Beneficial Effects of Intracoronary Adenosine as an Adjunct to Primary Angioplasty in Acute Myocardial Infarction

Mario Marzilli, MD; Enrico Orsini, MD; Paolo Marraccini, MD; Roberto Testa, MD

Background—The benefits of vessel recanalization in acute myocardial infarction (AMI) are limited by reperfusion damage. In animal models, adenosine limits reperfusion injury, reducing infarct size and improving ventricular function. The aim of this study was to evaluate the safety and feasibility of adenosine adjunct to primary PTCA in AMI.

Methods and Results—Fifty-four AMI patients undergoing primary PTCA were randomized to intracoronary adenosine or saline. The 2 groups were similar for age, sex, and infarct location. Adenosine administration was feasible and well tolerated. PTCA was successful in all patients and resulted in TIMI 3 flow in all patients given adenosine and in 19 given saline (P<0.05). The no-reflow phenomenon occurred in 1 adenosine patient and in 7 saline patients (P=0.02). Creatine kinase was lower in the adenosine group, and a Q-wave MI developed in 16 adenosine patients and in 23 saline patients (P=0.04). Sixty-four percent of dyssynergic segments improved in the adenosine group and 36% in the saline group (P=0.001). Function worsened in 2% of dyssynergic segments in the adenosine group and in 20% in the saline group (P=0.0001). Adverse cardiac events occurred in 5 patients in the adenosine group and in 13 patients in the saline group (P=0.03).

Conclusions—Intracoronary adenosine administration is feasible and well tolerated in AMI. Adenosine adjunct to primary PTCA ameliorates flow, prevents the no-reflow phenomenon, improves ventricular function, and is associated with a more favorable clinical course. (Circulation. 2000;101:2154-2159.)

Key Words: adenosine ■ myocardial infarction ■ ischemia ■ reperfusion

Early reperfusion of the ischemic myocardium by thrombolytic agents is effective in reducing mortality from acute myocardial infarction (AMI). Even better results can be achieved with direct PTCA, which, in randomized trials, has been demonstrated to further reduce mortality and recurrence of ischemia.1

Unfortunately, reperfusion, although it relieves or reduces ischemia and necrosis, is followed by morphological and functional changes that ultimately result in tissue damage known as reperfusion injury.2,3 Myocardium that is viable at the end of the ischemic period may therefore lose viability during reperfusion.4

Several mechanisms contribute to the ischemia-reperfusion injury, including production of oxygen free radicals, neutrophil activation, endothelial and myocyte edema, loss of antioxidant enzymes, and cardiomyocyte apoptosis.5 Given this complex pathogenesis, several strategies are currently under investigation to prevent or lessen myocardial damage.

Adenosine, an endogenous purine nucleoside, antagonizes many of the biochemical and physiological mechanisms implicated in ischemia-reperfusion injury and has been shown to reduce posts ischemic ventricular dysfunction and myocyte necrosis and apoptosis.6–8 The exact mechanism of the cardioprotective effect of adenosine is not fully understood, although inhibition of neutrophil activation and prevention of endothelial damage seem to play a major role.

Encouraged by this theoretical and experimental framework, we investigated the effects of adenosine as an adjunct to PTCA in AMI. Given the disappointing results of intravenous adenosine administration,9 we developed a strategy for the selective treatment of the ischemic territory right before the onset of reperfusion.

Methods

Patient Selection

Patients referred for PTCA within 3 hours from the onset of AMI were considered for the study. Patients underwent diagnostic coronary angiography. If the culprit lesion was suitable for PTCA and presented with a TIMI flow from 0 to 2, the patient was included in the study and randomized after informed consent had been obtained. Patients presenting with TIMI 3 flow were diagnosed as having spontaneous reperfusion and were not included in the study.

Patients who had a history of bronchospasm and/or were undergoing therapy with theophylline derivatives and patients who had received thrombolytics in the emergency room were also excluded from the study.

Invasive Procedure

After left and right coronary arteriography by the femoral approach, a temporary pacing wire was advanced into the right ventricle and connected with a pacemaker left on demand at 60 bpm.
The obstruction of the infarct-related artery was crossed with a 0.014-in guidewire, and an over-the-wire balloon catheter was positioned at the level of the obstruction. The wire was pulled out, and diluted contrast was injected through the central lumen of the catheter to confirm positioning of the catheter tip downstream of the obstruction and to assess patency of the distal vessel. The balloon was inflated, and either adenosine (4 mg in 2 mL saline) or saline (2 mL) was hand-injected into the distal vascular bed in a random fashion. The rate of injection was such as to complete treatment in ~1 minute. The guidewire was then readvanced into the distal vessel, and the balloon was deflated to initiate reperfusion of the ischemic territory. The dilatation procedure was completed according to standard technique. Stenting of the dilated coronary segment was performed only for suboptimal balloon results or flow-limiting dissections. After completion of the dilation procedure, patients were observed in the catheterization room for 30 minutes. The final angiogram was then obtained, and the patient was transferred to the intensive coronary care unit. If symptoms and/or ECG changes consistent with vessel reclosure occurred during this interval, coronary angiography was performed immediately, and therapeutic measures were applied. The dilation procedure was limited to the culprit lesion in all patients.

Angiographic Analysis
The angiograms were reread as a single group, in chronological sequence, by observers who had not participated in the invasive procedure and were blinded to the treatment received. Cine films were reviewed with an angiographic projection system (CAP/35 B II) allowing frame-by-frame analysis, selection, and magnification of the segments of interest. The region of interest was manually selected and digitized by a high-quality Vidicon camera. Diameter stenosis was measured by an automatic edge-detection system (Mipron, Kontron).

PTCA was considered successful when the residual stenosis was <50%, in the absence of dissection, thrombosis, or distal vessel embolization. Coronary flow was graded according to the TIMI study criteria. No-reflow was diagnosed when a reduction of ≥1 TIMI grades was observed in the final angiogram relative to the post-PTCA angiogram.

Left Ventricular Function
Left ventricular function was evaluated by 2D echocardiography within 24 hours from admission and after 1 week. Echocardiography was performed with the patient lying supine with a 2.5-MHz transducer fitted to a dedicated system (Hewlett-Packard Sonos 1500). Images were recorded on S-VHS tapes and analyzed offline by 2 experienced observers blinded to the angiographic data. Four views were used: the parasternal long- and short-axis (at the level of the papillary muscle) and apical 2- and 4-chamber views. The left ventricle was divided into 16 segments. In each segment, wall motion was graded as normal, hypokinetic, akinetic, or dyskinetic. Segmental motion at admission was compared with segmental motion at 1 week to detect changes of regional function.

Metabolic Data
Creatine kinase (CK) and CK-MB were assessed every 8 hours in the first day of admission and then every day up to discharge, unless clinical events suggested repeat measurements.

Study End Points
The primary end points of this study were feasibility and safety of intracoronary adenosine administration in the setting of primary PTCA and its effect on coronary blood flow. As secondary end points, indexes of myocardial damage, including left ventricular regional function, Q-wave MI, recurrence of angina, nonfatal MI, heart failure, and cardiac death were evaluated.

Physicians in charge of the patients in the intensive coronary care unit were informed of the angiographic results of the PTCA but were blinded to the intracoronary treatment administered during the procedure.

TABLE 1. Clinical and Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adenosine (n=27)</th>
<th>Saline (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.5±11</td>
<td>61.9±9</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>22 (81)</td>
<td>21 (78)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3 (11)</td>
<td>4 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Time from pain onset to PTCA, min</td>
<td>106±81</td>
<td>126±69</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure at admission, mm Hg</td>
<td>116±28</td>
<td>109±22</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate at admission, bpm</td>
<td>85±22</td>
<td>83±17</td>
<td>NS</td>
</tr>
<tr>
<td>Site of infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>14 (52)</td>
<td>16 (59)</td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>8 (30)</td>
<td>8 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Infarolateral</td>
<td>5 (18)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>13 (48)</td>
<td>15 (56)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>9 (33)</td>
<td>7 (26)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>2 (7)</td>
<td>3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Marginal</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Diagonal</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>16 (59)</td>
<td>16 (59)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending; LCx, left circumflex; and RCA, right coronary artery. Data are presented as mean value±SD or number (%) of patients.

Statistical Analysis
Data are expressed as mean±SD. Continuous variables were analyzed according to Student’s t test. Dichotomous variables were compared by χ² test. A value of P<0.05 was considered significant.

Results
Fifty-four patients were included in the study. Twenty-seven patients were randomized to adenosine and 27 to saline. The angioplasty procedure was successfully completed in all study patients. Coronary stents were implanted in 4 patients in the adenosine group and in 5 patients in the saline group (P=NS).

Demographic and clinical characteristics are presented in Table 1. The 2 groups were similar for age, sex distribution, and prevalence of previous MI. The mean times from symptom onset to first balloon inflation were similar in the 2 groups. Systolic blood pressure and heart rate at arrival in the catheterization laboratory were similar in the 2 groups. Approximately 50% of the patients presented with an anterior infarction associated with an occluded left anterior descending coronary artery and 33% with an occluded right coronary artery and inferior infarction. The remaining patients had an inferolateral infarction associated with an occluded left circumflex or marginal coronary branch. Two patients in the adenosine group had a lateral infarction associated with the occlusion of a large diagonal branch. The majority of the patients had multivessel disease.

Feasibility and Safety of Intracoronary Adenosine Administration
The intracoronary treatment procedure, including balloon inflation, removal of the guidewire, administration of the
treatment drug, readvancement of the wire into the distal vessel, and deflation of the balloon, was completed in <2 minutes in all patients.

The injections of adenosine or saline in the distal coronary bed were well tolerated and free of side effects. No patients complained of worsening of chest pain, and no patients suffered from hemodynamic instability. No bradycardias or tachyarrhythmias were associated with this protocol, including adenosine injection into the right coronary artery.

**Angiographic Results**

Angiographic success, defined as a residual stenosis <50% in the absence of dissection (grade 3 by American Heart Association/American College of Cardiology classification), thrombosis, or distal embolization was achieved in all patients. Residual diameter stenosis by quantitative coronary arteriography was 27.8±9.5% in the adenosine group and 34.4±8.7% in the saline group (P=NS). At the end of the dilation procedure, flow in the infarct-related artery was graded TIMI 3 in all adenosine patients. In the saline group, 19 patients achieved a TIMI 3 flow and 8 patients a TIMI 2 flow (P<0.05) (Figure 1).

The no-reflow phenomenon, defined as a drop of ≥1 TIMI grades of coronary flow in the final angiogram relative to the post-PTCA angiogram, was diagnosed in 1 patient in the adenosine group and in 7 patients in the saline group (P<0.02) (Figure 1). Of these 7 patients, 4 had achieved a TIMI 3 flow and 3 a TIMI 2 flow after PTCA.

In 6 patients, no-reflow manifested with recurrence or worsening of chest pain and/or ST-segment changes and occurred from 5 to 12 minutes after the last balloon inflation. Treatment of no-reflow included intracoronary nitrates (0.4 to 0.6 mg) and/or verapamil (0.2 to 0.3 mg) and repeat PTCA. A recovery of flow of ≥1 TIMI grade was eventually obtained in 3 patients.

**Clinical Course**

Patients received standard pharmacological treatment, including anticoagulant and antiplatelet agents, ACE inhibitors, β-blockers, and nitrates, unless contraindicated. Admission time was 9.1±0.8 days in the adenosine group and 10.2±0.6 days in the saline group (P=NS). Peak CK was 1994±1782 U/L in the adenosine group and 2803±1857 U/L in the saline group (P=NS). Peak CK-MB was 156±142 U/L in the adenosine group and 346±169 U/L in the saline group (P=NS). Three patients in the adenosine group and 2 in the saline group had recurrence of angina (Table 2). These patients underwent repeat angiography, which in 2 cases was followed by repeat PTCA for the treatment of early restenosis. One patient in the saline group suffered a nonfatal MI (Table 2). Two patients in the adenosine group had a clinical diagnosis of heart failure, versus 5 in the saline group (Table 2). None of these differences were statistically significant.

Five patients in the saline group died in hospital. Two deaths were associated with occlusion of the infarct-related artery and fatal MI, 2 with development of intractable cardiogenic shock, and 1 with AMI in a remote area. No deaths occurred in the adenosine group (P<0.02) (Table 2, Figure 2). Seven of the 8 patients presenting with the no-reflow phenomenon had adverse events.

Sixteen patients in the adenosine group and 23 in the saline group developed a Q-wave MI (P<0.04).

The composite end point of recurrent angina, nonfatal MI, heart failure, and cardiac death was present in 5 patients in the adenosine group and in 13 patients in the saline group (P<0.03) (Table 2, Figure 2).

**Left Ventricular Function**

Serial ventricular function data from good-quality echocardiograms were available in 23 patients of the adenosine group and in 20 patients of the saline group. A total of 114 dysynergic segments were identified in the admission echocardiogram of the patients included in the adenosine group and 109 in the admission echocardiogram of the patients included in the saline group. In the echocardiogram repeated after 1 week, wall motion was found to be improved in 73 (64%) of the initially dysynergic segments in the adenosine group.

**Figures**

- **Figure 1.** Effect of adenosine (ADO) on coronary blood flow. Intracoronary adenosine was associated with TIMI 3 flow and with a significant reduction in prevalence of no-reflow phenomenon.
- **Figure 2.** Effect of adenosine (ADO) on clinical course. In adenosine group, a significant reduction of death, Q-wave MI, and major adverse cardiac events (MACE) was observed.

**Table 2. Clinical Events**

<table>
<thead>
<tr>
<th></th>
<th>Adenosine (n=27)</th>
<th>Saline (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent angina and/or ischemia</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonfatal AMI</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (7)</td>
<td>5 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0 (0)</td>
<td>5 (18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cumulative clinical end points</td>
<td>5 (18)</td>
<td>13 (48)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of patients.

Cumulative clinical end-point: recurrent angina and/or ischemia, non-fatal AMI, heart failure, cardiac death.

*Note: AMI indicates acute myocardial infarction; MACE, major adverse cardiac event; TIMI, thrombolysis in myocardial infarction.*

*Table 2: Clinical Events*
group and in 39 segments (36%) in the saline group ($P=0.0001$) (Figure 3). Worsening of wall motion was observed in 3 segments (2%) in the adenosine group and in 22 segments (29%) in the saline group ($P=0.0001$) (Figure 3). Regional wall motion was unchanged in 38 segments in the adenosine group and in 48 segments in the saline group.

**Discussion**

Early reperfusion of the infarct-related artery might salvage a substantial amount of jeopardized myocardium and reduce mortality. Reperfusion, however, also results in morphological and biochemical events that limit the possible benefits of flow restoration.

The deleterious phenomena associated with reperfusion are generally called “reperfusion damage” and include impairment of cell volume regulation, prolonged depression of contractile function, increased vascular permeability, and neutrophil activation.

Interstitial edema, cell swelling, and capillary plugging by activated neutrophils and aggregated platelets all contribute to a progressive increase in resistance to flow at the microcirculatory level. Elevated resistance manifests at angiography with a progressive slowing of contrast progression in the infarct-related artery. Conversely, the extent of myocardial necrosis correlates with the severity and duration of myocardial ischemia. The net effects of reperfusion are usually beneficial, but strategies or interventions that could prevent its negative counterparts would optimize myocardial salvage and improve functional recovery.10

In humans, the clinical relevance of reperfusion damage and of the no-reflow phenomenon has recently been emphasized,11,12 but attempts to prevent reperfusion damage have been of limited efficacy.13-17 Thus, protection of the ischemic myocardium from ischemia-reperfusion injury remains an open issue.

**Incidence of No-Reflow**

In this study, 26% of the patients undergoing standard PTCA for AMI presented with no-reflow. This complication was effectively prevented by intracoronary adenosine.

We attribute the success of this approach to the pharmacological properties of adenosine that counteract many of the pathogenetic mechanisms of reperfusion damage and to the treatment strategy, namely the administration of the drug distal to the coronary obstruction and before the onset of reperfusion.

Oxygen-derived free radicals, major contributors to reperfusion damage, reach peak concentration in the coronary sinus as early as 2 to 3 minutes after return of oxygenated blood. Early production of oxygen-derived free radicals was recently reported in conjunction with primary angioplasty in humans.18

In experimental animals, antioxidant agents administered at the onset of reperfusion alleviate myocardial stunning. The same agent administered 1 minute after the start of reperfusion is without effect.19

In this study, the observation time of the coronary flow was limited to 30 minutes. We cannot exclude the possibility that additional cases of no-reflow could occur after this time interval. However, serial PET studies have demonstrated a trend toward progressive improvement of flow in infarct-related myocardial regions with time.20 In this study, the no-reflow phenomenon consistently manifested within 15 minutes, and the incidence we found is similar to that reported in studies with longer observation time.21-23

**Safety of Intracoronary Adenosine**

Intracoronary adenosine injection may be followed by transient AV block. This was the reason for the insertion of a temporary pacemaker. However, no AV block was observed with adenosine administration in the setting of acute MI. We have no explanation for this observation; we can only hypothesize that the sympathetic drive associated with acute MI can override the depressant action of adenosine on AV conduction. In fact, the temporary pacemaker never fired.

A second concern was related to the possible worsening of chest pain. Adenosine has been proposed as a mediator of anginal pain, and its administration has been associated with angina-like chest pain.24 In stable angina patients with documented coronary disease, however, intracoronary adenosine does not reproduce their typical anginal pain.25 Consistently, in this study, adenosine administration was never associated with worsening of chest pain or any other symptom.

**Mechanisms for the Cardioprotective Effect of Adenosine**

In experimental animals, adenosine reduces ischemic-reperfusion injury, limits infarct size, and improves ventricular function.26 The mechanisms of the cardioprotective effect of adenosine are not fully understood. It appears to be a receptor-mediated effect and involves inhibition of neutrophil-related processes.27

Adenosine, administered before ischemia, exerts a protective effect similar to preconditioning, and preconditioning in an animal model can be blocked by selective $A_1$ receptor antagonists.28 In this study, adenosine was administered after the onset of ischemia, so a preconditioning effect is not expected.

In isolated, perfused rat hearts, adenosine given at reperfusion increases glucose oxidation and inhibits glycolysis, reduces tissue lactate levels, and increases ATP levels.29 These effects of adenosine on glucose metabolism tend to
decrease cellular acidosis and Ca$^{2+}$ overload and are associated with beneficial effects on mechanical function.29

Cardiomyocyte apoptosis occurs after sustained ischemia and is more prominent after ischemia and reperfusion. Tumor necrosis factor (TNF) synthesized locally by macrophages and cardiac myocytes contributes to posts ischemic myocardial dysfunction by direct depression of contractility and induction of myocyte apoptosis. Adenosine decreases posts ischemic cardiac TNF production.8 Adenosine-induced suppression of cardiac TNF may represent a mechanism by which adenosine protects myocardium and may provide an anti-inflammatory link to preconditioning.8

The half-life of adenosine in human blood is $<$1 second, apparently too short to protect from oxygen free radicals, which peak at 2 to 3 minutes of reperfusion, even if reperfusion is started only 15 to 30 seconds after adenosine administration. However, half-life may underestimate the duration of the biological effects of adenosine. After a bolus injection of adenosine in a nonstenotic coronary artery, coronary flow remains elevated for several minutes, suggesting persistent receptor activation well beyond half-life.30 In case of injection into a stenotic coronary artery, flow remains elevated even longer. In this study, adenosine was injected into a vascular bed with minimal, if any, antegrade flow, and under these circumstances, its biological effects could last much longer than expected on the basis of its half-life. The short half-life of adenosine, however, provides an intrinsic protection from possible side effects.

In this study, a planned prospective collection of blood samples for the metabolic assessment of infarct size was not performed. Based on routine measurements, CK and CK-MB were lower in the adenosine group; the difference, however, did not achieve statistical significance. Methodological problems and small sample size may explain these results. It is also possible that the no-reflow phenomenon interferes with the time course of enzyme release, making difficult the metabolic assessment of infarct size under the circumstances of this study protocol.

Conclusions and Clinical Implications

Ischemia and reperfusion both contribute to myocardial damage in AMI. Adenosine has been shown to limit ischemia-reperfusion injury in animal models. In this study, we have shown that adenosine administration in the infarct-related artery is feasible in the setting of primary angioplasty and that this treatment is safe and well tolerated and does not prolong procedural time. In this pilot study, intracoronary adenosine administration was associated with beneficial effects on coronary flow, on ventricular function, and on clinical course. These observations are consistent with the hypothesis that a component of the ischemia-reperfusion injury can be prevented in humans by adenosine adjunct to primary PTCA.

Given the small sample size and the heterogeneity of the population included in this report, larger clinical studies are needed to confirm these observations.

References


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_Circulation_. 2000;101:2154-2159
doi: 10.1161/01.CIR.101.18.2154

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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