Cardioprotective Effects of the Na\(^+/\)H\(^+\) Exchange Inhibitor Cariporide in Patients With Acute Anterior Myocardial Infarction Undergoing Direct PTCA

Hans-Jürgen Rupprecht, MD; Jürgen vom Dahl, MD; Wolfram Terres, MD; Karl Melchior Seyfarth, MD; Gert Richardt, MD; Heinz-Peter Schultheiß, MD; Michael Buerke, MD; Florence H. Sheehan, MD; Helmut Drexler, MD

**Background**—Activation of Na\(^+/\)H\(^+\) exchange in myocardial ischemia and/or reperfusion leads to calcium overload and myocardial injury. Experimental studies have shown that Na\(^+/\)H\(^+\) exchange inhibitors can attenuate Ca\(^2+\) influx into cardiomyocytes. We therefore performed a multicenter, randomized, placebo-controlled clinical trial to test the hypothesis that inhibition of Na\(^+/\)H\(^+\) exchange limits infarct size and improves myocardial function in patients with acute anterior myocardial infarction (MI) treated with direct PTCA.

**Methods and Results**—One hundred patients were randomized to receive placebo (n=51) or a 40-mg intravenous bolus of the Na\(^+/\)H\(^+\) exchange inhibitor cariporide (HOE 642) (n=49) before reperfusion. Global and regional left ventricular functions were analyzed by use of paired contrast left ventriculograms performed before and 21 days after PTCA and myocardial enzymes (ie, creatine kinase [CK], CK-MB, and LDH) as markers for myocardial tissue injury were evaluated. At follow-up, the ejection fraction was higher (50% versus 40%; \(P<0.05\)) and the end-systolic volume was lower (69.0 versus 97.0 mL; \(P<0.05\)) in the cariporide group. Significant improvements in some indices of regional wall motion abnormalities were observed, such as the percentage of chords with hypokinesis < −2 SD (\(P=0.045\)) and the severity of hypokinesis in the border zone of the infarct region (\(P=0.052\)). In addition, CK, CK-MB, or LDH release was significantly reduced in the cariporide patients.

**Conclusions**—Our findings suggest that inhibition of Na\(^+/\)H\(^+\) exchange by cariporide may attenuate reperfusion injury and thereby improve the recovery from left ventricular dysfunction after MI. (*Circulation. 2000;101:2902-2908.*)

**Key Words:** reperfusion • sodium • cariporide • myocardial infarction • angioplasty • ventricles

Thrombolytic therapy and percutaneous transluminal coronary angioplasty (direct PTCA) have become the standard treatments for patients with acute myocardial infarction (MI).\(^1\)–\(^3\) Although early reperfusion is the goal of therapy, reperfusion itself may contribute to additional tissue damage called “reperfusion injury.”\(^4\) This injury has been attributed, in part, to the activation of the Na\(^+/\)H\(^+\) exchange system.\(^5\) Under physiological conditions, the Na\(^+/\)H\(^+\) exchange system permits the entry of extracellular Na\(^+\) into the cell in exchange for intracellular H\(^+\) equivalents and thus is involved in the regulation of intracellular pH and other cellular functions.\(^6\) The Na\(^+/\)H\(^+\) exchange system is activated by intracellular acidosis, which usually accompanies myocardial ischemia and/or reperfusion.\(^7\) This leads to an increase in intracellular sodium and subsequent intracellular calcium overload (due to coupling of sodium and calcium transport), which is thought to play a major role in the development of myocardial stunning and subsequent myocardial cell death.\(^7\)\(^8\)

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Over the past few years, several experimental studies have demonstrated that inhibition of Na\(^+/\)H\(^+\) exchange and subsequent inhibition of calcium overload can protect the myocardium after ischemia and reperfusion.\(^9\)–\(^13\) Blocking of Na\(^+/\)H\(^+\) exchange in isolated cells or organs resulted in improved myocardial function, decreased incidence of arrhythmias, and attenuated calcium uptake and preserved the ultrastructure.\(^14\)–\(^15\) Recent animal studies have demonstrated that blocking of Na\(^+/\)H\(^+\) exchange reduced myocardial cell death after ischemia and reperfusion and also limited infarct size.\(^16\)\(^17\)
However, no data are available on the effect of inhibition of Na\(^+/\)H\(^+\) exchange in a clinical setting of acute myocardial ischemia and reperfusion.

The present study was therefore designed to determine the effect of the Na\(^+/\)H\(^+\) exchange inhibitor cariporide on myocardial function and myocardial tissue injury in patients with acute anterior wall infarction undergoing direct PTCA as reperfusion strategy.

**Methods**

**Patient Selection**

Patients presenting with \(\geq 30\) minutes of chest pain unrelieved by sublingual nitroglycerin and ST-segment elevations of \(\geq 0.2\) mV in \(\geq 3\) of 6 chest ECG leads (typically V\(_2\) through V\(_4\)), compatible with a first acute transmural anterior infarction, underwent coronary angiography. Patients with an occluded (TIMI 0/1) left anterior descending coronary artery, who could be expected to undergo direct PTCA within 6 hours of the onset of symptoms, were enrolled into a multicenter, randomized, double-blind, placebo-controlled study. All patients gave written informed consent, and the study protocol was approved by each study center’s institutional review board.

Patients with left main stenosis (>50%), evidence of previous transmural anterior infarction, previous coronary bypass graft, cardiogenic shock, severe renal or hepatic insufficiency, thrombolytic therapy, left bundle-branch block, or progressive fatal disease were excluded.

**Experimental Protocol**

After coronary angiography, baseline global and regional left ventricular (LV) functions were assessed by contrast left ventriculography in the 30° right anterior and 60° left anterior oblique projections with nonionic contrast media. Patients who met the inclusion criteria were randomized to an intravenous bolus of either 40 mg cariporide (Hoechst Marion Roussel) or placebo given over 10 minutes, after which PTCA was performed.

All patients received 5000 to 10,000 U heparin IV after arterial access had been obtained, and an intravenous infusion of heparin was maintained for \(\geq 24\) hours to maintain the partial thromboplastin time at 2 to 2.5 times control. Intravenous nitroglycerin could be administered during the first 24 hours. Subsequent episodes of ischemic pain and/or congestive heart failure were managed as clinically indicated, including the use of \(\beta\)-blockers and ACE inhibitors.

**Study Sample**

In all, 104 subjects were enrolled; 4 were withdrawn in the pretreatment phase because of an open infarct-related artery. Medication was administered only if PTCA was definitely to be performed. One hundred patients were randomized and treated. Four patients in the cariporide and 3 patients in the placebo group died between treatment by PTCA and 3-week follow-up. One patient in the cariporide and 3 patients in the placebo group were withdrawn during the study period at the patient’s own request. One patient in each treatment group had unsuccessful PTCA. One patient in each treatment group was withdrawn because of other adverse events. Overall, 85 patients completed the study. Forty-six patients (55%) had evaluable ventriculograms at both baseline and follow-up and were included in the analysis of LV function, wall motion, and volumes. The reasons for rejection of left ventriculograms are given in Table 1. Patients were randomized per center.

**Methods of Data Acquisition and Analysis**

**Contrast Left Ventriculographic Studies**

Left ventriculograms acquired in the 30° right anterior oblique view were assessed quantitatively at a core laboratory (F.H.S.) for global LV function and regional wall-motion abnormality by the centerline method.\(^{18}\) Pretreatment and 3-week (18 to 24 days) follow-up left ventriculograms were analyzed blindly and independently. Data are expressed as SD units compared with normal wall motion (mean of a normal reference population) or percentage of chords with abnormal wall motion (Table 2). End-systolic and end-diastolic volumes and the ejection fraction were determined by the area-length method for evaluation of global LV function.\(^{19}\)

**Myocardial Injury**

Creatine kinase (CK), CK-MB, and LDH were determined in blood samples to assess the extent of myocardial tissue injury taken before and 4, 12, 24, 36, and 72 hours after reperfusion.

**Safety Variables**

Any adverse events were considered to be safety variables. Standard hematology, blood chemistry, and urinalysis were performed. Patients also underwent a physical examination, and blood pressure and heart rate were monitored.

**Statistical Methods**

Continuous variables are given as the mean±SEM and number of patients. The frequency distribution is given for categorical data. Baseline variables that might have influenced the progress of the disease were tested for treatment homogeneity on the basis of all randomized and treated patients. The Cochran-Mantel-Haenszel test was used to test categorical variables; continuous variables were tested by ANOVA.

Only patients who were randomized and treated and had evaluable baseline and follow-up ventriculograms in the right anterior oblique view were included in the ventriculographic analysis. The differences between the treatment groups with regard to the change in values between baseline and follow-up examinations were tested with an ANOVA model (2-sided, \(\alpha=0.05\), with treatment and center as fixed effects. A post hoc analysis was conducted for each of the ventriculographic variables with the same ANOVA model but with the baseline value for the respective variable as an additional covariate. Changes in values from baseline to follow-up were compared between the treatment groups by the Wilcoxon test. PTCA

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**TABLE 1. Main Reasons for Rejection of Left Ventriculograms**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast inadequate</td>
<td>15/49 (30.6)</td>
</tr>
<tr>
<td>No sinus rhythm beat</td>
<td>13/49 (26.5)</td>
</tr>
<tr>
<td>Misalignment during imaging</td>
<td>7/49 (14.2)</td>
</tr>
<tr>
<td>No LV angiogram</td>
<td>6/49 (12.2)</td>
</tr>
<tr>
<td>Diaphragm moving</td>
<td>4/49 (8.1)</td>
</tr>
<tr>
<td>Other</td>
<td>4/49 (8.1)</td>
</tr>
</tbody>
</table>

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**TABLE 2. Variables of Analysis of Regional LV Function**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of chords with akinesis/dyskinesis</td>
<td>Proportion of the LV contour with wall motion that is akinetic or that moves paradoxically outward at end systole</td>
</tr>
<tr>
<td>Percent of chords with hypokinesis&lt;−2SD</td>
<td>Proportion of the LV contour with hypokinesis more severe than 2 SD below the normal mean</td>
</tr>
<tr>
<td>Percent of chords with hypokinesis&lt;−1SD</td>
<td>Proportion of the LV contour with hypokinesis more severe than 1 SD below the normal mean</td>
</tr>
<tr>
<td>Hypokinesis in the central infarct region</td>
<td>Severity of hypokinesis in the central infarct region, expressed in units of SD from the normal mean</td>
</tr>
<tr>
<td>Hypokinesis in the border zone of the infarct region</td>
<td>Severity of hypokinesis in the periphery of the infarct region, expressed in units of SD from the normal mean</td>
</tr>
</tbody>
</table>

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TABLE 3. Clinical and Angiographic Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=51)</th>
<th>Cariporide (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>59.8±12</td>
<td>59.1±12</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>38 (75)</td>
<td>37 (76)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±13</td>
<td>75±14</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27±4</td>
<td>26±4</td>
</tr>
<tr>
<td>History of angina before acute MI, n (%)</td>
<td>19 (41)</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Previous inferior MI, n (%)</td>
<td>3 (6)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>No heart failure, n (%)</td>
<td>50 (98)</td>
<td>48 (98)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>27 (41)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Diabetes mellitus type II, n (%)</td>
<td>12 (24)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>16 (31)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (45)</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Concomitant medications, n (%)</td>
<td>42 (82)</td>
<td>41 (84)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>47 (92)</td>
<td>46 (94)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>43 (84)</td>
<td>42 (86)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>50 (98)</td>
<td>49 (100)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>51 (100)</td>
<td>47 (96)</td>
</tr>
<tr>
<td>Heparin</td>
<td>10 (20)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Abciximab</td>
<td>17/19/15</td>
<td>26/12/11</td>
</tr>
<tr>
<td>1/2/3-Vessel disease, n</td>
<td>47/4</td>
<td>47/2</td>
</tr>
<tr>
<td>TIMI grades 0/1/2/3, n</td>
<td>46/4/0/0</td>
<td>43/6/0/0</td>
</tr>
<tr>
<td>Collaterals absent/minimal/well developed, n</td>
<td>42/7/2</td>
<td>40/8/1</td>
</tr>
<tr>
<td>Pressure rate index (MABP×HR/1000)</td>
<td>8.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Before treatment</td>
<td>220±12</td>
<td>211±13</td>
</tr>
<tr>
<td>4 Hours after treatment</td>
<td>7.3</td>
<td>7.1</td>
</tr>
<tr>
<td>PTCA success, n (%)</td>
<td>46 (90)</td>
<td>48 (98)</td>
</tr>
<tr>
<td>Stent implantation, n (%)</td>
<td>20 (39)</td>
<td>27 (55)</td>
</tr>
<tr>
<td>No. of days in hospital</td>
<td>16.3±2.8</td>
<td>15.1±0.9</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; MABP, mean arterial blood pressure; and HR, heart rate.

success was defined as the achievement of a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow.

**Results**

**Patient Groups**

The clinical and angiographic characteristics of both groups are shown in Table 3. There were no significant differences for any of these variables for the entire sample of randomized patients or in the patient groups included in the primary efficacy analysis with paired left ventriculograms at baseline and follow-up. The angiographic characteristics of the patients with paired LV angiograms were similar (data not shown in Table 3). In 1 patient in the cariporide group, a TIMI 2 flow was obtained by PTCA; in all other patients with paired LV angiograms, a TIMI 3 flow was obtained after PTCA. A patent infarct vessel with TIMI 3 flow at follow-up was found in all patients of the placebo and cariporide groups.

**Clinical Outcomes**

There were 3 deaths in the placebo group and 4 in the cariporide group during hospitalization. One patient in the cariporide group died after failed direct PTCA and another after failed direct PTCA and emergency bypass grafting. One patient died of cerebral infarction, another of refractory heart failure. Two patients in the placebo group died after failed PTCA. One patient died of sepsis and multiorgan failure. Two patients in the cariporide group and 1 in the placebo group underwent repeat PTCA because of reocclusion with reinfarction. One patient with reocclusion in the placebo group underwent emergency CABG. Five patients in the placebo group developed heart failure, and 3 patients in the cariporide group had a period of hypotension. One patient in the placebo group underwent elective bypass surgery after successful PTCA.

**Global LV Function**

The end-systolic volume increased during the 3-week follow-up from 80.3±6.9 to 97.0±10.3 mL in the placebo group, whereas a decrease from 76.7±5.4 to 69±5.6 mL was observed in the cariporide group (P=0.048; Figure 1A).

The end-diastolic volume increased from 137.3±9.5 to 157.5±11.6 mL in the placebo group and decreased slightly, from 149.8±10.3 to 146.7±10.5 mL, in the cariporide group (P=NS; Figure 1B). The ejection fraction remained unchanged in the placebo group (40±2% versus 40±3%), whereas an increase from 44±2% to 50±2% was observed with cariporide (P<0.045; Figure 1C).

**Regional LV Function**

The proportion of the LV contour with akinesis or dyskinesis at end systole was 29.5±2.4% at baseline and 20.2±3.3% after 3 weeks in the placebo group, compared with 25.6±2.0% at baseline and 10.7±2.4% after 3 weeks in the cariporide group (P=NS; Figure 2A). The proportion of the LV contour with hypokinesis < −2 SD below the normal mean amounted to 54.2±2.7% at baseline and 48.9±4.6% after 3 weeks in the placebo group, compared with 47.2±3.4% at baseline and 31.0±4.4% after 3 weeks in the cariporide group (P=0.045; Figure 2B). The proportion of the LV circumference with hypokinesis < −1 SD below the normal mean amounted to 70.9±1.9% at baseline and 70.0±4.3% at 3 weeks in the placebo group, compared with 65.4±2.4% at baseline and 55.2±4.6% at 3 weeks in the cariporide group (P=0.082; Figure 2C). The hypokinesis in the central infarct region was −3.2±0.3 SD at baseline and −3.1±0.2 SD at 3 weeks in the placebo group and −2.7±0.3 SD at baseline and −2.3±0.2 SD at 3 weeks in the cariporide group (P=NS; Figure 3A). The severity of hypokinesis in the border zone of the infarct region improved from −2.3±0.2 SD at baseline to −2.0±0.2 SD after 3 weeks in the placebo group and from −1.7±0.1 to −1.1±0.2 SD in the cariporide group (P=0.052; Figure 3B).

**Cardiac Enzymes**

There were no significant differences for CK, CK-MB, or LDH at baseline between the placebo and cariporide patients. There was a trend for higher peak concentration, greater area
under the curve, and greater time to peak concentration for all cardiac enzymes in the placebo group. The peak concentration of CK was higher in the placebo group ($P=0.053$). The area under the curve for CK-MB was significantly lower in the cariporide group than in the placebo group ($P=0.047$). The time until peak concentration of LDH was lower in the cariporide group ($P=0.024$; Figure 4 and Table 4).

Safety Analysis
A local hemorrhage at the puncture site was seen in 7 patients in the placebo group and 5 patients in the cariporide group. Four patients in the placebo group and 2 in the cariporide group developed pneumonia. One patient of the cariporide group developed an acute exacerbation of a Guillain-Barré syndrome during hospital stay, and another developed heparin-induced thrombocytopenia, confirmed by determination of specific antibodies. There were no major differences in laboratory data or rhythm disturbances between the 2 treatment groups.

Discussion
Early reperfusion by either thrombolysis or PTCA has been shown to salvage the jeopardized myocardium and to improve the prognosis of patients with acute MI. Early reperfusion is also a source of reperfusion injury and cell damage. In fact, reperfusion after intravenous thrombolytic therapy has revealed disappointingly small improvements in the global ejection fraction in clinical trials. It has been suggested that the modest improvement in global LV function is related to reperfusion injury, which, in turn, may offset some of the expected benefit from reperfusion. Thus, prevention of reperfusion injury is likely to magnify the benefits derived from reperfusion. Several approaches to protecting the ischemic myocardium are under investigation, including antioxidant therapy, ischemic preconditioning, and inhibition of leukocyte adhesion and complement activation. However, only 1 of these approaches, antioxidant treatment with recombinant human superoxide dismutase, has been tested clinically in patients with acute MI, and it failed to demonstrate a beneficial effect on LV function.
Direct cell protection against the damage produced by ischemia represents an exciting approach as an alternative or complement to traditional therapies to improve oxygen delivery and reduce oxygen requirements. The accumulation of protons during ischemia stimulates the Na\(^+/\)H\(^+\) exchange system and subsequently, the Na\(^+/\)Ca\(^{2+}\) exchanger leading to cytosolic calcium overload, which may result in cell death. In fact, Na\(^+/\)H\(^+\) exchange inhibitors have been shown to limit infarct size in several animal species.\(^{9,17,25,26}\) The best effect was seen with preischemic administration of Na\(^+/\)H\(^+\) exchange inhibitor, but there was still a marked benefit with administration before reperfusion.\(^{16}\) Docherty et al\(^{27}\) evaluated the effects of dimethylamiloride given either before ischemia, at reperfusion, or at both time intervals on cardiac function and intracellular pH. All drug regimens caused a significant increase in the recovery of mechanical function after reperfusion and slowed the recovery of intracellular pH during reperfusion. In fact, as little as 1 minute of exposure to dimethylamiloride immediately at the time of reperfusion has been shown to protect the coronary perfused right ventricular wall.\(^{28}\) In the perfused whole heart, preischemic perfusion of the drug was necessary for cardioprotection. This may be a result of a limitation in drug delivery across the vascular wall. In our patients, the drug was given 10 minutes before reperfusion and thus may have reached the ischemic myocardium via collaterals. Although only 18% of the patients revealed angiographically visible collaterals, there is evidence that angiography may fail to visualize microvascular collaterals, which may provide blood flow to the periphery of an ischemic region. Because the drug is given a fair amount of time before PTCA, we cannot exclude that some of its effects could already be occurring during the ischemic period.

The present study was the first trial in humans to test the concept that inhibition of Na\(^+/\)H\(^+\) exchange has a beneficial effect on the recovery of LV function after MI and reperfusion. The rationale for the design of this study was that an occluded vessel had to be present to ensure that therapeutic intervention would be performed before reperfusion. Primary PTCA in acute MI was therefore an appropriate clinical measure. Because the improvement of regional and global LV function in previous reperfusion trials has been negligible in patients with inferior infarction, we enrolled only patients with substantial acute anterior infarction, assuming that this patient population would provide the greatest potential to demonstrate protection of jeopardized myocardium.

Our results demonstrate significant improvements in global and indices of regional LV function after cariporide compared with placebo in patients with acute MI undergoing PTCA. In addition, the reduced blood levels of cardiac enzymes are compatible with a reduction in tissue injury. Blood pressure, heart rate, and its product, pressure-rate index, a marker of oxygen consumption, did not differ significantly between the 2 groups at baseline and over the first 4 hours after reperfusion. This suggests that the beneficial effect of cariporide is not related to effects on myocardial oxygen consumption.\(^{29}\)

An established method for quantitative analysis of regional wall motion abnormalities on left ventriculograms is the method developed by Sheehan et al.\(^{18}\) The results of this analysis support the hypothesis that the beneficial effect of cariporide is related to myocardial protection in the ischemic area of the left ventricle. Improvement in the function of the central infarct region was not significantly greater in caripo-

![Figure 4. Enzyme activity at baseline and 4, 12, 24, 36, and 72 hours after PTCA in patients treated with placebo (A) and cariporide (B). A, CK; B, CK-MB; C, LDH. Significance between treatment groups refers to peak concentration (C\(_{\text{max}}\)), area under curve (AUC), or time until peak concentration (t\(_{\text{max}}\)).](http://circ.ahajournals.org/)

![Table 4. Significance of Differences in Enzyme Release Between Placebo or Cariporide-Treated Patients](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th></th>
<th>CK, U/L</th>
<th>CK-MB, U/L</th>
<th>LDH, U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>C(_{\text{max}})</td>
<td>t(_{\text{max}})</td>
<td>AUC</td>
</tr>
<tr>
<td>(p)</td>
<td>0.101</td>
<td>0.053</td>
<td>0.09</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; C\(_{\text{max}}\), peak concentration; and T\(_{\text{max}}\), time until peak concentration.
ride patients, but wall motion may increase in nonreper-
 fused patients because of retraction of dyskinesis.30 Instead,
 the increased ejection fraction may be attributed principally
to the reduction in extent of hypokinesis and akinesis/ dyskinesis and to the improved wall motion in the border zone. These findings are consistent with a previous study showing that reperfusion therapy exerted its greatest benefit in the peripheral or border zone.30

Global remodeling of the left ventricle after MI is also related to hypertrophy and dilation of the noninfarcted ventricle.31 In this respect, there is experimental evidence that the Na+/H+ exchanger is involved in postischemic adaptive hypertrophic responses.32,33 Therefore, it is conceivable that the beneficial effects of cariporide on global LV function extend beyond protection of ischemic myocardium after MI and are also attributable in part to attenuation of a remodeling process within the noninfarcted left ventricle.

Reperfusion-induced arrhythmias have been observed after successful reperfusion with intracoronary thrombolysis. Na+/H+ exchange inhibitors reduced the occurrence of reperfusion arrhythmias in animal experiments. In the present study, however, the incidence of arrhythmias was too low and the duration of monitoring of arrhythmias was too short to confirm the existence of an arrhythmia effect of caripo-
ride in patients with acute MI. Thus, our protocol did not allow us to observe a possible arrhythmia effect of Na+/H+ exchange inhibition.

Limitations of the Study

The proportion of patients with paired ventriculographic data was 55%. This is slightly higher than in the TIMI-1 trial, which also measured functional recovery.34 However, patients with versus those without paired ventriculographic data were similar in baseline characteristics. In particular, the angiographic characteristics of the patients with paired LV angiograms were very similar, including rate of successful reperfusion, number of patent left anterior descending coro-
angiograms were very similar, including rate of successful
angiographic characteristics of the patients with paired LV
were similar in baseline characteristics. In particular, the
administration of the Na+/H+ exchange inhibitor
cariporide (HOE 642) before reperfusion with direct PTCA in
acute MI is safe and appears to provide a novel means to limit
myocardial injury and improve global and regional LV function. Our observations are consistent with the notion that
reperfusion injury occurs after MI in humans and should be a
target for interventions, such as Na+/H+ exchange inhibition.
Large-scale clinical trials are warranted to establish this novel therapeutic principle in patients with large myocardium at
risk, ie, during bypass surgery or acute MI and reperfusion
to evaluate the impact on mortality.

Acknowledgments

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