Thromboxane synthetase inhibition with CGS 13080 improves coronary blood flow after streptokinase-induced thrombolysis

The focus of this investigation was to examine the potential beneficial effects of the selective thromboxane synthetase inhibitor CGS 13080 (imidazo [1,5-a] pyridine-5-hexanoic acid) on coronary blood flow after streptokinase-induced thrombolysis. Thrombotic occlusion of the circumflex coronary artery was produced by electrolytic (100 μA anodal current) injury to the intimal surface of the circumflex coronary artery at the site of a noncircumferential stenosis in dogs anesthetized with pentobarbital to have open-chest surgery. Intracoronary streptokinase, 6000 IU/kg in 3 ml saline solution, was infused at 0.05 ml/min for 1 hour, beginning 30 minutes after the formation of an occlusive thrombus. The animals were assigned randomly to two groups. In group I (n = 10) the intravenous infusion of vehicle was begun simultaneously with the intracoronary administration of streptokinase and continued for 2 hours after thrombolysis had been achieved. The animals in group II (n = 10) received intravenous CGS 13080 (1 mg/kg/hr) along with intracoronary streptokinase. Infarct size was assessed by a dual perfusion technique with Evans blue and triphenyltetrazolium stains to demarcate the normally perfused myocardium from the area at risk and the infarct zone within the risk region. The two groups did not differ with respect to baseline coronary blood flow, time to the development of coronary artery thrombotic occlusion, or time to achieve thrombolysis. Oscillations in coronary blood flow were more frequent in group I than in group II (group I, 9 ± 2.2; group II, 4.4 ± 0.8 oscillation/min × 100, $p < 0.05$ [mean ± SEM]). Reocclusion was observed more frequently in group I than in group II (8 of 10 [80%] vs 2 of 10 [20%], $p < 0.05$). Infarct size expressed as a percent of the total left ventricular mass was similar ([IZ/LV] group I, 5% ± 2%; group II, 4% ± 1%), as was the percent of the left ventricle dependent on the blood flow distribution from the left circumflex coronary artery or the area at risk of infarction ([AR/LV] 37% ± 2% vs 40% ± 3%, respectively). These results demonstrate that the thromboxane synthetase inhibitor CGS 13080, in combination with the thrombolytic agent streptokinase, is able to maintain patency of the injured coronary artery after thrombolysis and to decrease the frequency of oscillatory flow responses. The results suggest a possible role for thromboxane as a contributor to the process of thrombotic reocclusion after successful thrombolysis. (Am Heart J 1987;113:1345.)

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The early treatment of an evolving myocardial infarction with thrombolytic therapy, as with streptokinase, has become accepted.[1,2] The intracoronary administration of streptokinase provides an effective means of inducing thrombolysis, but the time frame for limiting irreversible myocardial injury and ultimate infarct size makes early intravenous administration of a thrombolytic agent a more practical approach to the preservation of the jeopardized myocardium.[3] Despite the success in affecting thrombolysis and myocardial reperfusion, reocclusion of the recanalized coronary artery is a frequent occurrence.[4] Failure to maintain coronary artery patency may result from continued platelet aggregation, coronary artery spasm, or "no reflow" in the distal region of the coronary vascular bed.[5] In an effort to maintain vessel patency, anticoagulation and antiplatelet drugs are generally accepted as important adjuncts to thrombolytic therapy.[6]

The selective thromboxane synthetase inhibitor CGS 13080 (imidazo [1,5-a] pyridine-5-hexanoic

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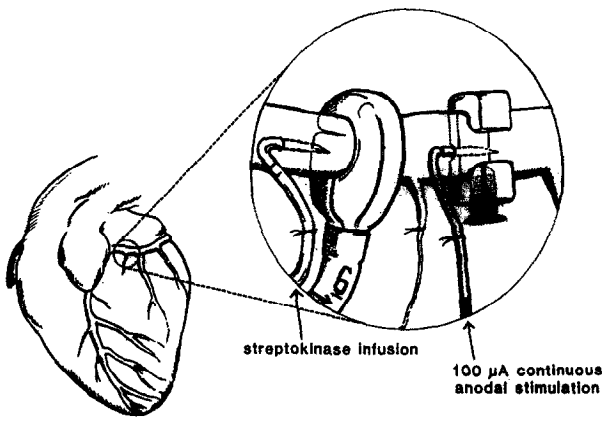

Fig. 1. Instrumentation of coronary artery. Proximal 2 cm of left circumflex coronary artery were isolated and instrumented proximal to distal (inset) with infusion cannula, electromagnetic flow probe, stimulation electrode, and screw occluder.

acid) may be an acceptable adjunct to thrombolytic therapy in view of the realization that thromboxane may play a role in facilitating platelet aggregation in response to vessel wall injury. CGS 13080 has been shown to inhibit thromboxane synthesis by platelets and to prolong the bleeding time.[7] These changes may be related to the ability of CGS 13080 to achieve a shunting of prostaglandin endoperoxide metabolism toward endogenous prostacyclin biosynthesis, as determined by the appearance of increased metabolic products (PGE_2, 6-keto PGI_{1a}, and the urinary metabolite, 2,3-dinor-6-keto PGF_{1a}[8,9]). In the in vivo setting the increased synthesis of prostacyclin may have significant coronary vasodilator and platelet antiaggregate properties that could serve to improve and maintain coronary blood flow after recanalization is established with a thrombolytic agent.

Infusion of CGS 13080 to anesthetized dogs undergoing open-chest surgery was effective in preventing coronary artery thrombus formation at the site of intimal injury.[10] This antithrombotic effect was accompanied by decreased ex vivo platelet aggregation after arachidonic acid stimulation and a marked decrease in thrombin-induced thromboxane B_2 generation in whole blood. CGS 13080 in venous whole blood of dogs also promotes endoperoxide shunting with increases in PGE_2 and 6-keto PGF_{1a}.[11] Both human and animal studies demonstrate that the selective thromboxane synthetase inhibitor CGS 13080 inhibits thromboxane production and enhances prostacyclin synthesis, suggesting that it may be effective in increasing vessel patency after streptokinase-induced thrombolysis. In the present study an experimental animal model of thrombosis-thrombolysis was employed, in which injury by electric stimulation of the intimal surface of the left circumflex coronary artery at the site of a moderate, fixed stenosis led to the development of an occlusive thrombus.[12] The results of this investigation demonstrate that the thromboxane synthetase inhibitor CGS-13080 reduced the frequency of rethrombosis and improved the pattern of coronary artery blood flow after successful recanalization of the thrombosed vessel with streptokinase.

METHODS

Thrombosis-thrombolysis myocardial injury. Twenty-seven male mongrel dogs (16 to 23 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously), 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, Mass.). The left carotid artery and internal jugular vein were exposed, and catheters were inserted for monitoring arterial pressure (Statham P23 DC pressure transducer, Gould Inc., Cardiovascular Products, Oxnard, Calif.) and infusion of drugs, 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 2 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, N.C.), stimulation electrode, adjustable mechanical occluder (Fig. 1). A Tygon catheter (0.03 cm, internal diameter) was attached to a 26-gauge hypodermic needle tip that was formed into a U shape and inserted into the proximal portion of the coronary artery and used as the intracoronary infusion cannula. The stimulation electrode was constructed from a 25-gauge hypodermic needle tip attached to a 30-gauge Teflon-insulated silver-coated copper wire. The mechanical occluder was constructed of stainless steel in a C shape with a Teflon screw (2 mm diameter), which could be manipulated to control vessel circumference. The occluder was adjusted to decrease the reactive hyperemic flow by 50% to 70% without affecting mean resting coronary blood flow. The small intervening coronary branches over the 1 to 2 cm segment were ligated.

Continuous recordings of blood pressure, left ventricular pressure, rate of rise in left ventricular pressure, lead II ECG, and mean and phasic left circumflex coronary artery blood flow were obtained on a model 7 polygraph (Grass Instrument Co., Quincy, Mass.). Zero flow and hyperemic flows were determined by occluding the circumflex coronary artery distal to the flow probe for 10 seconds. The flow probe was calibrated with heparinized whole blood. Thirty minutes after surgical preparation, a 100 μA continuous anodal direct current stimulation was initiated and maintained until the circumflex coronary artery blood

flow decreased to and remained at 0 ml/min for 30 minutes. The anodal direct current was delivered from a 9 V nickel-cadmium battery with the anode connected in series via a 250,000 Ω potentiometer to the intraluminal coronary artery electrode. The electric circuit was completed by placing the cathode in a subcutaneous site. At the time of thrombotic coronary artery occlusion, 30 mg of lidocaine hydrochloride was given intravenously, and the animal was observed for an additional 30 minutes, during which time blood flow in the left circumflex coronary artery remained at the predetermined calibrated point for zero flow. Intracoronary streptokinase (6000 IU/kg in 3 ml normal saline solution) was infused at a rate of 0.05 ml/min over a period of 60 minutes. Dogs were assigned randomly to two groups. In group I, 50 ml of vehicle (5% dextrose in water) was infused intravenously over 2 hours, beginning simultaneously with the intracoronary infusion of streptokinase. The animals randomly assigned to group II received CGS 13080 (imidazo [1,5-1] pyridine-5-hexanoic acid, Ciba-Geigy) 1 mg/kg/hr intravenously in 50 ml of vehicle while streptokinase was given via the intracoronary cannula. Two hours after reestablishing coronary artery reperfusion, the heart was fibrillated electrically and removed quickly for postmortem quantification of infarct size.

Only dogs that survived 2 hours after coronary artery reperfusion was established were included in the final data analysis. Six dogs fibrillated <30 minutes after coronary artery thrombosis and were not successfully resuscitated (fewer than three defibrillation attempts), 1 dog fibrillated during reperfusion with streptokinase alone and was not successfully resuscitated, and one dog fibrillated during streptokinase and CGS 13080 infusion and was successfully defibrillated.

Postmortem quantification of infarct size. Myocardial infarct size was quantified with 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 distribution was perfused with 1.5% triphenyltetrazolium hydrochloride in 20 mmol potassium phosphate buffer (pH 7.4, 38° C). The coronary ostia were perfused with 0.25% Evan's blue stain via the aortic cannula. Both the circumflex region and the remainder of the heart were perfused with the respective histochemical reagents at a constant pressure of 100 mm Hg for 5 minutes 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 because of its anatomic dependence on the circumflex coronary artery for blood flow was identified by the absence of Evan's blue stain. The region of infarcted myocardium within the area at risk was demarcated by the inability to react with triphenyltetrazolium hydrochloride and remained pale in color in contrast to the deep red coloration imparted by the formazan precipitate of the reduced tertazolium salt.[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 myocardium that had undergone irreversible injury. Ventricular sections were trimmed of right ventricular, valvular, and fatty tissue and were weighed. Infarct size was expressed as a 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]

Table I. Characteristics of coronary blood flow during thrombosis-thrombolysis myocardial injury

	*Group I**	*Group II**
Time to occlusion (min)	83 ± 14 (10)	73 ± 13 (10)
Time to reperfusion (min)	26 ± 6 (10)	21 ± 4 (10)
Time to reocclude (min)	17 ± 5 (8)	15 ± 15 (2)
Number reoccluded	8 (10)	2 (10)†
Oscillations/min (×100)	9.0 ± 2.2 (10)	4.4 ± 0.8 (10)†

Data are mean ± SEM.
*Number studied in parentheses.
†$p < 0.05$.

Reperfusion coronary blood flow. Mean left circumflex coronary blood flow, as determined by the extracorporeal electromagnetic flow probe, was plotted as a function of time during reperfusion at the following intervals: 0, 5, 10, 15, 20, 25, 30, 35, 60, 90, and 120 minutes. Oscillations in coronary blood flow, which occurred during reperfusion, appeared as cyclic decreases in mean blood flow to near zero flow, followed by abrupt increases in flow. These were quantitated by determining the number of oscillations per minute before flow decreased to zero, multiplying by the number of minutes (120), and arbitrarily multiplying the resulting number by 100.

Statistical analysis. The data are expressed as the mean ± SEM. Differences between the two groups were determined by Student's t test and were considered significant if $p < 0.05$. Differences within each group over time were determined by multiple pair wide comparisons (paired Student's t test) with an experimental alpha level of 0.05 (with Bonferroni's method).

RESULTS

Group characteristics. Twenty dogs were studied successfully in this thrombosis-thrombolysis model of myocardial injury (streptokinase + vehicle [group I, n = 10], streptokinase + CGS 13080 [group II, n = 10]). Despite randomization, there was a small difference in the weights of the dogs between the two groups (group I, 20.7 ± 0.6 kg; group II, 18.4 ± 0.6 kg; $p < 0.05$ [mean ± SEM]). There were no significant differences in recorded hemodynamic parameters (heart rate, left ventricular pressure, blood pressure, coronary blood flow) determined

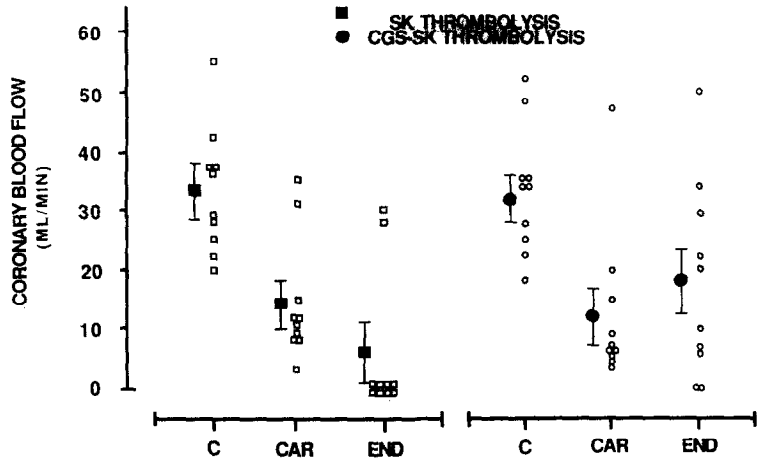

Fig. 2. Left circumflex coronary blood flow response. Blood flows were similar at baseline control *(C)* and decreased similarly 5 minutes after reperfusion *(CAR)* in both groups. However, 2 hours after reperfusion *(END)*, blood flow had improved in group II, streptokinase + CGS 13080 [1 mg/kg/hr (CGS-SK)], compared with group I, streptokinase + vehicle ($p < 0.05$). Data are mean ± standard error.

between the two groups at the beginning of the experiments.

Coronary artery thrombosis, thrombolysis, and rethrombosis. The mean time required for the development of a fully occlusive thrombotic lesion in the left circumflex coronary artery as a result of electrolytic injury to the intimal surface of the vessel did not differ significantly among the animals in each of the two groups: 83 ± 14 vs 73 ± 13 minutes in group I and group II, respectively. Coronary thrombolysis was achieved within a similar time frame in each of the dogs in groups I and II as a result of receiving streptokinase alone or in combination with CGS 13080. The time to achieve reperfusion was 26 ± 6 minutes for group I vs 21 ± 4 minutes for group II ($p > 0.05$).

Despite the efficacy of intracoronary streptokinase in achieving recanalization of the thrombosed circumflex coronary artery, reocclusion of the vessel occurred when the 1-hour infusion was completed, more frequently in the animals in group I (8 of 10, 80%) as compared with those in group II (2 of 10, 20%). The two dogs in group II, in which reocclusion did occur, did not differ from the group I dogs with respect to the time of reocclusion after discontinuing streptokinase (Table I).

Coronary Artery blood flow patterns. The development of an occlusive thrombus in the circumflex coronary artery resulted in a total and sustained reduction in blood flow (determined with an electromagnetic flow probe) in the distribution of the circumflex vessel. This was accompanied by discoloration of the myocardium in the region of distribution of the occluded vessel as well as ST-segment alterations in the lead II ECG consistent with the presence of acute myocardial ischemia and myocardial injury. Lysis of the occlusive thrombus was accompanied by a reactive hyperemia in the recorded blood flow. The restoration of blood flow in the circumflex coronary artery was associated with a reversal of cyanosis of the myocardium in the region of distribution of the vessel and the appearance of ECG changes showing restoration in the ST segment and the onset of reperfusion arrhythmias.

The control and resting circumflex coronary artery blood flows in each of the two groups, determined with an electromagnetic flow probe, were similar before the initiation of an occlusive thrombus. Once thrombolysis had been achieved, the coronary artery blood flows progressively decreased from the initial reperfusion value in group I, 14 ± 3.5 to 6 ± 3.8 ml/min, which was significantly lower than the coronary blood flow before thrombotic occlusion, 33 ± 3.5, $p < 0.001$. In group II the initial coronary artery blood flow on reperfusion was less than baseline, 12 ± 4 vs 32 ± 3.1 ml/min, $p < 0.05$, but improved steadily over the next 2 hours to 18 ± 5 ml/min (Fig. 2). The mean circumflex coronary artery blood flow in group II was greater than that in group I ($p < 0.05$) animals, which received only streptokinase, when the study was terminated 2 hours after the initial recanalization had been achieved.

The characteristic coronary artery blood flow patterns differed between the two groups of animals. The number of oscillations in the circumflex coronary artery blood flow were more frequent in the streptokinase treated group as compared with the

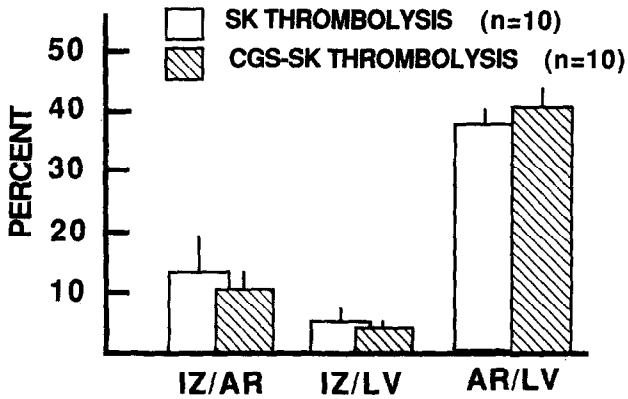

Fig. 3. Myocardial infarct size. Quantitation of infarct size is expressed with respect to infarct zone *(IZ)* as a percent of area of left ventricle at risk *(AR)* and as percent of total left ventricle *(LV)* after histochemical demarcation of respective myocardial regions. There was no difference in infarct size between the two groups: group I = streptokinase + vehicle *(SK)*, and group II = streptokinase + CGS 13080 (1 mg/kg/hr *[CGS-SK]*).

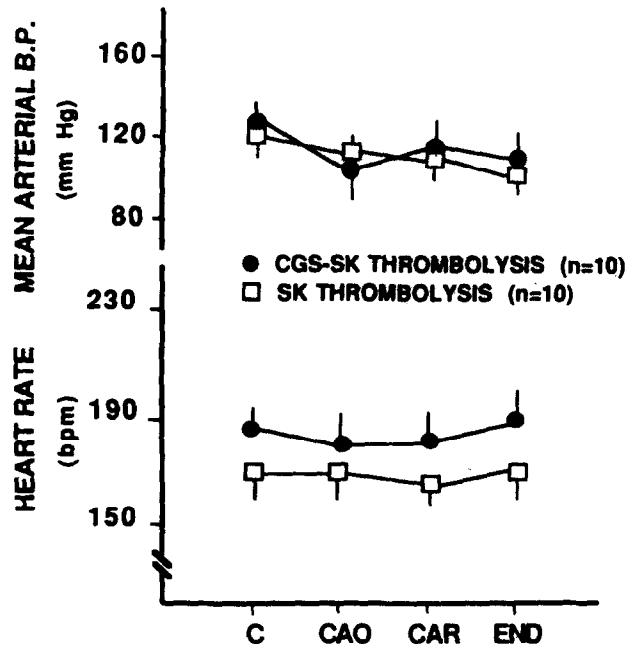

Fig. 4. Hemodynamic responses. Over the course of the experiment there was no difference in heart rate or mean arterial blood pressure between the two groups: group I = streptokinase *(SK)* + vehicle, and group II = streptokinase + CGS 13080 (1 mg/kg/hr *[CGS-SK]*). Time points are *C* = baseline control, *CAO* = 15 minutes after coronary artery occlusion, *CAR* = 5 minutes after initial reperfusion, *END* = 2 hours after initial reperfusion.

animals that received streptokinase along with CGS 13080 (Table I, $p < 0.05$). The increased incidence of oscillations correlated with an increased incidence of reocclusion. Two hours after initial recanalization had been achieved, only 2 of 10 dogs in group I as compared with 8 of 10 dogs in group II ($p < 0.05$) continued to manifest pulsatile flow recordings in the circumflex coronary vessel as determined with an electromagnetic flow probe placed proximal to the site of the external mechanical constrictor.

Effects of reperfusion on myocardial infarct size. The areas of the left ventricle at risk for infarction (AR/LV) were similar in the two groups, demonstrating that the anatomic dependence on the proximal circumflex coronary artery was similar (Fig. 3). The infarct sizes expressed as a percentage of the area at risk (IZ/AR) or as a percent of the total left ventricle (IZ/LV) were similar for the two groups. However, infarct size determined after 2 hours of reperfusion must be interpreted with caution.[17] In group I most coronary arteries had reoccluded less than 1 hour before determination of infarct size, and the extent of this second ischemic insult may not have been fully apparent. The increased incidence of reocclusion prolonged the total duration of the coronary artery blood flow deficit in the dogs in group I as compared with those in group II (Group I, 109 ± 9 minutes; group II, 52.5 ± 4 minutes; $p < 0.001$).

Hemodynamic responses. In both groups the main hemodynamic parameters (heart rate and blood pressure) remained essentially unchanged throughout the experiment (Fig. 4). The heart rate was slightly faster in group II before the induction of thrombosis (group I, 158 ± 9 vs group II, 174 ± 8; $p > 0.05$). The blood pressure was slightly lower in group II during the thrombotic occlusion, but by the end of the 2-hour reperfusion the blood pressure was slightly higher than group I (Group I, 115 ± 7 to 106 ± 7 mm Hg vs group II, 104 ± 14 to 112 ± 9 mm Hg; $p > 0.05$). None of the differences in the hemodynamic parameters at the recorded intervals varied significantly.

DISCUSSION

Maintenance of thrombolysis. The intracoronary infusion of streptokinase, beginning 30 minutes after thrombotic occlusion, was effective in reestablishing left circumflex coronary artery blood flow within 30 minutes in each of the 20 animals included in this study. During the 2-hour reperfusion period, despite initial thrombolytic therapy, mean coronary blood flow was significantly less than the baseline flows in each of the groups. Furthermore, coronary blood flow in the recanalized vessel declined progressively in the group I animals compared with those in group II. This observation would suggest that the ability to maintain and autoregulate coronary artery blood flow in the stenosed, recanalized

vessel was benefited by the addition of CGS 13080 to the thrombolytic regimen.

Frequent oscillations in coronary blood flow occurred in 8 of the 10 dogs in group I that had undergone successful coronary artery thrombolysis and that had reocclusion early after discontinuation of the intracoronary administration of streptokinase. Although streptokinase was effective initially in restoring myocardial blood flow, it did not alter the thrombogenic potential of the injured vascular endothelial surface. Thus reocclusion of the injured vessel was common among the animals in group I and was preceded by frequent oscillations in coronary artery blood flow. The repetitive oscillatory events might indicate the persistence of platelet aggregation, enhanced vasomotor activity, or intermittent occurrences of the no reflow phenomenon in the distal coronary vascular bed.

The administation of the thromboxane synthetase inhibitor CGS 13080 was associated with an overall enhancement in the coronary artery blood flow throughout the period of observation, after having achieved thrombolysis. Most important was the finding that the administration of CGS 13080 prevented reocclusion in 8 of 10 dogs that had been recanalized with streptokinase, as opposed to the animals in group I, in which only 2 of 10 dogs were capable of maintaining vessel patency for the duration of the study protocol.

Possible mechanism for the beneficial effect of CGS 13080. Thromboxane synthetase inhibitors have permitted the transfer of platelet-derived prostaglandin endoperoxides to endothelial cells for the synthesis of prostacyclin.[18,19] The synthesis of prostacyclin from platelet-derived endoperoxides has been demonstrated by incubating platelets with endothelial cell cultures treated with aspirin so as to inhibit the endogenous formation of prostanoids by the cultured cells.[20] Furthermore, the transfer of cyclic endoperoxides is unidirectional; i.e., reciprocal transfer of the endoperoxides from endothelium to platelets does not result in thromboxane A_2 production.[21] It is hypothesized that the inhibition of platelet thromboxane synthetase by CGS 13080 would provide additional amounts of the endoperoxides to serve as substrate for the synthesis of prostacyclin by other cells, i.e., endothelial cells and leukocytes. Experimental support for this conclusion has been provided recently by Mehta et al.[11] who demonstrated the production of prostacyclin by neutrophils in the presence of platelets and thromboxane synthetase inhibition by CGS 13080. In our laboratory, Simpson et al.[10] have demonstrated that the addition of CGS 13080 to collagen-activated whole blood in vitro leads to a marked increase in prostacyclin metabolites 6-keto PGF_{1a} and PGE_2 and decreased thromboxane B_2 production compared with blood samples with no thromboxane synthetase inhibitor. Furthermore, they found that thrombin-stimulated thromboxane generation in whole blood was prevented with CGS 13080 (control, 46.7 ± 18.2 ng/ml [n = 10]; CGS 13080, 1.7 ± 0.7 ng/ml [n = 10]; $p < 0.05$).

It is proposed that the beneficial effect of CGS 13080 in reducing the frequency of the oscillatory coronary artery flow pattern and in maintaining coronary artery blood flow after thrombolysis may be related to an enhancement of regional prostacyclin synthesis by the vascular endothelium as a result of endoperoxide shunting localized to the vascular site, at which the residual thrombus mass remains adherent to the injured vessel wall. The establishment of a "microenvironment" formed by the blood cells that constitute the thrombus mass at the interface, where the thrombus attaches to the vessel wall, provides an opportunity for maximal exchange of platelet endoperoxides with other cells in the thrombus and with the surviving endothelial cells. The resulting synthesis of prostacyclin and perhaps other prostanoids would affect the ability of the residual thrombus mass from serving as a nidus for the continued formation of the occlusive lesion and reocclusion of the vessel.

Prostacyclin may reduce the potential for thrombus formation by several different mechanisms. It causes disaggregation of aggregated platelets by increasing platelet cyclic adenosine monophosphate (cAMP). Thromboxane synthetase inhibition alone does not change platelet cAMP concentrations, whereas thromboxane A_2 decreases cAMP and results in platelet activation. Inhibition of thromboxane synthetase alone would not be expected to prevent platelet aggregation by stimuli that can directly alter platelet cAMP (collagen, adenosine diphosphate). Futhermore, thromboxane synthetase inhibition would not promote cAMP-dependent disaggregation.[9,10] Another known effect of prostacyclin on platelet function is to inhibit platelet prothrombinase activity.[22] In the absence of prothrombinase, the conversion of prothrombin to thrombin would not occur, thereby impairing the conversion of fibrinogen to fibrin. The net result is to alter the formation and stabilization of an organized thrombus mass capable of occluding the injured blood vessel.

Among the reported actions of prostacyclin is a profibrinolytic action leading to the release of plasminogen activator. In patients with peripheral vas-

cular disease, prostacyclin caused release of tissue plasminogen activator and a shortened euglobulin lysis time.[23] When the actions of prostacyclin are viewed together, the prostanoid predominantly inhibits the coagualtion cascade.

Despite the duration of coronary artery occlusion being different in groups I and II, infarct size in the two groups did not differ significantly. The initial occlusion time included the 30-minute period allowed in the protocol for stabilization of the occlusive thrombus, plus the time necessary for streptokinase-induced reperfusion to be established. Because there were few reocclusions in group II, this was the total occlusion time for dogs receiving CGS 13080 in addition to streptokinase. In group I, streptokinase alone, 80% of the coronary arteries reoccluded, resulting in a significantly greater total occlusion time. Infarct size assessed by the dual perfusion technique with Evan's blue stain and triphenyltetrazolium 1 hour after reocclusion may have underestimated the total extent of irrversible injury when only streptokinase was infused. The time necessary for detection of infarction by tetrazolium, while often a subject of controversy, may be as short as 2 hours in the presence of regional reperfusion.[17, 24] In the group that received streptokinase plus CGS 13080, 80% of the recanlized vessels remained patent. We did not observe a difference between the two groups with respect to ultimate infarct size, which may be related to the fact that the duration of regional myocardial ischemia was not of sufficient duration to permit full expression of damage in the risk region, thereby limiting our ability to detect significant differences between the two treatment groups. Furthermore, the determination of infarct size reduction in either of the groups may have been made difficult by virture of the fact that both CGS 13080 and streptokinase may be able to protect the ischemic myocardium against the development of irreversible injury. Burke et al.[25] found that plasma creatine kinase concentrations and myocardial creatine kinase depletion in the infarct zone were reduced when CGS 13080 was infused during left anterior descending coronary artery ligation in cats. In several experimental models, streptokinase, independent of its thrombolytic activity, had positive effects on the globally ischemic myocardium and prevented the decrement in left ventricular function.[26, 27]

Of interest are the recent studies by Mehta et al.,[11] describing CGS 13080 as having activity that inhibits its thromboxane production and allows neutrophils to form prostacyclin from the platelet-derived cyclic endoperoxides. Prostacyclin has also been shown to limit infarct size by inhibition of neutrophil activation.[28] These are relevant issues, since limitation of infarct size, when reperfusion is induced by thrombolytic therapy, will probably require an agent that can mitigate the accelerated inflammatory response. Reperfusion of ischemic myocardium is accompanied by a neutrophil infiltration that may be a major contributor to the development of myocardial necrosis. Thus the selective thromboxane synthetase inhibitor CGS 13080 has several clinically appealing properties. It may limit reperfusion injury by shunting neutrophil prostanoid metabolism toward prostacyclin production, thereby modulating the damaging effect of the neutrophils infiltrating ischemic myocardium. In addition, CGS 13080 stabilizes and maintains regional myocardial blood flow by maintaining vessel patency during reperfusion after streptokinase-induced thrombolysis of a coronary artery thrombotic occlusion, despite the continued presence of a vessel wall lesion and nonobstructive thrombus mass.

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