Antiarrhythmic Efficacy of Dipyridamole in Treatment of Reperfusion Arrhythmias

Evidence for cAMP-Mediated Triggered Activity as a Mechanism Responsible for Reperfusion Arrhythmias

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Background—Intracellular calcium overload is believed to play an important role in development of reperfusion arrhythmias. Dipyridamole, an inhibitor of cellular uptake of adenosine, may prevent or terminate reperfusion arrhythmias by reducing intracellular calcium overload.

Methods and Results—First, we tested for a preventive effect of dipyridamole. Sixty-one patients who underwent primary PTCA for treatment of acute anterior wall myocardial infarction were enrolled in this prospective study. Patients were divided into dipyridamole (DP) and nondipyridamole (non-DP) groups. The 2 groups had similar baseline characteristics. In the DP group, dipyridamole 0.5 mg/kg was infused intravenously for 3 minutes immediately before reperfusion during primary PTCA. Arrhythmias after reperfusion were analyzed from continuous ECG recordings. None of the patients in the DP group (n = 23) had accelerated idioventricular rhythms (AIVR) or ventricular tachycardia (VT). In contrast, 7 (18.4%) had AIVR and 3 (7.9%) had VT in the non-DP group (n = 38; P < 0.01). Second, we tested for a termination effect of dipyridamole. Dipyridamole 0.5 mg/kg was infused intravenously while continuous ECG recordings were obtained in 9 patients who had either sustained AIVR (n = 7) or sustained VT (n = 2) after reperfusion of occluded coronary artery. Arrhythmias were terminated in all patients.

Conclusions—These results indicate that administration of dipyridamole can prevent and terminate reperfusion arrhythmias such as AIVR and VT. cAMP-mediated triggered activity may, at least in part, be responsible for reperfusion-induced AIVR and VT. (Circulation. 2000;101:624-630.)

Key Words: adenosine □ arrhythmia □ myocardial infarction □ reperfusion

Reperfusion arrhythmias, such as accelerated idioventricular rhythm (AIVR) and ventricular tachycardia (VT), are frequently observed after reperfusion of an occluded coronary artery in the setting of acute myocardial infarction (AMI).

Intracellular calcium overload is believed to play a critical role in development of reperfusion arrhythmias. Furthermore, adenosine has been shown to suppress reperfusion injury and to terminate idiopathic VT caused by intracellular calcium overload. Dipyridamole, an inhibitor of cellular transport of adenosine, is thought to exert the same antiarrhythmic activity as adenosine by increasing interstitial myocardial concentration of adenosine. Although dipyridamole is expected to prevent or terminate reperfusion arrhythmias caused by intracellular calcium overload, its antiarrhythmic efficacy in treatment of reper-
fusion arrhythmias has not been clarified. The purpose of the present study was to determine the effect of dipyridamole on reperfusion arrhythmias in patients with AMI.

**Methods**

**Study Patients**

One hundred twenty-three consecutive patients with AMI who presented within 6 hours of onset of symptoms were enrolled in the present study. Coronary angiography confirmed that the infarct-related artery was completely occluded. Primary PTCA was performed in all patients. Studies were approved by the institutional review committee, and informed consent was obtained from all patients before they entered the study.

Excluded from the study were patients with a prior history of MI, insulin therapy for diabetes mellitus, or coronary artery bypass surgery; with severe stenoses of ≥90% that affected arteries other than the infarct-related artery, pulmonary edema, or cardiogenic shock; or who had undergone unsuccessful reperfusion or had experienced no-reflow phenomenon at reperfusion.

The study population consisted of 91 men and 32 women aged 31 to 85 years (64±11 years). The infarct-related artery was the right coronary artery (RCA) in 45 patients, left main trunk (LMT) in 3, left anterior descending coronary artery (LAD) in 61, and left circumflex coronary artery (LCx) in 14. Primary PTCA was performed in all patients, and the occluded vessel was successfully reperfused in all.

**Coronary Angiography and Primary PTCA**

Coronary angiography and primary PTCA were performed within 6 hours of onset of symptoms of AMI. Once the femoral artery was catheterized, 10 000 IU of heparin was administered and additional boluses of 1000 IU were given as needed to achieve an activated clotting time of ≥350 s. Coronary angiograms were obtained in ≥2 projections. Intracoronary nitroglycerin was administered before diagnostic angiography and primary PTCA. LAD occlusions were considered proximal if located before the origin of the first well-developed septal branch, distal if located after the origin of the third diagonal branch, and mid if located between these limits. Primary PTCA was performed by use of a conventional catheter balloon technique. Reperfusion was considered successful when flow in the infarct-related artery was improved to Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3.

**Data Recording**

Continuous recordings of 6- to 12-lead ECGs and blood pressure were obtained simultaneously from the start of coronary angiography until completion of PTCA at a paper speed of 10 mm/s. When arrhythmias appeared, recordings were obtained at a paper speed of 25 mm/s. ECG and blood pressure recordings were analyzed by 3 of the authors (Y.Y., M.H., N.T.). Differences of opinion were settled through discussion.

**Definitions**

Rapid ventricular rhythms were divided by use of heart rate into AIVR (≥60 bpm but <120 bpm) and VT (≥120 bpm). AIVR and VT were also classified by their duration: sustained (lasting ≥30 s) and nonsustained (lasting <30 s).

**Effect of Dipyridamole on Prevention of Reperfusion Arrhythmias**

The ability of dipyridamole to prevent reperfusion arrhythmias was investigated in a subset of patients with AMI caused by a culprit artery other than the infarct-related artery. Patients were prospectively divided into dipyridamole (DP) and nondipyridamole (non-DP) groups. For patients in the DP group, 0.5 mg/kg of dipyridamole (Persantine injection; Behring-Ingelheim, Japan) was administered intravenously for 3 minutes immediately before reperfusion during primary PTCA. Elimination half-life of dipyridamole administered intravenously is 24.6 minutes.13 Type and frequency of ventricular arrhythmias that occurred during the 30 minutes after reperfusion were compared between groups.

**Effect of Dipyridamole on Termination of Reperfusion Arrhythmias**

The ability of dipyridamole to terminate reperfusion arrhythmias was determined in patients with AIVR or VT developed within 10 minutes after reperfusion. The DP group for the prevention study was excluded from the termination study. As for AIVR, if tachycardia continued for >30 s, dipyridamole (0.5 mg/kg) was primarily infused intravenously while continuous ECGs and blood pressure recordings were obtained simultaneously. To assess precisely the effect of dipyridamole on AIVR, patients whose arrhythmias were nonsustained or terminated spontaneously before infusion of dipyridamole were excluded. As for VT, patients who had severe hemodynamic compromise were cardioverted, and 100 mg of bolus intravenous lidocaine was injected into the remaining patients with VT. If lidocaine injection was ineffective, dipyridamole 0.5 mg/kg was infused intravenously. Termination of sustained AIVR or sustained VT during or for 1 minute after the infusion of dipyridamole was defined as successful termination of arrhythmia. If AIVR or VT resumed within 20 minutes after cessation of the arrhythmia after dipyridamole infusion, cessation of the arrhythmia was considered unsuccessful.

**Statistical Analysis**

Data are expressed as mean±SD or number (percentage) of patients. Differences between categorical variables were analyzed by χ² analysis or Fisher’s Exact Test, and differences between continuous variables were analyzed by Student’s t test. P<0.05 was considered statistically significant.

**Results**

**Effect of Dipyridamole for Prevention of Reperfusion Arrhythmias**

In 61 patients, the infarct-related artery was the LAD. These patients were divided into non-DP (first 38 patients) and DP (next 23 patients) groups to investigate the effects of dipyridamole for prevention of reperfusion arrhythmias. No significant differences existed between groups with respect to age, number of diseased vessels, lesion location, collateral flow grade, or time from onset to reperfusion (Table 1). No patients in the DP group had reperfusion-induced AIVR or VT, whereas 7 patients (18.4%) had AIVR and 3 (7.9%) had VT (10 patients; 26.3%) in the non-DP group (P<0.01). Vfib was noted in 2 patients (5.3%) in the non-DP group and was preceded by monomorphic VT in both. Although Vfib did not occur in the DP group, no significant statistical difference

| TABLE 1. Characteristics of 61 Study Patients With Anterior AMI |
|---------------------|---------------------|----|
| Age, y              | 63.0±13.7           | 65.9±11.3 |
| No. of diseased vessels (S/D/T) | 17/5/1 | 30/5/3 |
| Lesion location (proximal/mid) | 15/8 | 26/12 |
| Collateral (TIMI) flow grade | 0.7±0.6 | 0.8±0.6 |
| Time from onset to repertusion, h | 4.7±0.8 | 4.8±1.0 |

Values are expressed as mean±SD or number. S indicates single; D, double; and T, triple.
existed in the incidence of Vfib between groups. Premature ventricular complexes (PVC; $\geq 1$ bpm) occurred at the same frequency in the 2 groups (Table 2). No patients developed chest pain, tachypnea, shortness of breath, or hypotension as a result of dipyridamole administration. In the DP group, no arrhythmias except sporadic PVCs were observed for at least 60 minutes after dipyridamole infusion.

**Effect of Dipyridamole on Termination of Reperfusion Arrhythmias**

Reperfusion arrhythmias developed in 52 (52%) of the 100 patients who had not received dipyridamole at the time primary PTCA was performed, and 66 arrhythmic episodes were observed in these patients. The infarct-related artery was the RCA in 45 patients, LMT in 3, LAD in 38, and LCx in 14. Arrhythmias included sinus bradycardia in 9 patients (9%), PVC in 33 (33%), AIVR in 12 (12%), VT in 7 (7%), and Vfib in 5 (5%) (see Table 3). Sinus bradycardia tended to be associated with RCA or LCx occlusion and AIVR with LAD occlusion. On the other hand, PVC, VT, and VIb occurred at similar frequencies for infarctions in the 3 coronary arteries. The ability of dipyridamole to terminate reperfusion arrhythmias was investigated in 19 patients in whom AIVR (n = 12) or VT (n = 7) developed.

AIVR was nonsustained or subsided spontaneously before administration of dipyridamole in 5 (RCA, 2; LAD, 2; and LCx, 1) of the 12 patients with AIVR. Consequently, AIVR was sustained in 7 patients. VT degenerated into Vfib or was terminated with cardioversion because of hypotension in 4 (LMT, 1; LAD, 3) of the 7 patients with VT. In the other 3 patients with VT, 100 mg of lidocaine was injected intravenously. One patient with an occluded LCx received cardioversion, and the remaining 2 patients with RCA occlusions had sustained monomorphic VT. As a result, VT was sustained in 2 patients.

Dipyridamole was successfully administered to 9 patients with sustained AIVR (n = 7) or sustained VT (n = 2). Arrhythmias terminated during or immediately after administration of dipyridamole in all 9 patients (see Figures 1 through 3). AIVR or VT cycle length did not accelerate in any patient in response to dipyridamole. Dipyridamole had minimal effects on systolic and diastolic blood pressure ($\leq 10$ mm Hg). No resumption of arrhythmia was observed until completion of PTCA (for at least 60 minutes after dipyridamole infusion) in all 9 patients.

**Discussion**

**Main Findings**

In the present study, we investigated the efficacy of dipyridamole for treatment of reperfusion arrhythmias such as

| Arrhythmia Type | Group | No. (% of patients) | p-
<table>
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</thead>
<tbody>
<tr>
<td>PVC $\geq 1$ bpm</td>
<td>DP (n=23)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>AIVR/VT</td>
<td>0/0 (0)</td>
<td>7/3 (26.3)</td>
</tr>
<tr>
<td>Vfib</td>
<td>0 (0)</td>
<td>2 (5.3)</td>
</tr>
</tbody>
</table>

Values are expressed as No. (%) of patients.

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>No. of Patients With Arrhythmia</th>
<th>Culprit Coronary Artery (RCA/LMT/LAD/LCx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Bradycardia</td>
<td>9 (9%)</td>
<td>6/0/0/3</td>
</tr>
<tr>
<td>PVC</td>
<td>33 (33%)</td>
<td>11/3/14/5</td>
</tr>
<tr>
<td>AIVR</td>
<td>12 (12%)</td>
<td>4/0/7/1</td>
</tr>
<tr>
<td>VT</td>
<td>7 (7%)</td>
<td>2/1/3/1</td>
</tr>
<tr>
<td>Vfib</td>
<td>5 (5%)</td>
<td>2/0/2/1</td>
</tr>
</tbody>
</table>

Values are expressed as No. (%) of patients.

Figure 1. ECG recordings show response of AIVR to dipyridamole administration. A, After 2 minutes of reperfusion, ECG showed AIVR at 71 bpm. A 2-minute interval occurred between end of trace A and beginning of trace B. B, Administration of dipyridamole during sustained AIVR resulted in progressive diminution of AIVR (sustained tachycardia--ventricular bigeminy). Vertical arrow indicates end of dipyridamole injection. C, Complete abolition of ventricular ectopy $\sim 15$ s after end of dipyridamole.

### TABLE 2. Incidence of Reperfusion Arrhythmias in Patients With Anterior AMI Treated With Primary PTCA

| Arrhythmia Type | Group | DP (n=23) | Non-DP (n=38) | p-
<table>
<thead>
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<tbody>
<tr>
<td>PVC $\geq 1$ bpm</td>
<td>9 (39.1)</td>
<td>14 (36.8)</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>AIVR/VT</td>
<td>0/0 (0)</td>
<td>7/3 (26.3)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Vfib</td>
<td>0 (0)</td>
<td>2 (5.3)</td>
<td>0.52</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as No. (%) of patients.

### TABLE 3. Incidence of Reperfusion Arrhythmias in the 100 Patients Treated With Primary PTCA for AMI

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>No. of Patients With Arrhythmia</th>
<th>Culprit Coronary Artery (RCA/LMT/LAD/LCx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Bradycardia</td>
<td>9 (9%)</td>
<td>6/0/0/3</td>
</tr>
<tr>
<td>PVC</td>
<td>33 (33%)</td>
<td>11/3/14/5</td>
</tr>
<tr>
<td>AIVR</td>
<td>12 (12%)</td>
<td>4/0/7/1</td>
</tr>
<tr>
<td>VT</td>
<td>7 (7%)</td>
<td>2/1/3/1</td>
</tr>
<tr>
<td>Vfib</td>
<td>5 (5%)</td>
<td>2/0/2/1</td>
</tr>
</tbody>
</table>

Values are expressed as No. (%) of patients.
AIVR and VT in patients with AMI. To our knowledge, the present study is the first to demonstrate that dipyridamole can prevent or terminate AIVR and VT that develops at the time of reperfusion. AIVR has been reported not to require special treatment because this arrhythmia has minimal hemodynamic consequences. However, in some patients with depressed cardiac function, AIVR also may induce hypotension. In the setting of VT, blood pressure may quickly drop, and a high risk exists of degeneration to Vfib. Because of the widespread use of reperfusion therapy, management of reperfusion arrhythmias is an increasingly important clinical issue. The preventive effect of dipyridamole on reperfusion arrhythmias shown in the present study suggests that premedication with dipyridamole immediately before reperfusion can improve safety of reperfusion therapy.

Because AIVR occasionally terminates spontaneously and VT causes abrupt hypotension, few studies have been published on the use of antiarrhythmic drugs to terminate reperfusion-associated AIVR and VT. In the present study, only 9 patients with sustained AIVR (n = 7) or sustained VT (n = 2) could be treated with dipyridamole. However, because the tachyarrhythmias were terminated during or immediately after administration of dipyridamole in all 9 patients, we conclude that this agent may be efficacious for termination of reperfusion arrhythmias.

Antiarrhythmic Action of Adenosine and Dipyridamole

Adenosine is thought to terminate idiopathic VT, which is caused by intracellular calcium overload. This type of VT is probably precipitated by cAMP-mediated triggered activity. The mechanism of tachycardia is believed to be catecholamine-induced delayed afterdepolarizations (DADs). DADs have been reported to be dependent on intracellular calcium overload that results from cAMP stimulation.

Adenosine has no known direct electrophysiological effects on adult ventricular tissue or Purkinje fibers. However, it antagonizes the inotropic and electrophysiological effects of catecholamines that are mediated by stimulation of adenylate cyclase. Adenosine inhibits adenylate cyclase through activation of the adenosine A1 receptor. After the agonist binds to the adenosine A1 receptor, intracellular GTP binds to the GTP-dependent regulatory protein (Gi). This process results in dissociation of Gi from the A1 receptor and inhibition of the catalytic subunit of adenylate cyclase, thereby preventing cAMP formation, intracellular calcium overload, afterdepolarizations, and triggered activity. As a result, VT is terminated.

Dipyridamole is an inhibitor of the cellular uptake of adenosine and exhibits the same antiarrhythmic actions as adenosine. However, dipyridamole has less negative chronotropic and dromotropic effects (atrioventricular block-
Dipyridamole possesses a selective effect on tachyarrhythmias induced by cAMP-mediated triggered activity, the agent can be used to elucidate the mechanism of arrhythmias even in patients with acute coronary syndromes such as AMI. Dipyridamole may prevent or terminate reperfusion arrhythmias by reducing intracellular calcium overload. However, no studies have been published concerning efficacy of dipyridamole for prevention or termination of reperfusion arrhythmias. The present study is the first study to demonstrate the efficacy of dipyridamole for treatment of reperfusion arrhythmias.

Dipyridamole is also known to have a coronary vasodilating effect through activation of the adenosine A2 receptor on endothelial and vascular smooth muscle cells. Therefore, it is possible that the antiarrhythmic efficacy of dipyridamole is due to improved coronary flow. However, in the present study, intracoronary nitroglycerin showed little effect toward prevention of reperfusion arrhythmias. Furthermore, nicorandil, which improves coronary microvascular circulation in the same manner as adenosine, has been reported not to reduce the incidence of reperfusion arrhythmias. Therefore, although a coronary vasodilating effect might be a possible mechanism for antiarrhythmic action of dipyridamole, we believe that the antiarrhythmic efficacy of dipyridamole results mainly from inhibition of intracellular calcium overload through stimulation of the adenosine A1 receptor on cardiomyocytes.

Electrophysiological Mechanisms of Reperfusion Arrhythmias
Electrophysiological mechanisms of reperfusion arrhythmias are still being disputed. Arrhythmias in experimental models of ischemia and reperfusion were previously believed to be reentrant arrhythmias that resulted from heterogeneous recovery of the refractory period and conductivity. However, more recently, Kaplinsky et al found that reperfusion arrhythmias after 30 minutes of ischemia consist of 2 types: an instantaneous ventricular arrhythmia (onset at 0 to 1 minute) and a delayed ventricular arrhythmia (onset at 2 to 7 minutes). They demonstrated that the former was a reentrant arrhythmia caused by electrical inhomogeneity and associated with a high frequency of Vfib. In contrast, the latter was caused by increased ventricular automaticity and associated with a low frequency of Vfib. On the other hand, Ferrier et al reported that in isolated tissue preparation, DADs and triggered rhythms occurred during conditions that mimicked reperfusion after a 40-minute ischemic episode. Subsequently, this mechanism has also attracted considerable attention as the underlying mechanism of reperfusion arrhythmias, although this has not been demonstrated clinically in patients who have undergone reperfusion therapy because of AMI.
Purkinje fibers. In contrast, VT is caused by either reentrant or nonreentrant mechanisms and in some cases by triggered activity as a result of DAD. However, the reperfusion arrhythmias found in the clinical setting may differ from those observed in experimental models, because factors such as lesion location, collateral flow grade, time to reperfusion, and coronary flow volume can vary. Even among clinical studies, varied incidence of reperfusion arrhythmias has been demonstrated. These results suggest that mechanisms responsible for AIVR and VT in clinical cases might be somewhat different from those observed in experimental models. In the present study, we clinically demonstrated for the first time that AIVR and VT that occur after reperfusion are probably cAMP-mediated arrhythmias and are therefore likely to be triggered arrhythmias.

The incidence of Vfib in clinical settings has been reported to be low. In the present study, Vfib occurred in only 2 patients (5.3%) in the non-DP (control) group. In both patients, acceleration of VT occurred before Vfib. These findings are consistent with the mechanism of Vfib described by Moe et al. No patients had Vfib in the DP group. This is thought to be attributable to the fact that, by preventing VT from developing immediately after reperfusion, dipyridamole may prevent the acceleration and degeneration of VT into Vfib. Furthermore, because triggered activity has been demonstrated as the mechanism responsible for Vfib, it is possible that dipyridamole prevents development of Vfib by suppressing intracellular calcium overload.

Study Limitations
The present study has several limitations. First, it was not a randomized clinical study. However, the incidences of AIVR, VT, and Vfib in the control group were similar or even lower than in previous reports. Therefore, we believe that the control group is representative and that the results of the study have clinical significance even though the study was not randomized. Second, dipyridamole is known to cause coronary steal. No patients who received dipyridamole in this study had stenosis (≥90%) of any coronary artery other than the infarct-related artery. In patients with severe stenoses in arteries other than the infarct-related coronary artery, coronary steal might occur and exert a proarrhythmic effect. This issue will require additional study. Third, it remains to be clarified whether administration of dipyridamole can prevent development of Vfib. To define the antiarrhythmic efficacy of this agent against reperfusion-induced Vfib, further studies that include greater numbers of patients are needed.

References


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