occlusion (fig. 7). In animals in which recannalization did not occur, systolic wall motion within the infarcted area (i.e., within the distribution of the LAD) went from thickening (22.2 ± 1.8% of end-diastolic thickness, $n$ = 12) to wall thinning (−7.6 ± 1.5% of end-diastolic thickness, P < .05 compared to preocclusion



**Fig. 7.** Time course of regional myocardial wall thickening (upper panel) and end-diastolic wall thickness (lower panel) in a nonischemic, normally perfused area of the myocardium and in an area rendered ischemic by thrombotic LAD coronary artery occlusion. The time axis is the same as that described in the previous figure. Wall thickening in the normal region showed only a slight decrease over time, whereas end-diastolic wall thickness in the normal region remained unchanged (O, $n$ = 15). In the ischemic region in animals that did not recannalize (□, $n$ = 12), both wall thickening and end-diastolic wall thickness decreased significantly with the onset of LAD occlusion and remained depressed for the experimental duration (P < .05 from the preocclusion value by two-way ANOVA and Dunnetts test). Reperfusion with streptokinase (■, $n$ = 5) failed to result in a recovery of wall thickening, whereas end-diastolic wall thickness increased significantly above the control value, most likely due to the hydraulic effect of returning blood flow.

value, $n$ = 12) after LAD occlusion, and remained depressed for the duration of observation. Reperfusion with streptokinase had no effect on acute recovery of wall motion within the 30 to 60 min period of observation after reperfusion (fig. 7; $n$ = 5).

Control end-diastolic wall thickness in nonischemic myocardium was 10.1 ± 0.5 mm, and this remained unchanged over time. In nonreperfused animals, ischemic zone end-diastolic wall thickness decreased after LAD occlusion (from 9.2 ± 0.3 mm to 8.1 ± 0.3 mm post-LAD occlusion, P < .05; $n$ = 12) and remained at this level for the remainder of the observation period. In animals that reperfused after treatment with streptokinase, ischemic zone end-diastolic wall thickness decreased slightly but not significantly after LAD occlusion and then increased significantly after reperfusion (fig. 7).

## Discussion

The principal aim of the present study was to examine the dose-response effects of coronary thrombolysis after the i.v. administration of streptokinase. Although numerous reports of the thrombolytic efficacy of streptokinase in both experimental animals (Ruegsegger et al., 1959; Moschos et al., 1970; Karsch et al., 1983; Warltier et al., 1984) and humans (Rentrop et al., 1981; Ganz et al., 1981; Cowley et al., 1981, 1983; Rizner et al., 1985) have appeared, no single study has examined whether or not the thrombolytic efficacy of streptokinase is related to the administered dose. Kanmatsuse et al. (1979) used intracoronary rates of infusion of 20, 50 and 100 IU/kg/min of fibrinolysin to dissolve 1-, 2- and 4-hr thrombi in canine coronary arteries (LAD), but presented no data on the dose-response relationship for the thrombolytic effect they observed. Similarly, based on the composite results of several clinical studies, Cowley (1983) has recently suggested that the thrombolytic effect of streptokinase in humans is related to the administered dose, but he correctly points out that the data are derived from studies at different medical institutions using different experimental protocols. In addition, there currently exists no dose-ranging data relating to the thrombolytic effectiveness of streptokinase administered by the i.v. route, which is now becoming the preferred route of administration. Marder and Francis (1984) suggest that i.v. thrombolytic therapy may be preferable to intracoronary therapy because of 1) the ability to administer agents more quickly after the onset of symptoms, and 2) the ability to administer thrombolytic therapy to a wider patient population, inasmuch as trained cardiac catheterization personnel are not required for i.v. thrombolytic administration, which could be performed in many more hospitals. Because the acute incidence of bleeding disorders is similar whether streptokinase is given by the intracoronary route or systemically, and the systemic lytic effect of thrombolytic agents may represent an important component of their local thrombolyticaction (Marder and Francis, 1984), the i.v. administration of thrombolytic agents, such as streptokinase, may be an important new therapy for acute coronary artery thrombosis.

We herein report, in a single study, the thrombolytic dose-response characteristics of i.v. streptokinase in a canine model of coronary thrombosis in which a variety of hemodynamic variables, indices of left ventricular function as well as thrombus weight and infarct size, were monitored. This model results in a homogeneous red blood cell thrombus that adheres to the luminal surface of the coronary artery and thereby prevents coronary blood flow. In order to assess the dose-dependent
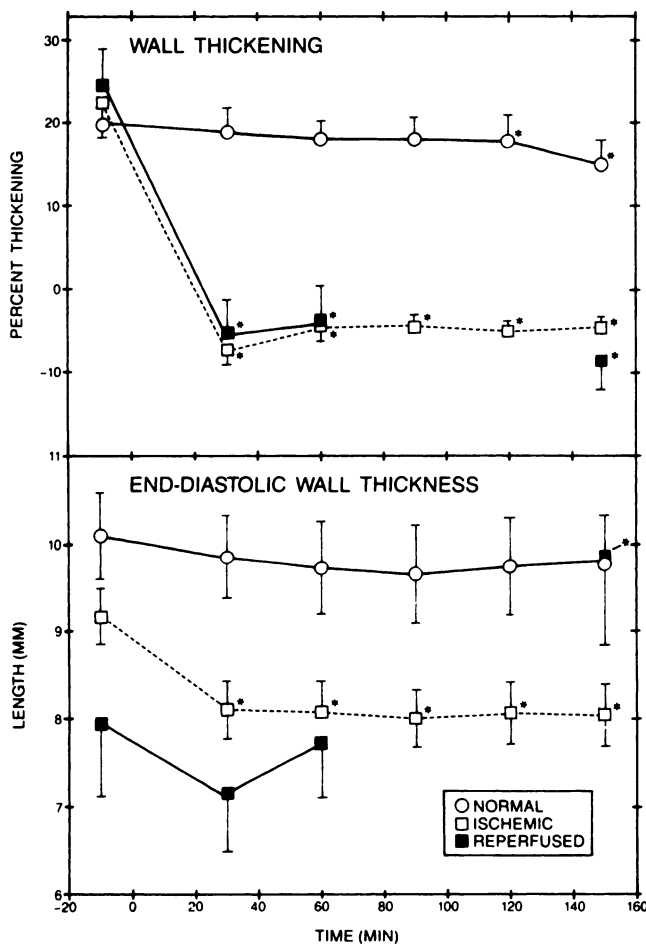
thrombolytic effectiveness of streptokinase, we administered various bolus doses followed by infusions of streptokinase in a manner similar to that used clinically for thrombolytic therapy. The degree of blood clot lysis, as measured by three different parameters: 1) thrombus wet weight, 2) the time required for blood flow to return after thrombus formations and 3) the number of animals demonstrating a return of blood flow, was related to the administered dose of streptokinase. Thus, animals receiving the highest dose of streptokinase were more likely to reperfuse, demonstrated a more rapid return of blood flow and had smaller (or no) residual LAD thrombi than animals given lower doses of streptokinase. This represents, to our knowledge, the first complete dose-response study for a systemically administered thrombolytic agent.

The hemodynamic consequences of the LAD blood flow deficit are reflected in an increase in left ventricular end-diastolic pressure and myocardial wall dysfunction within the area rendered ischemic by thrombotic coronary artery occlusion. Both of these events are characteristic of acute myocardial infarction. Alleviation of these hemodynamic sequele of coronary artery thrombosis showed no obvious relationship to the administered dose of streptokinase and were, in fact, unaltered by treatment with streptokinase. The lack of effect of reperfusion after streptokinase on wall motion is consistent with the findings of others (Puri, 1975; Lavallee et al., 1983; Bush et al., 1983; Heyndrickx et al., 1985) who have shown that recovery of myocardial function after coronary artery occlusion of 2 to 3 hr does not occur acutely in severely dyskinetic tissue due to "myocardial stunning," and slightly or moderately damaged tissue requires days to weeks for even partial recovery to take place.

An unexpected finding of this study is the observed decrease in myocardial infarct size in animals that received streptokinase, but which failed to recannalize. Although it has been shown previously that infarct size is related to the duration of coronary artery occlusion (for review, see Jennings and Reimer, 1983), it has been generally assumed that any reduction in infarct size observed with a thrombolytic agent would be due to the early re-establishment of coronary artery blood flow via thrombus dissolution, thus resulting in a salvage of myocardial tissue. However, our study demonstrates that the average infarct size, as assessed by tetrazolium staining, was smaller (relative to saline-treated controls) in animals receiving streptokinase, even if recannalization had not occurred. This is a novel observation of possible clinical relevance. Several explanations for this observation are possible: 1) streptokinase may be exerting a direct protective effect on ischemic myocardial tissue; 2) streptokinase may increase collateral blood flow to the ischemic region and thus decrease the mass of tissue at risk of infarction and 3) streptokinase-induced reperfusion through small microchannels within the thrombus may have occurred before detectable blood flow had been observed by means of our electromagnetic flow probe. Although our study was not designed to examine any of the above possibilities, our data suggest that streptokinase may possess a degree of myocardial protectant activity that is over and above that protection of myocardial tissue attributed to re-established coronary artery blood flow.

Extrapolation of the observations from the present study to the clinical setting suggests that patients with suspected or demonstrated coronary artery thrombi found to be refractory to the thrombolytic effects of streptokinase may nonetheless still derive some benefit from higher doses of this thrombolytic agent. In addition, the dose-dependent coronary thrombolytic effect of streptokinase that we demonstrated in this study suggests that higher doses of streptokinase than presently used clinically may result in a greater incidence of coronary artery reperfusion, and in a shorter period of time, in humans suffering from acute myocardial infarction. Because attainment of a systemic lytic state might appear to be a limiting factor for the systemic administration of large doses of streptokinase, systemic fibrinolysis is also a common occurrence even after intracoronary administration of streptokinase (Rothbard et al., 1983; Cowley et al., 1983; Marder and Francis, 1984), and may be an important component of the thrombolytic action of streptokinase (Rothbard et al., 1983). Inasmuch as it has been shown that restoration of coronary artery blood flow via thrombolytic therapy salvages myocardium (Markis et al., 1981; Warltier et al., 1984), and may reduce mortality (Spann and Sherry, 1984; Anderson et al., 1983; Patel and Kloner, 1985), the risk of inducing a systemic lytic state may be less than the benefit of improved outcome if successful thrombolysis is achieved. The present report demonstrates, in an experimental animal model of coronary artery thrombosis, that successful dose-dependent thrombolysis can be achieved repeatedly by systemic administration of streptokinase, and that this thrombolytic agent, through an as yet unestablished mechanism, may provide some degree of myocardial protection against infarction regardless of whether reperfusion occurs.

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