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Streptokinase improves reperfusion blood flow after coronary artery occlusion

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Streptokinase is an effective thrombolytic agent which, with early restoration of coronary blood flow, has the potential for limiting infarct size. Distinct from thrombolysis, we studied the effects of streptokinase on reperfusion coronary blood flow and infarct size. Open-chest anesthetized canines underwent a 90 minute snare occlusion of the left circumflex coronary artery followed by release and reperfusion through a critical stenosis for 6 hours. The animals were assigned randomly to two groups. Intracoronary streptokinase [group 1 ($n = 8$): 6000 IU/kg in 3 ml of saline] or saline [group 2 ($n = 8$): 3 ml of saline] was infused at 0.05 ml/min for 60 minutes beginning 30 minutes before reperfusion. Coronary blood flow was stable in group 1 during reperfusion, while in group 2 it fell during 6 hours of reperfusion (30 ± 4 ml/min to 18 ± 2 ml/min, $P = 0.05$). The ST-segment elevation on the limb lead II electrocardiogram 15 minutes after coronary artery occlusion was similar in both groups (group 1: 3.9 ± 0.6 mV, group 2: 2.3 ± 0.5 mV), suggesting the extent of myocardial ischemia was also similar in both groups. The infarct sizes were similar when expressed both as a percent of the total left ventricular mass [(IZ/LV) group 1: 17 ± 2.5%, group 2: 17.5 ± 2.5%] or as a percent of the area at risk of infarction [(IZ/AR) group 1: 39 ± 6%, group 2: 39 ± 5%]. In both groups, the mass of left ventricle dependent on the blood flow distribution of the left circumflex coronary artery was similar when compared to total left ventricular mass [(AR/LV) group 1: 41 ± 3%, group 2: 44 ± 4%]. These results demonstrate that streptokinase maintains reperfusion coronary blood flow through a critical stenosis at a rate similar to baseline levels. Despite the fact that coronary blood flow remained stable with streptokinase during reperfusion, infarct size was not limited after 90 minutes of fixed coronary artery occlusion in this canine model of myocardial injury.

Key words: Reperfusion; Streptokinase; Coronary blood flow; Infarction

Introduction

It has become increasingly apparent that myocardial infarction is most often the result of

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intracoronary thrombus formation, frequently at or near a stenotic artherosclerotic lesion [1,2]. Although the subsequent extent of myocardial necrosis is dependent on collateral blood flow to the ischemic area, it is known that myocardial contractility in the ischemic area is markedly decreased immediately after coronary artery occlusion [3], whereas irreversible damage progresses over several hours [4]. Attempts to restore coronary blood flow as early as possible are undertaken with the intent of decreasing functional myocardial damage and improving patient survival [5–8]. Restoration of coronary blood flow can frequently be accomplished with early administration of thrombolytic agents such as streptokinase or tissue plasminogen activator.

After reperfusion, high-grade stenosis may be present at the site of previous thrombosis. The residual lumen size can change significantly during the first two weeks after successful thrombolytic therapy as ruptured atherosclerotic plaques are remodeled, vasospasm resolves and persistent microthrombi are lysed endogenously. Coronary arteries with residual stenotic cross-sectional areas less than 0.4 mm^2 are at high risk for rethrombosis [9]. The clinical problems embodied in rethrombosis include reinfarction with concomitant loss of functional myocardium and the increased risk of sudden death [10].

Estimates of residual luminal area are used as an indicator of coronary blood flow in the clinical situation, because direct measurements are not available [11]. In the present study, coronary blood flow was continuously monitored in an experimental animal model of coronary artery occlusion with reperfusion through a critical stenosis. The extent of myocardial injury was directly measured after 6 hours of reperfusion. Distinct from its thrombolytic activity, the effect of streptokinase on the pattern of reperfusion coronary blood flow and the extent of myocardial necrosis was determined. The results of this investigation indicate that streptokinase does maintain reperfusion coronary blood at a rate similar to baseline levels. Despite persistently stable coronary blood flow, the extent of myocardial infarction which resulted after a 90 minute coronary artery occlusion and 6 hours of reperfusion was not limited by intracoronary streptokinase administration in this experimental model.

Methods

Occlusion–reperfusion myocardial injury

Male mongrel canines (13–16 kg) were anesthetized with dial urethane intravenously (500 mg/kg), endotracheally intubated and ventilated with room air at a tidal volume of 30 ml/kg and a frequency of 12 breaths/min (Harvard respirator, Harvard Apparatus, S. Natick, MA). The left carotid artery and internal jugular vein were exposed and catheters were inserted for monitoring arterial pressure (Statham P23DC pressure transducer, Gould Inc., Cardiovascular Products, Oxnard, CA) and infusing fluids, respectively. A left thoracotomy was performed in the fifth intercostal space and the heart was suspended in a pericardial cradle. A catheter was advanced from the left atrium into the left ventricle for monitoring left ventricular pressure.

A two cm section of the left circumflex coronary artery was isolated proximal to the first obtuse marginal branch and instrumented proximal to distal as follows: infusion cannula, electromagnetic flow probe (Model 501, Carolina Medical Electronics, Inc., King, NC), and critical stenosis. The small intervening coronary branches over the two cm segment were ligated (Fig. 1). A 26-gauge hypodermic needle tip was formed into a "u" and inserted into tygon tubing (0.03 cm, internal diameter) to be used as the intracoronary infusion cannula. The critical stenosis was produced by constricting the circumflex coronary artery with 0-silk tied around the artery and an 18-gauge blunt needle. The needle was quickly removed, thus leaving a smaller residual arterial lumen. The mean resting coronary blood flow was not affected by the critical stenosis; however, a 50% decrease in hyperemic blood flow was produced.

Angiographic evaluation of a critical stenosis which limited by 50% the hyperemic response to a 10 sec occlusion of the circumflex coronary artery was performed in a representative experimental preparation. Biplane digital coronary angiograms were obtained in projections that optimized sep-

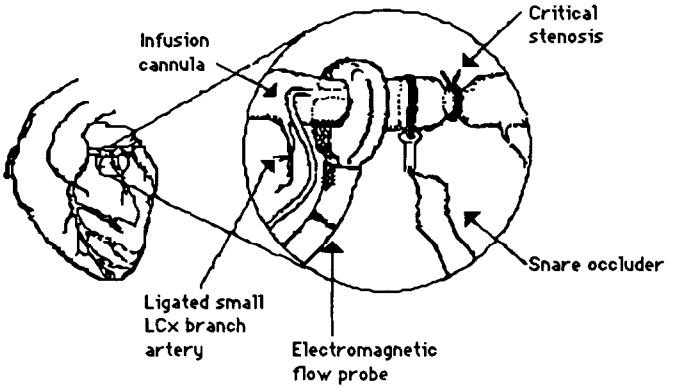

Fig. 1. Instrumentation of the left circumflex (LCx) coronary artery. The proximal 2 cm of the artery were isolated and instrumented (inset) with an infusion cannula, electromagnetic flow probe, snare occluder and critical stenosis.

aration of the circumflex stenosis from surrounding vessels. Angiograms were acquired on a digital angiographic computer (DPS-4100C, ADAC Laboratories, Edenvale, CA) interfaced to a standard cineangiographic system (Philips Optimus M200, Eindhoven, The Netherlands). The images were processed and analyzed with a previously described automatic coronary quantitation program [12].

Continuous recording of blood pressure, left ventricular pressure, left ventricular $\pm dP/dt$, limb lead II electrocardiogram, and mean and phasic left circumflex coronary artery blood flow were obtained on a polygraph recorder (Model 7, Grass Instrument Co., Quincy, MA).

Protocol

Thirty minutes after the surgical preparation was completed, the left circumflex coronary artery was occluded proximal to the critical stenosis but distal to the infusion cannula by compression with soft teflon tubing and a snare for 90 minutes. Either intracoronary streptokinase [group 1 ($n = 8$): 6000 IU/kg in 3 ml of 0.9% saline] or saline [group 2 ($n = 8$): 3 ml of 0.9% saline] was infused at a rate of 0.05 ml/min for 60 min, beginning during the last 30 min of occlusion and continuing the first 30 min of reperfusion. Reperfusion was accomplished by slowly loosening the snare over a 30 minute period and then observation was continued for a total of 6 hours. The heart was fibrillated electrically and removed quickly for postmortem quantification of infarct size.

Only canines which had electrocardiographic evidence of ischemia (ST-segment elevation) and then survived 6 hours of reperfusion were included in the data analysis. Four canines fibrillated during coronary artery occlusion and only one was successfully resuscitated (< 3 defibrillation attempts). One canine fibrillated upon reperfusion, during a streptokinase infusion, and it was successfully resuscitated. Four animals were excluded because left circumflex coronary artery blood flow fell outside the range established for the cohort (15–40 ml/min). Two other animals were excluded because they had a significant fall in mean arterial blood pressure (MAP $\leq$ 80 mm Hg) at the time of coronary artery occlusion, prior to randomization into either group, which was probably secondary to dehydration. The number of canines successfully studied in each of the two groups was eight.

Postmortem quantification of infarct size

Myocardial infarct size was quantified using an in vitro dual perfusion method described previously [13]. Cannulas were inserted into the circumflex coronary artery at the site of the stenosis and into the aorta above the coronary ostia. The circumflex bed was perfused with 1.5% triphenyltetrazolium hydrochloride in 20 mM potassium phosphate buffer (pH 7.4, 38°C). The coronary

ostia were perfused via the aorta retrogradely with 0.25% Evans blue stain. Both the circumflex region and the remainder of the heart were perfused with their respective stains at a constant pressure of 100 mm Hg for 5 min at 37°C. The heart was cut into six equal sections, 1.0 cm thick, perpendicular to the apex–base axis. The area of the left ventricle at risk for infarction due to it anatomic dependence on the circumflex coronary artery for blood flow was identified by the lack of Evans blue staining. The region of infarcted myocardium within the area at risk was demarcated by the lack of staining with triphenyltetrazolium hydrochloride [14,15]. Transverse ventricular sections were traced onto clear plastic overlays. Planimetry was used to determine the total left ventricular area, the area at risk and the area of infarction. Ventricular sections were trimmed of right ventricular, valvular, and fatty tissue and weighed. Infarct size was expressed as percent of the anatomic area at risk and the total left ventricle. In a previous study, gravimetric analysis agreed closely with determinations of infarct size obtained from planimetry of the overlay tracings [16].

Platelet and coagulation studies

In a second group of male mongrel canines, blood (20 ml) was withdrawn from the internal jugular cannula into a plastic syringe containing 3.2% sodium citrate as the anticoagulant [1 : 10 citrate/blood (vol : vol)] at baseline, 15 minutes of reperfusion, and 6 hours of reperfusion after treatment with intracoronary streptokinase (6000 IU/kg over 1 hour). The platelet count was determined with a Haema Count MK-4/HC system. Platelet rich plasma (PRP), the supernate present after centrifuging anticoagulated whole blood at 1000 rpm for 5 minutes ($140 \times g$), was diluted with platelet poor plasma (PPP) to achieve a platelet count of 200,000/mm^3. PPP was prepared after the PRP was removed by centrifuging the remaining blood at $12{,}000 \times g$ for 10 minutes and discarding the bottom cellular layer. Ex vivo platelet aggregation was measured by established spectrophotometric methods using a four channel aggregometer (BioData-PAP-4) by recording the increase in light transmission through a stirred suspension of PRP maintained at 37°C [17]. Aggregation was induced with collagen (1 : 10 and 1 : 80 dilution of Ethicon Collagen Dispersion-TD 150) and archidonic acid [0.65 mM and 0.325 mM (AA)]. Epinephrine (550 nM) was used to prime the platelets prior to AA stimulation. Values were expressed as percentages of light transmission standardized to PRP and PPP samples yielding 0% and 100% light transmission, respectively.

At similar time points, fibrinogen levels and fibrin/ogen split products (FSP) were measured. Fibrinogen was determined with thrombin reagent [lyophilized bovine thrombin, 100 NIH units/ml (Becton, Dickinson and Co., Rutherford, NJ 07070)] and Owren's veronal buffer (0.0284 M sodium barbital in 0.125 M NaCl, pH 7.35). The clotting time obtained was compared with that of a standardized fibrinogen preparation. Control plasma for this assays was a lyophilized preparation of human plasma [Ci-Trol Coagulation Control, Level I (American Dade, Aguada, Puerto Rico 00602)]. Sample tubes for FSP assays contained thrombin (20 NIH units) and soy bean trypsin inhibitor [approx 3600 NF units (Wellcome Laboratories, Beckenham, UK)]. The FSP were detected with immunological methods observing the agglutination or clumping of Latex Anti-Fibrinogen [0.6% suspension of polystyrene latex particles coated with rabbit anti-human fibrinogen in buffer (American Dade, Aguada, Puerto Rico 00602)] and Sorensen's buffer (0.1 M glycine and 0.1 M saline, pH 8.2).

Statistical analysis

Data were expressed as mean ± SEM. Differences between the two groups were determined by Student's t-test, and were considered significant if $P < 0.05$. When appropriate in the analysis of measured parameters, differences within and between groups over time were determined by repeated measures analysis of variance using Newman-Keul's multiple range test to detect where differences were located among the subpopulation means. A P value < 0.05 was considered significant.

Results

Group characteristics

Sixteen canines were successfully studied in this occlusion-reperfusion model of myocardial injury [streptokinase (group 1, $n = 8$), saline (group 2, $n = 8$)]. There was no difference in the weights of canines between the two groups [group 1: 15.0 ± 1.4 kg, group 2: 15.0 ± 0.9 kg (mean $\pm$ SEM)], nor in the weights of the hearts (group 1: 135 ± 7 g, group 2: 129 ± 8 g). There were no significant differences in recorded parameters (heart rate, left ventricular pressure, blood pressure, left circumflex coronary artery blood flow) determined between the groups at the beginning of the experiments.

Critical stenosis quantitative arteriography

The orthogonal image that showed the stenosis optimally was processed both with and without mask subtraction. After subtraction, the visual percent stenosis determined with calipers was 60% in the proximal left circumflex coronary artery (Fig. 2a). Subtracted and nonsubtracted digital

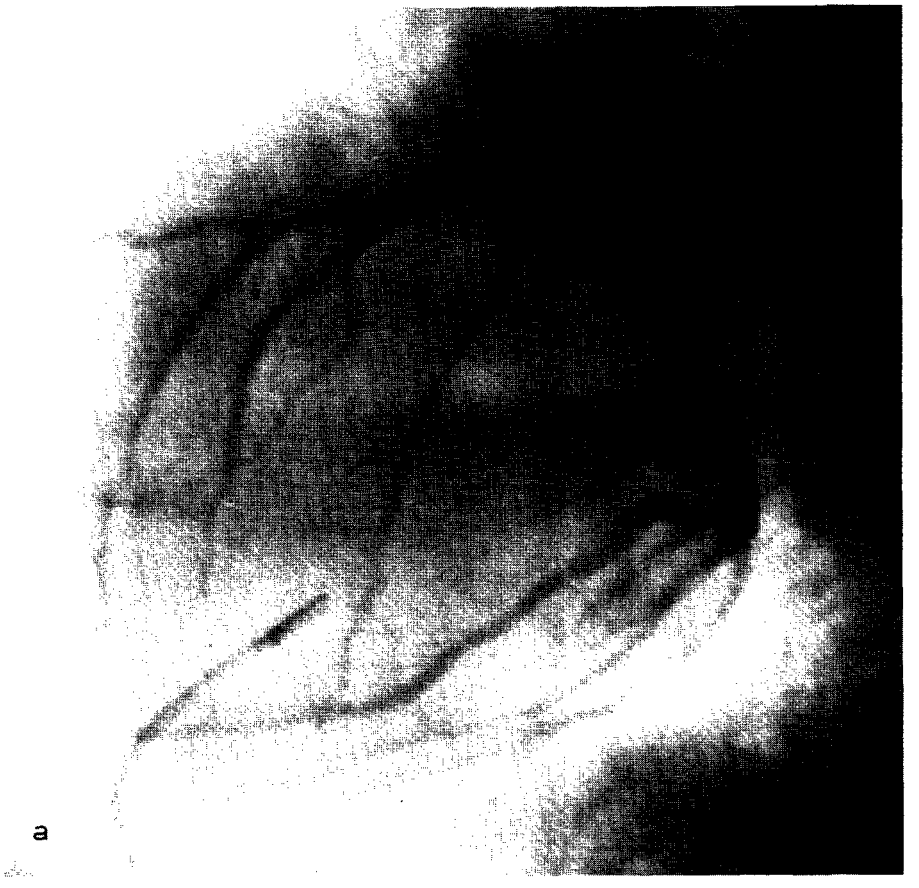

Fig. 2. Quantitative arteriography of circumflex coronary artery stenosis. The image showing the stenosis optimally was processed both with and without mask subtraction. (a) After subtraction, there was a 60% stenosis determined visually with calipers (arrow). (b) Digital images underwent gray-scale inversion producing white-on-black pictures with a four-fold magnification. (c) The final computer output consisted of the arterial image with arterial edges, centerline, and plots of geometric diameter, densitometric relative cross-sectional area, and maximal diameter stenosis. The arterial diameter at the critical stenosis was 1.46 mm. From this information, a 56.5% diameter stenosis and an 81% cross-sectional area stenosis were calculated.

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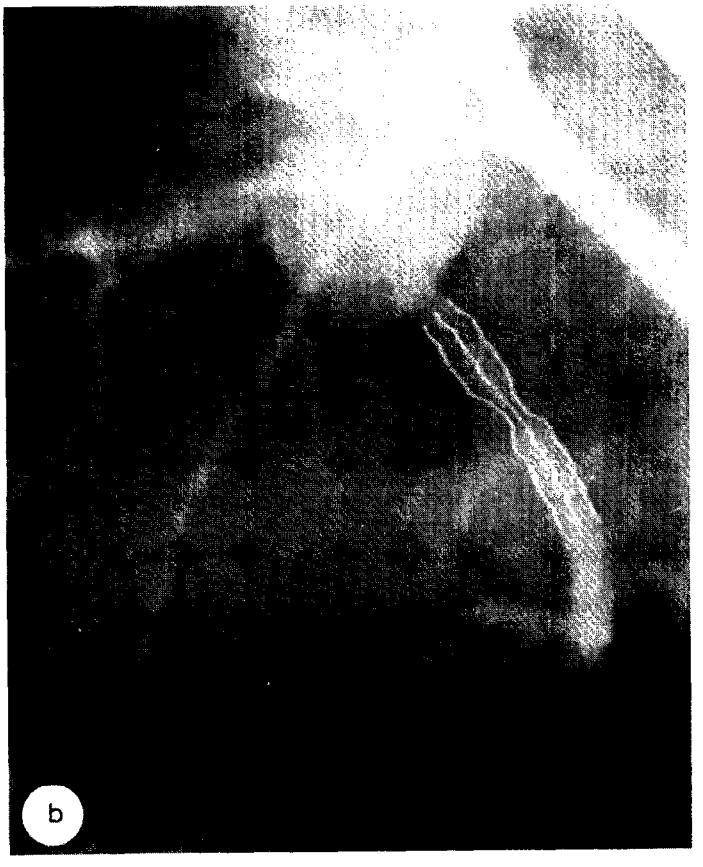

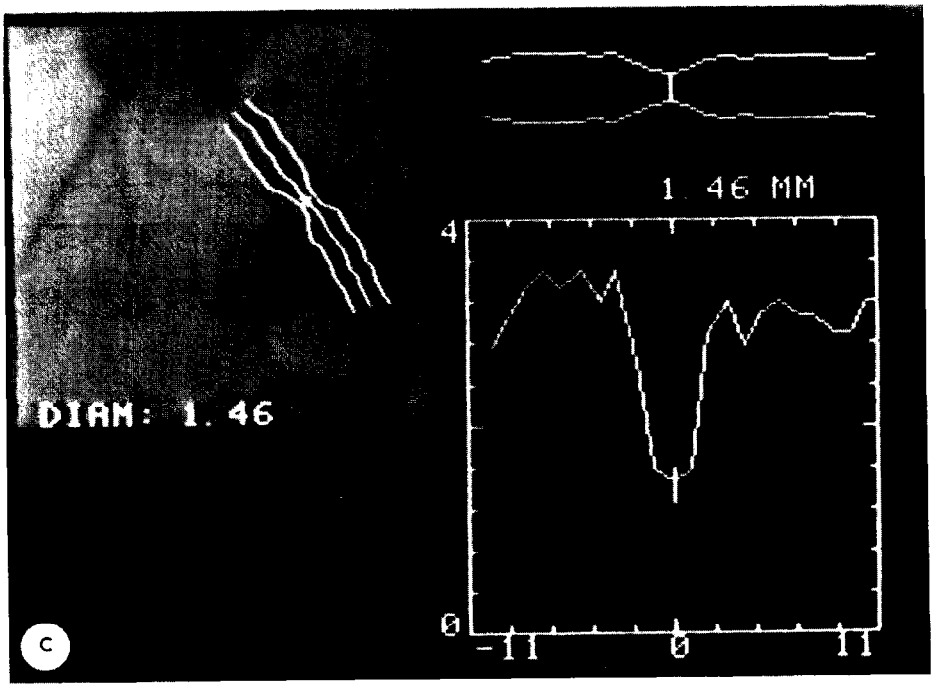

Fig. 2 (continued).

TABLE 1

Hemodynamic profiles in control and streptokinase-treatment groups.

	MAP *		Heart rate		RPP *	
	CT	SK	CT	SK	CT	SK
Baseline	118 ± 6	111 ± 5	134 ± 7	143 ± 5	181 ± 16	178 ± 13
15 min occ	110 ± 6	95 ± 6	141 ± 6	135 ± 5	173 ± 12	155 ± 10
15 min rep	108 ± 4	97 ± 5	134 ± 6	132 ± 7	155 ± 19	162 ± 12
1 hr rep	109 ± 6	96 ± 4	135 ± 7	133 ± 6	173 ± 19	156 ± 6
2 hr rep	111 ± 11	92 ± 12	141 ± 7	136 ± 7	179 ± 15	164 ± 5
3 hr rep	107 ± 7	97 ± 13	141 ± 4	136 ± 7	189 ± 11	171 ± 9
4 hr rep	110 ± 8	92 ± 12	149 ± 5	138 ± 8	201 ± 12	170 ± 8
5 hr rep	104 ± 7	95 ± 14	154 ± 2	144 ± 6	203 ± 12	184 ± 12
6 hr rep	102 ± 5	97 ± 12	156 ± 3 **	140 ± 6	196 ± 16	180 ± 13

Data are expressed as mean ± SEM; CT = control ($n = 8$); SK = streptokinase ($n = 8$); MAP = mean arterial pressure (mm Hg); RPR = rate pressure product (mm Hg/min × 100); heart rate = beats/min; occ = occlusion; rep = reperfusion.

* No significant difference between groups at the same time point but significant change over time (MAP $P = 0.02$, RPP $P < 0.05$). Control heart rate increased over time and compared to streptokinase at 6 hour rep (** $P = 0.02$).

images underwent gray-scale inversion to produced white-on-black pictures with a four-fold magnification (Fig. 2b). The final computer output consisted of the arterial image with arterial edges, centerline, and plots of geometric diameter, densitometric relative cross-sectional area, and maximal diameter stenosis (Fig. 2c). The arterial diameter at the critical stenosis was 1.46 mm. From this information, a 56.5% diameter stenosis and an 81% cross-sectional area stenosis were calculated.

Hemodynamic responses

There was no difference in mean arterial blood pressure recorded between the two groups over the course of the experiment. In both groups, the animals experienced a moderate fall in mean arterial blood pressure 15 min after left circumflex coronary artery occlusion which persisted throughout reperfusion (Table 1). The initial decrease in mean arterial pressure was more prominent in group 1 than the change which occurred in group 2, however this difference was not significant. The fall in mean arterial pressure induced by coronary artery occlusion occurred before streptokinase had been infused. After 6 hours of reperfusion, the heart rate of canines in group 2 had increased significantly over time, from 134 ± 7 bpm to 156 ± 3 bpm ($P = 0.02$). This final heart rate in group 2 was higher than that observed in group 1 ($P = 0.02$). Despite these hemodynamic changes, there was no point in time when the rate pressure product was different between groups. However, overtime within groups there was a significant change in the rate pressure product ($P < 0.05$).

Circumflex coronary artery blood flow patterns

The baseline circumflex coronary blood flow in groups 1 and 2 were not significantly different

TABLE 2

Left circumflex coronary artery blood flow in control and streptokinase-treatment groups.

	Blood flow (ml/min)	
	SK	CT
Baseline	20 ± 2	26 ± 3
15 min rep	24 ± 3	30 ± 4
1 hr rep	19 ± 3	25 ± 5
2 hr rep	17 ± 3	21 ± 4
3 hr rep	18 ± 3	20 ± 4
4 hr rep	15 ± 3	20 ± 4
5 hr rep	16 ± 3	19 ± 4
6 hr rep	16 ± 2	18 ± 2 *

Data are expressed as mean ± SEM: CT = control (n = 8): SK = streptokinase (n = 8); rep = reperfusion. No significant difference between groups at the same time point but significant change over time in control group (* $P < 0.05$).

(20 ± 2 ml/min vs 26 ± 3 ml/min, respectively, Table 2). During the 6 hour reperfusion period, blood flow in group 1 was stable and did not decrease significantly (24 ± 3 ml/min to 16 ± 2 ml/min). In contrast, the coronary blood flow in group 2 slowly decreased over the 6 hour reperfusion period, from 30 ± 4 ml/min to 18 ± 2 ml/min ($P = 0.05$). There were no oscillations or spontaneous hyperemias detected in coronary blood flow during the reperfusion period in either group.

Effect of occlusion–reperfusion on myocardial ischemia and infarct size

The ST-segment elevation on the limb lead II electrocardiogram 15 minutes after coronary artery occlusion was similar in both groups (group 1: 3.9 ± 0.6 mV, group 2: 2.3 ± 0.5 mV), suggesting the extent of myocardial ischemia was also similar in both groups. During the course of the protocol ST-segment elevation tended to resolve and was replaced by Q waves and T wave inversion in all cases, and this then corresponds with evolution of a transmural myocardial infarction. The areas of the left ventricle at risk for infarction (AR/LV) were similar in the two groups (Fig. 3), demonstrating that the anatomic dependence on the proximal circumflex artery was similar. The region of infarcted myocardium within the area at risk (IZ/AR) and the total left ventricle (IZ/LV) were similar for the two groups. The weight of the left ventricle (group 1: 85 ± 6 g, group 2: 75 ± 4 g) and of the infarcted mass of tissue were similar in the two groups (group 1: 14 ± 3 g, group 2: 13 ± 3 g). These infarct sizes were determined after a fixed time of occlusion (90 minutes) and a fixed time of reperfusion (6 hours), and these timing intervals should have been adequate for determining the full extent of myocardial injury. Thus when streptokinase was used as an adjunct during occlusion–reperfusion myocardial injury, infarct size was not limited in this experimental model.

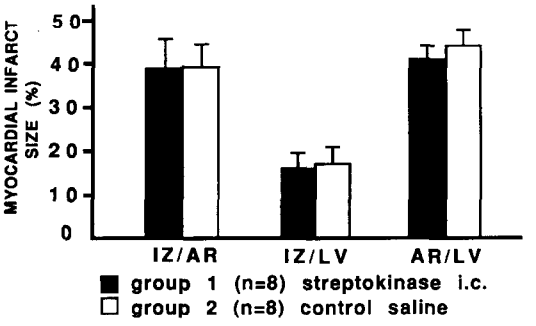

Fig. 3. Myocardial infarct size. Quantitation of infarct size is expressed with respect to infarct zone (IZ) as a percent of the area at risk (AR) and as a percent of the total left ventricle (LV). There was no difference in infarct size between group 1 (streptokinase) and group 2 (saline), nor was there a difference in the area of left ventricle at risk for infarction (AR/LV).

Platelet and coagulation studies

The platelet counts tended to fall over the course of the study but this decrease did not reach a significant level (Table 3). The platelet aggregation studies were similar at baseline, 15 minute reperfusion, and 6 hour reperfusion for both agonists (collagen and arachidonic acid). It seems

TABLE 3

Platelet and coagulation studies in canines treated with intracoronary streptokinase.

	Platelet count ($\times 10^3$/mm^3)	Aggregation studies *				Fibrinogen (mg/dl)	FSP (μg/ml)
		Collagen		Arachidonic acid (mM)			
		1 : 10	1 : 80	0.325	0.650		
Baseline	332 ± 46	78 ± 9	44 ± 10	83 ± 7	83 ± 6	385 ± 30	49 ± 5
15 min rep	281 ± 41	74 ± 8	64 ± 9	80 ± 7	76 ± 7	352 ± 27	153 ± 21 **
6 hr rep	285 ± 31	71 ± 9	33 ± 12	72 ± 9	74 ± 8	355 ± 33	214 ± 42 **

Data are expressed as mean $\pm$ SEM ($n = 13$); rep = reperfusion; FSP = fibrinogen split products.

* Platelet aggregation reported as % light transmittance or % aggregation.

** $P < 0.001$ compared to baseline.

that the streptokinase had no demonstrable effect on ex vivo platelet reactivity. At the beginning of each experiment, coagulation studies including, fibrinogen levels and fibrin/ogen split products (FSP), were performed. The fibrinogen level fell slightly after the intracoronary streptokinase infusion and remained at this level after 6 hours of reperfusion (P = NS). The FSP were consistently elevated after initiation of the streptokinase infusion and remained so for the 6 hours duration of the protocol ($P < 0.001$).

Discussion

The intravenous infusion of streptokinase is effective in reestablishing coronary blood flow during acute myocardial infarction. Although reocclusion related reinfarctions and deaths occur after thrombolytic therapy, there are clinical trials in which long-term survival improved in those patients treated with streptokinase [18–20]. The reported reinfarction rates are determined by intention to treat, often without establishing effective thrombolysis, and may be underestimated. However, the reinfarction rates appear to be similar for streptokinase and tissue plasminogen activator [21]. Those vessels with more severe residual stenosis comprise one anatomic subgroup at risk for rethrombosis, both with streptokinase and tissue plasminogen activator [9,22].

There are animal models which have been developed to study thrombotic coronary artery occlusion [23,24]. Electrical induction of thrombosis has been employed to define several clinical interventions [25]: anti-thrombotic agents, thrombolytic agents and prevention of rethrombosis. Recent interest has focussed on the latter two points. The electrically induced thrombus closely resembles the clinical situation with respect to clot composition, presence of a critical stenosis and an intimal lesion. In this model, if the thrombolytic agent is effective, mean coronary blood flow during reperfusion is significantly lower than baseline flow [26,27]. Inspite of this reduction in coronary blood flow, infarct size is smaller after thrombosis–thrombolysis myocardial injury than occlusion–reperfusion myocardial injury. When the data from our previous study [28] were compared to the data from the study presented herein, those infarcts produced in the thrombosis–thrombolysis model were smaller (IZ/AR $P < 0.005$, IZ/LV $P < 0.005$), while the area at risk for infarction (AR/LV) was similar. There are several possible reasons for the descrepancies. Initial coronary artery occlusion time is somewhat unpredictable in thrombosis–thrombolysis studies when compared to performing a snare occlusion for a fixed period. Furthermore, in most studies evaluating thrombolytic efficacy of an agent, reocclusion is not reported or heparin is used with the thrombolytic agent to prevent reocclusion, so assessing infarct size or the incidence of rethrombosis is dependent upon more than one variable [29,30]. There has been some suggestion that streptokinase may limit infarct size by mechanisms in addition to thrombolysis, i.e. scavenging oxygen-derived free radicals or a decrease in vascular resistance of the coronary circulation within the ischemic zone.

Although streptokinase is adequate for inducing thrombolysis acutely in the electrical induction model of coronary artery thrombosis, alone it does not alter the thrombogenic nature of this insult enough for the vessel to remain patent after the infusion is stopped [26]. Initial reperfusion coronary blood flow is lower than preocclusion flow and often has an unstable pattern which terminates in rethrombosis after several hours. This oscillating coronary blood flow pattern does not occur in the occlusion–reperfusion model used in this study; however, the occlusion–reperfusion model is compromised by diminished reperfusion coronary blood flow which can be improved upon with streptokinase. Oscillations and/or the decreased blood flow patterns seen in these two models may represent a spectrum of the same problem: persistent platelet aggregation, intermittent distal no-reflow due to leukocyte plugging, or vasospasm. The histology of experimentally evoked thrombi [24,31], as well as those found in coronary arteries at necropsy of patient with acute myocardial infarction, further support an important role for platelets [32]. In this study, streptokinase did not alter ex vivo platelet reactivity; however, no attempt was made to determine if there were platelet aggregates within the ischemic zone.

The role of leukocytes in occlusion–reperfusion injury involves both the myocardium, i.e. infarct size [33], and the coronary microcirculation [34]. The possibility that diminished reperfusion blood flow in the infarct vessel is due to distal no-reflow and leukocyte plugging has been studied using prostaglandin E_1 (PGE_1) in the occlusion–reperfusion model [35]. Neutrophil migration into inflammatory areas, production of superoxide anion in vitro, and infarct size were all decreased with PGE_1, while reperfusion blood flow improved compared to control animals. Although reperfusion coronary blood flow was not continuously monitored by Chatelain et al. [36], after 3 hour occlusion and 30 minute reperfusion, a hyperemic response in coronary blood flow was evident in neutropenic, but not control animals. Interstitial and microvascular leukocyte accumulation were found in the controls but not in the neutropenic animals, thus the presence of neutrophils may effect reperfusion coronary blood flow. Forman et al. [37] found regional myocardial blood flow diminished after 90 minute occlusion and 1 hour reperfusion; however, the vasodilatory reserve was preserved when an antineutrophil agent, perfluorochemical, was infused during reperfusion. Light and electron microscopy of the ischemic region revealed capillary obstruction by endothelial cell protrusions and neutrophils in control animals not the perfluorochemical-treated animals. In the present study, we did not assess neutrophil accumulation within the ischemic zone.

Neutrophils have also been implicated in myocardial dysfunction which occurs after brief periods of coronary artery occlusion and reperfusion [38]. Aside from physically obstructing flow in the capillary bed, neutrophils release substances, i.e. superoxide radical, arachidonic acid metabolites and enzymes, which effect coronary vascular tone and contribute to myocardial dysfunction and injury. Products of the 5-lipoxygenase pathway of arachidonic acid metabolism, leukotrienes, have been shown to induce diffuse peripheral constriction in the coronary arteries [39]. In a previous study, we found that streptokinase did not alter in vitro neutrophil free oxygen radical production, not did it act as a hydroxyl or superoxide radical scavenging agent [40]. In vitro studies may not predict in vivo effects of streptokinase on platelets, neutrophils, and the vasoactive substances released. However, it appears that these factors are important and may need to be eliminated or modified in order to establish adequate stable reperfusion coronary blood flow.

Reperfusion coronary blood flow, myocardial function, and infarct size are clinically relevant issues. In acute anterior myocardial infarction, after either thrombolysis or angioplasty, a high grade residual stenosis or a prolonged period of ischemia prior to reperfusion limit the increase in estimated coronary blood flow upon reperfusion. Functional recovery at 10 days directly correlated with acute increases in coronary blood flow [41]. Early establishment of adequate myocardial perfusion, not just the restoration of coronary blood flow, should be used as a guideline to assure the success of interventions designed to limit infarct size. The findings of this animal study using an occlusion–reperfusion model of myocardial injury, suggest that streptokinase can increase reperfusion coronary blood flow. Although coronary blood flow upon reperfusion was similar to baseline levels, infarct size was not limited in this animal model.

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