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Does Antiplatelet Therapy Enhance Myocardial Salvage After Coronary Reperfusion?

YI SHI, MD, ANDREW ZALEWSKI, MD, PAUL WALINSKY, MD, SHELDON GOLDBERG, MD

Philadelphia, Pennsylvania

The aim of this study was to test the hypothesis that either the cyclooxygenase inhibitor aspirin or the thromboxane A_2 receptor antagonist sulotroban exerts a direct myocardial effect that enhances myocardial salvage afforded by reperfusion. Accordingly, 21 anesthetized dogs underwent suture occlusion of the left anterior descending coronary artery. At 2.5 h after occlusion, all dogs received intravenous streptokinase (20,000 U/kg body weight over 30 min) and were randomized to the following groups: group I (n = 7) received no additional treatment, group II (n = 7) received aspirin (5 mg/kg intravenously) and group III (n = 7) received sulotroban (10 mg/kg followed by 10 mg/kg per h intravenously). At 3 h after occlusion, the dogs underwent coronary reperfusion for the next 3 h.

Myocardial infarct size as a percent of the hypoperfused zone was similar among dogs in group I (42 ± 8%), group II (41 ± 10%) and group III (45 ± 11%). The incidence and the extent of myocardial hemorrhage were similar in all three study groups. Infarct size as a percent of the hypoperfused zone was significantly smaller in dogs without hemorrhage irrespective of treatment (35 ± 9% versus 63 ± 5%, $p < 0.01$).

In conclusion, 1) in the presence of 3 h coronary occlusion and reperfusion, neither a cyclooxygenase inhibitor nor a specific thromboxane A_2 receptor antagonist enhanced myocardial salvage by means of a direct myocardial effect as compared with reperfusion alone; 2) any potential benefits of combined thrombolytic and antiplatelet therapy are likely to be limited to their vascular effects (for example, reperfusion efficacy and prevention of reocclusion); and 3) myocardial hemorrhage may limit myocardial salvage afforded by coronary reperfusion.

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Recent interest in thrombolytic therapy for acute myocardial infarction raised the possibility that myocardial salvage after coronary artery reperfusion could be enhanced by adjunctive pharmacologic therapy. This concept was supported by the findings of the International Study of Infarct Survival (ISIS-2) Trial (1), which showed a reduction in early mortality rates in patients with suspected myocardial infarction treated with a combination of streptokinase and aspirin. These results could be related to 1) an increased reperfusion efficacy, 2) a reduced reocclusion rate, 3) an effect on the microvasculature in the reperfused zone, or 4) a direct myocardial effect of combined therapy.

Platelets are a major component of occlusive coronary thrombus (2,3). In addition, they accumulate in the infarcting myocardium (4), and the platelet-derived mediator thromboxane A_2 is a potent vasoconstrictor, platelet aggregator and membrane lytic agent (5,6). Accordingly, agents that affect platelet aggregation or thromboxane A_2 metabolism, or both, have been extensively studied in various models of myocardial ischemia (7–14). However, little attention has been given to their additive effects on myocardial salvage in the presence of successful thrombolytic therapy.

The goal of this study was to evaluate a direct myocardial effect of the cyclooxygenase inhibitor aspirin and the thromboxane A_2 receptor antagonist sulotroban (15,16) on myocardial infarct size in the presence of coronary artery reperfusion. Specifically, the effect of these interventions on infarct size and myocardial hemorrhage in combination with the thrombolytic agent streptokinase was studied independent of their effect on clot lysis at the site of coronary occlusion.

Methods

Experimental preparation. Twenty-five dogs were anesthetized with sodium pentobarbital (30 mg/kg body weight intravenously), intubated endotracheally and ventilated with

From the Division of Cardiology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

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Address for reprints: Andrew Zalewski, MD, Cardiac Catheterization Laboratory, Room 5611, Thomas Jefferson University Hospital, 111 South 11th Street, Philadelphia, Pennsylvania 19107.

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room air using a volume respirator (Harvard Apparatus). Systemic arterial pressure (Statham P23Db pressure transducer) and electrocardiographic (ECG) lead aVF were recorded continuously throughout the 6 h experiments on a polygraph (Gould Instruments). A thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free from the adjacent tissue proximal to the major branches. A 2-0 silk suture was placed around the left anterior descending coronary artery. The experiments performed conform to the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984 by the American Heart Association.

Protocol. Thirty minutes after completion of all surgical procedures, the left anterior descending coronary artery was occluded using a silk suture. One minute after occlusion, 2×10^6 (12 mCi) of techetium-99m–labeled albumin microspheres were injected into the left atrium through a polyethylene cannula for subsequent assessment of the hypoperfused zone (that is, risk area) (17,18). At 2.5 h after coronary occlusion, all dogs received intravenous streptokinase (20,000 U/kg over 30 min; Hoechst-Roussel) and were randomized to the following groups: group I (n = 10), control dogs that received no additional treatment; group II (n = 7), dogs that received aspirin (5 mg/kg intravenously as a bolus injection); and group III (n = 7), dogs that received sulotroban, a specific thromboxane A_2 receptor antagonist (10 mg/kg intravenously followed by infusion of 10 mg/kg per h; Smith Kline & French Laboratories).

After completion of the streptokinase infusion (that is, at 3 h), reperfusion was carried out by release of the occlusion. Six hours after occlusion (that is, 3 h after reperfusion), the dogs were killed with an intravenous injection of potassium chloride, and the heart was excised. The left ventricle was then removed, frozen at −70°C and cut into 3 mm thick slices from the apex to the site of occlusion.

Data analysis. Infarct size and hypoperfused zone were calculated by planimetry after incubation of the left ventricular slices with triphenyltetrazolium chloride and after autoradiography, respectively, according to the technique described previously (17–19). In each dog, the following variables were calculated: 1) percent of cross-sectional areas of the slices of the left ventricle that showed myocardial necrosis; 2) percent of cross-sectional areas of the slices of the left ventricle that was initially (1 min after occlusion) hypoperfused as determined by autoradiography ("cold spot"); 3) percent of hypoperfused zone that evolved to infarction (this method expressed infarct size as a percent of the hypoperfused zone in each dog and was used to examine whether the intervention was effective in salvaging myocardial cells); and 4) extent of gross myocardial hemorrhage, as determined by planimetry and graded in a semiquantitative fashion as follows: grade 0 = no gross hemorrhage, grade 1+ = hemorrhage ≤10% of the hypoperfused zone, grade 2+ = hemorrhage ≤20% of the hypoperfused zone, and grade 3+ = hemorrhage ≤30% of the hypoperfused zone.

Four dogs were excluded from the study because of inadequate autoradiography (three from group I and one from group III). Thus, seven dogs in each study group were included for final analysis.

Statistical analysis. Results were expressed as mean values ± SEM. Analysis of variance (ANOVA) was used for comparisons between control dogs and dogs treated with either aspirin or sulotroban. The Fisher exact test was used to evaluate the incidence of myocardial hemorrhage in the study groups. A p value <0.05 was considered significant.

Results

To verify whether the control and treated groups were comparable before intervention, heart rate and mean arterial pressure were analyzed. Accordingly, at the time of randomization but before the interventions were begun, heart rate was 90 ± 6, 110 ± 7 and 103 ± 9 beats/min in the control, aspirin and sulotroban groups, respectively (p = NS). At the time of randomization, mean arterial pressure was 106 ± 4, 117 ± 5 and 112 ± 5 mm Hg in the control, aspirin and sulotroban groups, respectively (p = NS, Table 1).

Analysis of the extent of myocardial damage. The hypoperfused zone was 26 ± 3%, 27 ± 2% and 32 ± 3% of the left ventricle in the control, aspirin and sulotroban groups, respectively (p = NS). Infarct size was 12 ± 3%, 12 ± 3% and 15 ± 4% of the left ventricle in the control, aspirin and sulotroban groups, respectively (p = NS). The percent of the hypoperfused zone that evolved to infarction was 42 ± 8%, 41 ± 10% and 45 ± 11% in the control, aspirin and sulotroban groups, respectively (p = NS) (Fig. 1).

Myocardial hemorrhage. Gross myocardial hemorrhage occurred in two dogs in each study group. The grades for the extent of hemorrhage were 3, 3 and 4 in the control, aspirin and sulotroban groups, respectively (p = NS). Thus, there was no significant difference in the incidence and extent of myocardial hemorrhage in the aspirin and sulotroban groups compared with the control group. The ratio of infarct size to hypoperfused zone was 63 ± 5% in dogs with myocardial hemorrhage (n = 6) versus 35 ± 9% ($p < 0.01$) in those without hemorrhage (n = 15) despite a comparable hypoperfused zone in both groups (Fig. 2).

Hemodynamics. There were no significant differences in systolic, diastolic and mean arterial pressure among the control, aspirin and sulotroban groups before and after coronary artery occlusion and after reperfusion. The heart rate in the aspirin group was faster ($p < 0.05$) 4 h after occlusion compared with that in the control group (Table 1).

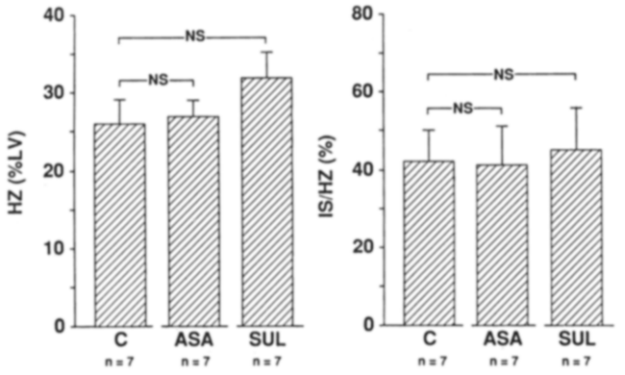


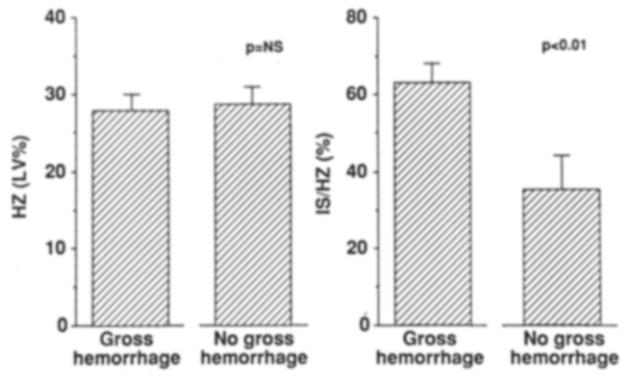
Figure 1. Left panel, Extent of the hypoperfused zone (HZ) expressed as a percent of the left ventricle (%LV). The extent of the hypoperfused zone was similar in the three study groups. **Right panel,** Infarct size (IS) expressed as a percent of the hypoperfused zone (HZ). Values were similar in the three study groups. C = group I control dogs that received streptokinase intravenously; ASA = group II dogs that received streptokinase and aspirin intravenously; SUL = group III dogs that received streptokinase and sulotroban intravenously.

Discussion

Our findings indicate that neither the cyclooxygenase inhibitor aspirin nor the thromboxane A_2 receptor antagonist sulotroban directly enhances myocardial salvage in an occlusion-reperfusion model.

Effects of antiplatelet agents on myocardial ischemia. *Aspirin.* The cyclooxygenase inhibitor aspirin and the thromboxane A_2 receptor antagonists have been shown to abolish spontaneous cyclic reductions in coronary flow that are associated with platelet aggregation at the site of critical coronary artery stenosis (20–22). This concept provided the rationale for the widespread use of aspirin in patients undergoing thrombolytic therapy for myocardial infarction. The goal was to enhance clot lysis or prevent sudden coronary reocclusion, or both. The role of aspirin in myocardial infarction independent of its effect on coronary thrombus is more controversial. Aspirin has been found to reduce the extent of myocardial necrosis induced by epinephrine infusion, which is associated with increased platelet aggregation (23). Furthermore, aspirin reduced the incidence of ventricular fibrillation in dogs after coronary artery occlusion (4,24). Although aspirin increased collateral flow to the border of ischemic regions in some studies (25,26), its effect on infarct size has not been uniformly demonstrated. Ogletree and Lefer (27) found no changes in either creatine kinase release or ST segment elevation after permanent coronary artery occlusion in cats pretreated with aspirin. Bonow et al. (26) demonstrated that aspirin failed to reduce infarct size in dogs despite inhibition of platelet aggregation and a significant increase in collateral flow. It could be postulated that the lack of effect of aspirin on infarct size was related to the inhibitory effect of aspirin on endothelial cell cyclooxygenase and a decrease in prostacyclin production.

Figure 2. Left panel, Comparable size of the hypoperfused zone (HZ) expressed as a percent of the left ventricle (LV%) in dogs with (28 ± 2%) and without (29 ± 3%) gross myocardial hemorrhage. **Right panel,** Significantly larger infarct size/hypoperfused zone (IS/HZ) ratio was found in the presence of myocardial hemorrhage, indicating less myocardial salvage.



Thromboxane A_2 receptor antagonists. More recently, thromboxane A_2 synthetase inhibitors and thromboxane A_2 receptor antagonists have been developed. Theoretically, the latter group of agents may be more advantageous than cyclooxygenase inhibitors in treating myocardial ischemia because thromboxane A_2 receptor antagonists do not decrease prostacyclin production. Furthermore, they do not result in accumulation of endoperoxide intermediates, which may have a deleterious effect on the ischemic myocardium (28). Different thromboxane A_2 receptor antagonists have been shown to reduce infarct size after permanent coronary artery occlusion (29–31); in those studies, sulotroban was found to reduce the decrease in myocardial creatine kinase activity in the ischemic myocardium if the intervention was started early (15 to 30 min) after coronary occlusion and no reperfusion was carried out. In addition, Osborne and Lefer (32) suggested that long-term therapy with a thromboxane A_2 receptor antagonist may have an antiatherogenic effect in atherosclerotic rabbits. Our study showed that in a 3 h occlusion-reperfusion model, neither a cyclooxygenase inhibitor nor a specific thromboxane A_2 receptor antagonist afforded additional myocardial salvage compared with reperfusion alone. These results differ from studies by others (33,34) who reported a further reduction in infarct size after thromboxane A_2 receptor antagonist administration in the presence of coronary reperfusion.

Effects of thromboxane A_2 antagonists on myocardial salvage: comparison with previous studies. There are several reasons that may account for these observed differences. First, the duration of ischemia was 3 h in our study as opposed to only 90 min in the studies by Grover et al. (33) and Bhat et al. (34). It is conceivable that the thromboxane A_2 receptor antagonist and reperfusion therapy have an additive effect on myocardial salvage only in the very early

Table 1. Heart Rate (beats/min) and Mean Arterial Pressure (mm Hg) in 21 Dogs

	Before Coronary Occlusion		After Coronary Occlusion				During Infusion		Reperfusion			
			15 min		2 h 30 min		2 h 45 min		4 h		6 h	
	HR	$\overline{AP}$	HR	$\overline{AP}$	HR	$\overline{AP}$	HR	$\overline{AP}$	HR	$\overline{AP}$	HR	$\overline{AP}$
SK (group I, n = 7)	103 ± 12	108 ± 8	115 ± 8	101 ± 8	90 ± 6	106 ± 4	82 ± 7	99 ± 5	103 ± 5	98 ± 5	125 ± 10	93 ± 3
SK + ASA (group II, n = 7)	105 ± 4	102 ± 7	107 ± 7	97 ± 9	110 ± 7	117 ± 5	88 ± 7	103 ± 7	134 ± 24	86 ± 4	128 ± 7	80 ± 4
SK + SUL (group III, n = 7)	94 ± 14	107 ± 5	117 ± 11	104 ± 4	103 ± 9	112 ± 5	98 ± 13	109 ± 7	117 ± 9	90 ± 9	130 ± 10	86 ± 9
p value	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS

*$p < 0.05$ streptokinase versus streptokinase + aspirin. All results are mean values ± SEM. $\overline{AP}$ = mean arterial pressure; ASA = aspirin; HR = heart rate; SK = streptokinase; SUL = sulotroban.

stages of myocardial infarction. We chose a period of 3 h of occlusion followed by reperfusion, with aspirin or sulotroban started at 2.5 h after occlusion, because this interval more closely corresponds to the clinical setting. In addition, in our study, streptokinase was administered before reperfusion to simulate thrombolytic therapy in patients with myocardial infarction. It has been reported (35) that streptokinase enhances platelet activation and thromboxane A_2 synthesis, which may result in reocclusion, thereby providing the rationale for antiplatelet therapy. Second, species differences may account for different results (for example, Bhat et al. (34) used a feline model of coronary occlusion and reperfusion as opposed to the canine model used in our study). However, species differences seems an unlikely explanation, because sulotroban in the dose used in our study effectively inhibited platelet aggregation in the canine model (36). Third, the lack of enhanced myocardial salvage could be attributed to exacerbation of myocardial hemorrhage after combined therapy with antiplatelet and thrombolytic agents after reperfusion. Our study, however, showed a comparable incidence and severity of gross myocardial hemorrhage in the control group (which received only streptokinase) and groups treated with combined therapy. Interestingly, myocardial salvage was limited in dogs with gross myocardial hemorrhage irrespective of treatment. In addition, the lack of enhanced myocardial salvage in groups treated with the cyclooxygenase inhibitor and the thromboxane A_2 receptor antagonist in our study could not be explained on the basis of differences in myocardial oxygen consumption between the treated and control groups.

Thus, our study did not demonstrate enhanced myocardial salvage with antiplatelet therapy after 3 h of coronary occlusion and reperfusion, an interval that is more relevant to the clinical setting as opposed to shorter periods of ischemia studied previously (33,34). In addition, although myocardial hemorrhage limited myocardial salvage, the combination of thrombolytic and antiplatelet agents did not increase the incidence of myocardial hemorrhage.

Limitation of the study. Platelet aggregation was not evaluated in this study. However, it has been previously shown that comparable doses of aspirin and sulotroban exerted a marked antiaggregatory effect on canine platelets (26,36). Because inhibition of platelet activation and thromboxane A_2 synthesis is thought to exert beneficial effects on ischemic myocardium, it is unlikely that a different dosing regimen would result in enhanced myocardial salvage. However, this study does not preclude an important effect of antiplatelet agents on establishing or maintaining coronary artery patency. There is ample evidence (7,22) that agents affecting thromboxane A_2 synthesis or its receptor antagonists prevent platelet accumulation at the site of high grade coronary artery stenosis. In addition, these agents may facilitate coronary reperfusion and reduce the risk of reocclusion when combined with thrombolytic agents (36). These effects, rather than a direct myocardial effect, may result in enhanced myocardial salvage when the combination of antiplatelet and thrombolytic agents is administered.

Conclusions. 1) In the presence of successful reperfusion, neither the cyclooxygenase inhibitor aspirin nor the specific thromboxane A_2 receptor antagonist sulotroban enhanced myocardial salvage by means of a direct myocardial effect. 2) Any potential benefits of combined thrombolytic and antiplatelet therapy are likely to be limited to their vascular effects (for example, increased reperfusion efficacy or reduced reocclusion rate, or both). 3) Myocardial hemorrhage may limit myocardial salvage afforded by coronary reperfusion.

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