Myocardial protection during transient coronary artery occlusion in man: beneficial effects of regional \(\beta\)-adrenergic blockade

ANDREW ZALEWSKI, M.D., SHELDON GOLDBERG, M.D., JOHN P. DERVAN, M.D., SONYA SLYSH, M.D., AND PETER R. MAROKO, M.D.

ABSTRACT The goal of this study was to verify whether myocardial protection could be achieved via the intracoronary administration of propranolol in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Accordingly, 21 patients undergoing PTCA were randomly assigned to receive either intracoronary placebo (group A, \(n = 10\)) or intracoronary propranolol (group B, \(n = 11\)). Three balloon inflations (i.e., coronary artery occlusions) were performed in each patient. Inflations I and II (maximum duration 60 sec) served as control occlusions. Inflation III (maximum duration 120 sec) was performed either after intracoronary administration of saline (2 ml) or propranolol (1.1 ± 0.2 mg). The following electrocardiographic index of myocardial ischemic injury were measured: (1) time to the development of ST segment elevation equal to 0.1 mV and (2) magnitude of ST segment elevation after 60 sec of coronary artery occlusion. Both indexes did not differ significantly between the groups during inflations I and II. In group A the time to development of ST segment elevation of 0.1 mV remained unchanged between the second and third occlusions (25 ± 5 and 26 ± 4 sec during inflations II and III, respectively). In group B subselective injection of propranolol into the affected coronary artery significantly prolonged the time to ST segment elevation of 0.1 mV from 19 ± 4 sec (inflation II) to 53 ± 9 sec (inflation III; \(p < .001\)). Administration of placebo did not change the magnitude of ST segment elevation 60 sec after coronary artery occlusion between the second and third occlusion in group A (0.16 ± 0.02 and 0.18 ± 0.03 mV, respectively). In group B, after intracoronary administration of propranolol, ST segment elevation 60 sec after occlusion decreased significantly from 0.23 ± 0.06 mV (inflation II) to 0.12 ± 0.04 mV (inflation III; \(p < .005\)). There were no significant differences in heart rate and mean aortic pressure between groups A and B during inflations I, II, and III. In conclusion, our results suggest that (1) repetitive episodes of transient coronary artery occlusion are associated with similar degrees of myocardial ischemic injury, (2) intracoronary propranolol significantly reduces the electrocardiographic indexes of myocardial ischemic injury, and (3) the myocardial protection afforded by intracoronary propranolol is most likely mediated by a regional effect of the drug.

Circulation 73, No. 4, 734–739, 1986.
ischemic injury in the first minutes after occlusion. In addition, the effects of potential therapeutic interventions aimed at reducing ischemic injury during interruption of coronary blood flow can be assessed in this controlled setting.

Accordingly, the goal of this study was to verify whether the electrocardiographic indexes of transmural myocardial ischemia could be ameliorated by intracoronary administration of propranolol in patients undergoing PTCA.

Methods

Patients. Ninety-seven consecutive patients undergoing PTCA of coronary artery stenosis were evaluated for this study. The patients entered the study when the following criteria were met: (1) myocardial ischemic injury occurred during the first balloon inflation (myocardial ischemic injury was defined in this study as ST segment elevation of 0.1 mV or more during 60 sec of coronary artery occlusion) and (2) the resting electrocardiogram showed normal sinus rhythm with a QRS complex duration of less than 0.12 sec.

Twenty-one patients, aged 37 to 72 years, met the entry requirements for the study. All patients were in New York Heart Association functional class III or IV and had objective evidence of ischemia obtained from noninvasive testing (resting electrocardiogram or treadmill exercise test combined with thallium-perfusion imaging). All underwent angioplasty of a coronary artery stenosis for persistence of anginal symptoms despite intense medical therapy with nitrates, β-adrenergic blockers, and calcium-channel antagonists. The drugs were stopped 12 hr before PTCA.

Angioplasty procedure. All patients underwent PTCA in the postabsorptive state and were sedated with diazepam (5 to 10 mg) and diphenhydramine (50 mg). PTCA was performed by the percutaneous transluminal technique as previously described.12 Inform consent was obtained for each patient in the study. The use of multiple balloon inflations is part of our routine PTCA protocol. All patients received 200 μg of intracoronary nitroglycerin before dilatation regardless of further randomization. Three electrocardiographic leads were monitored throughout the study. Each lead was calibrated before the procedure (10 mm = 1 mV). Two of three electrocardiographic leads reflected the potentially ischemic region of the myocardium. The following combinations of leads were used: V3, V4, and limb lead II in patients with left anterior descending coronary artery stenoses; V4 or AVL, and V2 in patients with left circumflex coronary artery stenoses; III, AVF, and V5 in patients with right coronary artery stenoses. Mean aortic pressure obtained through the guiding catheter was monitored continuously during the procedure. These variables were recorded continuously on a polygraph (Electronics for Medicine, Model VR-12) with a paper speed of 25 mm/sec.

Protocol. All 21 patients who demonstrated ST segment elevation of 0.1 mV during the first balloon occlusion underwent three balloon inflations and formed the study group. Each balloon inflation was initiated at least 60 sec after the last dye injection to minimize the effect of radiographic contrast medium on the electrocardiogram. The time between inflations varied from 2 to 5 min. Inflations I and II served as control inflations and were maintained for a maximum of 60 sec. Just before inflation III the patients were randomly assigned to receive placebo (group A, n = 10) or propranolol (group B, n = 11). Randomization was performed by an investigator not involved in the catheterization procedure. Therefore the nature of the injectate (i.e., propranolol or placebo) was not known to the investigators performing the procedure. In patients assigned to group A, 2 ml of 0.9% NaCl (placebo) was injected into the coronary artery through the dilatation catheter whose distal tip was positioned across the stenosis. In patients assigned to group B, propranolol hydrochloride (Ayerst Laboratories, Inc., New York), 0.5 to 2.0 mg (1.1 ± 0.2 mg, mean ± SEM), was injected into the coronary artery through the dilatation catheter positioned across the stenosis. Therefore the injectate was always delivered directly into the region of myocardium supplied by the coronary artery undergoing dilatation. Inflation III was performed 2 min after the intracoronary injections of propranolol or placebo. This inflation continued for a maximum of 120 sec. During any one of the occlusions, the balloon was deflated when significant chest pain or ST segment elevation exceeding 0.3 mV occurred. In one patient, inflation II was excluded from further analysis because inflation pressure was not comparable to that of inflations I and III. In two other patients, only inflations II and III were analyzed because of the inadequate quality of the electrocardiographic tracings during inflation I.

Data analysis. The following electrocardiographic indexes of myocardial ischemia were measured in each patient: (1) time (sec) to development of ST segment elevation equal to 0.1 mV and (2) magnitude (mV) of ST segment elevation after 60 sec of balloon inflation. The ST segment elevations were measured at the J point, with the TP interval considered to be the isoelectric line.

Heart rate and mean aortic pressure were measured during the three consecutive inflations at the time of ST segment elevation equal to 0.1 mV.

Statistical analysis. Student’s paired t test was used for comparisons within the groups. Comparisons between groups were made with Student’s t test for group observations. The results were expressed as means ± SEM.

Results

Clinical characteristics of the patients. The characteristics of the groups assigned to placebo (group A) and propranolol (group B) are listed in table 1. The average ages and severity of coronary artery disease in the groups were similar. There was no angiographic evi-

<table>
<thead>
<tr>
<th>Clinical characteristics of the study group (mean ± SEM)</th>
<th>Group A (n = 10)</th>
<th>Group B (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>51–72</td>
<td>37–69</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/1</td>
<td>9/2</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vessel undergoing PTCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>LCX</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>RCA</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Severity of stenosis before PTCA (%)</td>
<td>94 ± 1</td>
<td>91 ± 2</td>
</tr>
<tr>
<td>Severity of stenosis after PTCA (%)</td>
<td>26 ± 1</td>
<td>34 ± 3</td>
</tr>
</tbody>
</table>

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.
idence of collateral circulation in the study group. Ejection fraction was 66 ± 4% in group A and 66 ± 6% in group B (NS). One patient from group A and three patients from group B had a positive history of myocardial infarction. Segmental hypokinesia within the distribution of the vessel undergoing dilatation was seen in four patients from group A and in three patients from group B. PTCA of the left anterior descending coronary artery was performed in 19 patients. In the remaining two patients, the left circumflex coronary artery (one patient) and the right coronary artery (one patient) were dilated. Before PTCA, the mean stenosis severity was 94 ± 1% and 91 ± 2% in groups A and B (NS), respectively. There was no difference in inflation time and inflation pressures during three consecutive inflations between groups A and B. After PTCA the mean stenosis severity was 26 ± 1% in group A and 34 ± 3% in group B (NS).

**Electrocardiographic indexes of myocardial ischemia during repetitive coronary artery occlusion.** Time to development of ST segment elevation of 0.1 mV (figure 1) was 21 ± 3 and 25 ± 5 sec (NS) during inflations I and II, respectively, in patients later assigned to group A. In patients later assigned to group B, time to development of ST segment elevation of 0.1 mV was 22 ± 6 and 19 ± 4 sec (NS) during inflations I and II, respectively (i.e., before intracoronary injection of propranolol). There were no statistically significant differences between groups A and B during inflations I and II.

The magnitude of ST segment elevation (figure 2) 60 sec after coronary artery occlusion was 0.16 ± 0.02 and 0.16 ± 0.02 mV (NS) during inflations I and II, respectively, in patients later assigned to group A. In patients later assigned to group B, ST segment elevation at 60 sec was 0.19 ± 0.04 and 0.23 ± 0.06 mV (NS) during inflations I and II, respectively. There were no significant differences between groups A and B during inflations I and II. Therefore comparable degrees of myocardial ischemic injury were produced during the first two balloon occlusions in groups A and B before randomization.

**Effects of intracoronary propranolol on indexes of myocardial ischemia.** In group A time to the development of ST segment elevation of 0.1 mV after intracoronary administration of placebo was 26 ± 4 sec during inflation III (NS vs inflation II) (figure 1). In contrast, in group B the time to ST segment elevation after intracoronary administration of propranolol was significantly prolonged to 53 ± 9 sec during inflation III (p < .001). Furthermore, time to ST segment elevation after the administration of propranolol was significantly longer than that in patients who received intracoronary placebo (p < .02).

In group A, ST segment elevation after intracoronary placebo was 0.18 ± 0.03 mV at 60 sec of inflation III (NS vs inflation II) (figure 2). In group B, after intracoronary administration of propranolol, ST segments were elevated to 0.12 ± 0.04 mV (p < .005 vs inflation II). Although lesser ST segment elevation was observed in patients after the administration of propranolol in comparison with the placebo group, this difference did not reach statistical significance.

Figure 3 illustrates the typical electrocardiographic changes during brief coronary artery occlusions in the control state and after drug administration in a patient randomly assigned to group B (intracoronary administration of propranolol).

Time to beginning of the chest pain was reported accurately in only one patient from group A and four patients from group B. In group A the time to the beginning of chest pain was 30 and 35 sec for inflations II and III. In group B it was 60, 15, 20 and 10 sec and
120, 60, 34, and 40 sec, respectively, for inflations II and III.

**Hemodynamic effects of intracoronary administration of propranolol.** Heart rate at the time of ST segment elevation of 0.1 mV was 79 ± 4, 80 ± 4, and 75 ± 4 beats/min during inflations I, II, and III, respectively, in group A. In group B, heart rate was 81 ± 5, 76 ± 4, and 74 ± 4 beats/min during inflations I, II, and III. There was no significant differences when comparing heart rate between groups during inflations I, II, and III.

Mean aortic pressure at the time of ST segment elevation of 0.1 mV was 82 ± 4, 79 ± 5, and 81 ± 5 mm Hg during inflations I, II, and III, respectively, in group A. In group B, mean aortic pressure was 83 ± 7, 79 ± 6, and 81 ± 5 mm Hg during inflations I, II, and III, respectively. There was no significant differences in mean aortic pressure between groups during inflations I, II, and III.

**Adverse effects.** Propranolol was well tolerated. Adverse effects occurred in only one patient; after injection of 2 mg of propranolol into the right coronary artery, a period of 120 sec of second-degree atrioventricular block was observed without concomitant hemodynamic compromise.

**Discussion**

The major findings of this study are: (1) repetitive episodes of brief coronary artery occlusion in man result in comparable, transient myocardial ischemic injury if no intervention is given, (2) intracoronary administration of propranolol protects the myocardium by delaying the development and reducing the magnitude of ischemic injury during coronary artery occlusion, and (3) because no differences in heart rate and mean arterial blood pressure between the placebo- and propranolol-treated groups occurred, the protective properties of intracoronary propranolol are presumed to be mediated by a local effect.

**Myocardial protection by β-adrenergic blocking agents.** Previous experimental studies have shown that the intravenous administration of propranolol before or after coronary artery ligation significantly reduced ST segment elevation recorded from epicardial and surface leads.1,2 Because the amplitude of ST segment elevation has been found to predict the extent of subsequent myocardial damage,1,2 a protective effect of β-adrenergic blockade was suggested. Administration of propranolol in the setting of coronary artery ligation was also associated with preservation of myocardial creatine kinase and limitation in histologic damage of the ischemic region.3 Further investigations1,4,5 have directly demonstrated reduction of infarct size in animals subjected to prolonged coronary artery occlusion treated with β-adrenergic blocking agents. Miura et al.6 demonstrated the critical importance of the timing of intervention after the onset of myocardial ischemia; the degree of reduction of infarct size varied inversely with the delay in instituting treatment with propranolol. Other experimental studies,4 however, have failed to demonstrate a beneficial effect of propranolol on infarct size. The intravenous administration of β-adren-
ergic blocking agents has been shown to reduce ST segment elevation in some patients in the early phase of myocardial infarction. Coronary angiography demonstrated that the reduction in ST segment elevation was striking only in those patients with residual blood flow to the ischemic myocardium. These observations suggested that the protective effect of intravenous propranolol was dependent on residual flow to the ischemic region rather than on the systemic effect of the drug. Several clinical investigations have found a reduction in infarct size after β-adrenergic blockade on the basis of enzymatic and electrocardiographic analyses. In contrast, some studies failed to demonstrate a reduction in the extent of myocardial necrosis. The latter finding was most likely related to a significant delay in instituting treatment after the onset of symptoms. Furthermore, the protective effect of propranolol in the setting of suspected myocardial infarction remains unclear.

In this study, intracoronary propranolol prolonged the time to the development of ST segment elevation and reduced the magnitude of ST elevation during transient coronary artery occlusion. The significant and uniformly beneficial effect of intracoronary propranolol in this study was most likely related to the administration of the drug just before coronary artery occlusion and its delivery directly to the myocardial area at risk. Several hypotheses have been advanced to explain the beneficial effects of β-adrenergic blockers on the ischemic myocardium. Propranolol-induced reduction of myocardial oxygen consumption could be caused by decreases in heart rate, afterload, and contractility. In this study, the protective effect of intracoronary propranolol occurred without changes in heart rate and arterial pressure, which suggests that a regional reduction in contractility was the factor most likely responsible for the protective effect. This result is in accordance with the experimental study of Hillis et al., who demonstrated that the reduction in acute myocardial injury by propranolol is independent of the negative chronotropic effect of the drug. Furthermore, Gold et al. have shown that intracoronary administration of propranolol in patients with angina pectoris was associated with minimal changes in resting heart rate but with significant prolongation in the time to pacing-induced ischemia. Although intracoronary propranolol did not significantly change global left ventricular contractility, it is conceivable that regional β-adrenergic blockade resulted in a reduction of local myocardial oxygen consumption in the jeopardized zone. Furthermore, although injection of propranolol into the affected coronary artery was efficacious, its administration into the contralateral coronary artery did not improve the time to pacing-induced ischemia. The direct effect of β-adrenergic blockade on the ischemic myocardium is supported by the observation of Goodlett et al. who demonstrated that local coronary artery perfusion with propranolol partially preserved high-energy phosphates. Kloner et al. have shown that propranolol decreases mitochondrial damage, suggesting that mitochondrial salvage may be important in preserving adenosine triphosphate content and thus protecting the ischemic myocardium. The membrane-stabilizing effect of propranolol seems to be an unlikely mechanism for its anti-ischemic action, since d-propranolol, which exerts this effect but lacks β-blocking properties, failed to reduce myocardial ischemic damage.

Repetitive episodes of brief coronary artery occlusion. The magnitude of myocardial ischemia as reflected by the amplitude of ST segment elevation 60 sec after coronary artery occlusion remained unchanged during three consecutive inflations in the placebo group. This observation indicates that repetitive episodes of brief coronary artery occlusion in man are associated with similar degrees of myocardial ischemic injury. These results are consistent with the findings of Serruys et al., who demonstrated similar degrees of lactate production from the ischemic myocardium in patients subjected to several balloon inflations during coronary angioplasty.

Limitations of the study. There are several limitations to this study. Electrocardiographic indexes of ischemic injury provide only a qualitative estimate of the magnitude of myocardial reversible damage. Each patient, however, served as his own control; therefore, changes in the measured indexes reflected directional changes in ischemic injury. Furthermore, extrapolation of these results to patients with other types of myocardial ischemia or with acute myocardial infarction should be made with extreme caution, since only brief and transient episodes of coronary artery occlusion were studied. In addition, although it was not observed in this study, high doses of intracoronary propranolol administered in patients with severe left ventricular dysfunction may cause hemodynamic deterioration. Thus caution is advised in selecting such patients until the hemodynamics of this intervention are better elucidated.

Clinical applications. This study shows that intracoronary propranolol is safe and effective in reducing acute myocardial ischemic injury during coronary artery occlusion. By delaying the development of myocardial ischemia, this intervention may allow for pro-
longed balloon inflations to enhance the efficacy of PTCA, since longer inflations may increase the primary success rate of balloon angioplasty. This was observed in three patients in whom we were unable to obtain an initially satisfactory result with brief coronary artery occlusions before the injection of propranolol. In addition, prolonged balloon inflation may enhance plaque molding and reduce the restenosis rate.

In conclusion, the administration of intracoronary propranolol substantially delayed the development of myocardial ischemic injury in patients undergoing PTCA. Furthermore, the setting of PTCA provides a means of studying other myocardial protective modalities during coronary artery occlusion in patients.

We express our gratitude to Ms. Mary A. Mastrone, Ms. Catherine Francoz, and Ms. Laraine J. Bartlett for their excellent secretarial assistance, and to the nurses and technicians in the Cardiac Catheterization Laboratory.

References

A Zalewski, S Goldberg, J P Dervan, S Slysh and P R Maroko

Circulation. 1986;73:734-739
doi: 10.1161/01.CIR.73.4.734

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/73/4/734