Na⁺/H⁺-Exchange Inhibition by Cariporide (Hoe 642): A New Principle in Cardiovascular Medicine

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INTRODUCTION

Acute myocardial infarction is one of the most common causes of death in Western industrialized countries. Many patients with acute myocardial infarction develop lethal cardiac arrhythmias that are often the final cause of death. Both basic and clinical research efforts have been directed toward a new therapeutic strategy, to reduce ischemic damage and/or the incidence of arrhythmias in the course of ischemia and reperfusion. The purpose of this article is to summarize the experimental pharmacology and clinical data on the new Na⁺/H⁺-exchange inhibitor, cariporide.

The pathophysiology of regional ischemia is complex. In addition to intracellular acidification, many other factors are thought to contribute to ischemic cardiac injury. There are at least two transporters regulating intracellular pH: the Na⁺/H⁺-exchanger and the Na⁺/HCO₃⁻ symport. Intracellular acidification, occurring in the course of regional ischemia, is likely to activate both transporters, leading to a net sodium influx. Under certain conditions (see below), intracellular sodium may be exchanged for calcium. Intracellular acidification will have at least three consequences: 1) it will close gap-junctional channels, thereby isolating the ischemic area electrically, 2) it will lead to a Na⁺ influx via Na⁺/H⁺-exchange (12,50) that is activated by low intracellular pH (13,29), and 3) it will activate Na⁺/K⁺-ATPase, leading to an increase in ATP consumption (12,46). Eventually the intracellular acidification will “arrest” the cells, a process called “acid freezing.” In addition, an increase in intracellular sodium concentration will enhance calcium overload during recovery from ischemia (53).

Amiloride and its derivatives, 5-(N,N-dimethyl)amiloride hydrochloride, N-(ethyl-N-isopropyl)amiloride, 5-N-(methyl-N-isobutyl)amiloride, and 5-(N,N-hexamethylene)amiloride,
were found to be weak antagonists of the cardiac Na+/K+ -exchanger. Amiloride derivatives, administered prior to regional ischemia, prevent ischemia-associated arrhythmias and reduce ischemic damage (22,33,35,43,49). However, these amiloride derivatives are not specific for the cardiac Na+/H+ -exchanger.

The Na+/H+ -exchanger is a family of at least four exchanger subtypes (NHE-1 to NHE-4), all of them now cloned. The NHE-1 subtype is found in the heart as well as other tissues, while the other three subtypes are expressed selectively in such tissues as the kidney or walls of the small intestine. The specific distribution of the subtypes reflects their different functions, including regulation of intracellular pH and cell volume by NHE-1 and the regulation of Na+ -uptake in the gut and kidney by NHE-2 and NHE-3, respectively. Cardioprotective agents are expected to be specific for NHE-1, since this is the only subtype expressed in the heart (32), and not to affect kidney or gut function.

One of the newest approaches to cardioprotection involves the use of 3-methylsulfonyl-substituted guanidine-methanesulfonates with Na+/H+ -inhibitory properties. Among them are Hoe 694 and cariporide (Hoe 642) (16). Several investigators reported cardioprotective effects of these inhibitors in different animal models: anesthetized pig, subjected to regional ischemia for 45 min followed by 24-h reperfusion (27); rabbit heart in vivo, subjected to 30-min regional ischemia and 180-min reperfusion (4); canine heart in vitro, subjected to coronary occlusion (56); and working rat heart exposed to low-flow ischemia (23, for review see 21).

Cariporide (Hoe 642; 4-isopropyl-3-methylsulfonylbenzoyl-guanidine methanesulfonate) is more specific for NHE-1 than is Hoe 694 (3-methylsulfonyl-4-piperidinobenzoyl-guanidine methanesulfonate) (7,48) and has, therefore, been favored for cardiovascular therapy. In addition to its high relative selectivity for NHE-1, cariporide has no effect on other ion currents (48 and see below).

Possible clinical indications for cariporide include acute cardiac ischemia, preinfarction syndrome, unstable angina pectoris, and cardioprotection in cardiac surgery (transplantation and cardioplegia during aortocoronary venous bypass grafting).

Ventricular arrhythmias (including fibrillation) are the most critical complications of acute cardiac ischemia. Among the many factors that contribute to arrhythmogenicity in cardiac ischemia is cellular uncoupling via closure of gap-junction channels. This uncoupling is caused by several factors, including calcium and sodium overload, ATP depletion, accumulation of acylcarnitines, and intracellular acidification (for reviews, see 8,40). Cellular uncoupling is likely to cause the dispersion of action potential duration (30) and a deterioration of the activation pattern. In addition, this uncoupling could lead to electrical insulation of the ischemic area. Potassium efflux, depolarization, and intercellular uncoupling will finally produce electrical inactivity, an electrically silent area. Theoretically, acidification may enhance the inhibition of NHE-1, leading to a broader silent area, reduction in the energy consumption, and an antiischemic effect. On the other hand, inhibition of NHE-1 could also lead to slower recovery upon reperfusion and interference with calcium overload.

CHEMISTRY

The chemical structures of amiloride, Hoe 694, and cariporide are shown in Fig. 1. All three compounds possess a guanidino function that seems to be essential for NHE-
inhibitory activity. As reported in a structure-activity study (2) substitution in positions 3 and 6 reduces NHE-inhibitory activity, while 2-methyl substitution enhances it. The 2-methyl-5-(methylsulfonyl)benzoyl guanidines showed a higher in vitro activity than did the respective desmethyl compounds. In the structure-activity study, the compounds were dispersed in water with the help of 1% dimethyl sulfoxide. Amiloride, Hoe 694, or cariporide can be administered parenterally or orally (48). The chemical synthesis of cariporide was described by Weichert et al. (55). Cariporide is available as mesilate salt.
EXPERIMENTAL PHARMACOLOGY OF CARIPORIDE

Selectivity of Cariporide for NHE-1

The selectivity of cariporide was tested in NHE-deficient fibroblast PS 120 cell lines stably transfected with and expressing NHE-1, NHE-2, or NHE-3 subtypes (6,48). These cells were acidified using the NH₄⁺ prepulse technique measuring ²²Na⁺-uptake in the absence and presence of cariporide. All NHE subtypes were inhibited by cariporide but with different apparent $K_i$ (0.05 μmol for NHE-1, 3 μmol for NHE-2, and 1 mmol for NHE-3) (48). Other ion currents were not affected, and the Na⁺/Ca²⁺-exchange current and veratridine-induced Na⁺ current specifically remained unaltered (48). The action potential morphology was not altered by cariporide (8).

Effects on Isolated Cells

The shape change in human platelets induced by intracellular acidification using sodium propionate was slowed by cariporide with an IC₅₀ of 0.2 μmol (48). Amiloride-sensitive sodium influx into rabbit erythrocytes was inhibited by cariporide with a similar IC₅₀ in the same study.

In rat cardiomyocytes, cariporide slowed the recovery of intracellular pH following a second NH₄Cl prepulse as compared with the first prepulse. The IC₅₀ for this effect was between 0.1 and 1 μmol (48). To study the effects of cariporide on intracellular sodium, calcium, and proton concentrations, Russ et al. (47) used rat anoxic cardiomyocytes (metabolically uncoupled by 1.5 mM cyanide). Anoxia led to intracellular acidification (pH was reduced from 7.2 to 6.8) and an increase in the intracellular Ca²⁺ (from 50 nmol to 1 μmol).

Upon reoxygenation, pH returned to normal value while Ca²⁺ oscillated as previously reported (28). Cariporide, at 10 μmol added at the beginning of the experiment, inhibited the recovery of pH, but not the Ca²⁺ oscillations. The IC₅₀ of cariporide for its effect on pH recovery was 0.4 μmol. It is noteworthy that Russ et al. (47) reported that, in cariporide-treated rat ventricular myocytes, anoxia did not enhance acidification. This finding is supported by Pike et al. (43), who showed that during ischemia NHE plays an important role in the rise in Na⁺ but not of pH. Russ et al. (47) also monitored Na⁺ and found that cariporide has no effect on the rise in intracellular sodium concentration following acidification and inhibition of oxidative phosphorylation. It is noteworthy to mention that these authors worked with a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)-buffered saline solution without bicarbonate. In their experiments, Russ et al. concluded that sodium influx into rat ventricular myocytes is controlled by both NHE and other Na⁺-channels.

During evaluation of the various studies on the effects of drugs on NHE, it is important to know what buffer was used since, in the presence of bicarbonate, intracellular pH can also be regulated by Na⁺/HCO₃⁻-symport.

The rate of pH recovery in metabolically inhibited rat cardiomyocytes (HCO₃⁻-free buffer) was slowed in the presence of cariporide (15), so it is reasonable to assume that secondary transport systems, such as the Na⁺/Ca²⁺-exchange that is linked to the rise in intracellular Na⁺, may also be slowed.

Using isolated rat ventricular cardiomyocytes, Shipolini et al. (51) demonstrated the
dependence of cariporide activity on intracellular pH. At normal pH, 1 μM cariporide inhibited NHE by 80%. When cells were intracellularly acidified by a 3-min pulse of 20 mM NH₄Cl followed by a 1-min Na⁺-free superfusion and washout, cariporide blocked NHE with an IC₅₀ of approximately 0.01 μmol. Upon washout, pH normalized at a rate similar to that observed in untreated cells. To study the pathophysiological significance of lysophosphatidylcholine (lysoPC) in ischemia, Hoque and Karmazyn (18) superfused rat cardiomyocytes with 3 μM lysoPC, activating NHE as indicated by a faster pH recovery after NH₄Cl prepulse. Cariporide antagonized the effects of lysoPC on isolated hearts in the same study (see below).

**Effects on Papillary Muscles**

Cellular uncoupling due to intracellular sodium or calcium overload, as well as to acidification, is thought to contribute to ischemia-related arrhythmia. Dhein et al. (8) tested the hypothesis that cariporide might antagonize cellular uncoupling in right ventricular guinea pig papillary muscles superfused with bicarbonate-buffered Tyrode solution. Uncoupling was produced with 25 mmol/L of Na-propionate for 20 min in the absence or presence of 1 μmol/L of cariporide. The stimulus-response delay between the stimulus and the propagated action potential was used as a measure of conduction velocity. It was prolonged by Na-propionate without any effect on resting membrane potential, overshoot potential, action potential duration, or maximal repolarization velocity of the action potential (dV/dt_max), indicating cellular uncoupling. This Na-propionate-induced reduction in conduction velocity was fully prevented by cariporide without affecting the action potential morphology or resting membrane potential.

Prolongation of the stimulus-response interval can be due to either gap-junctional uncoupling or reduced I_Na availability. In the case of reduced I_Na availability, a marked reduction in dV/dt_max should also occur (3). On the other hand, if reduction in conduction velocity is caused by gap-junction uncoupling, resting membrane potential and dV/dt max should not change, except for a small increase in dV/dt_max (8). This phenomenon is explained by current loss to adjacent cells after uncoupling (36,52). Several weak organic acids, such as acetic, lactic, and propionic acids, have been reported to cause gap-junctional uncoupling by intracellular acidification and accumulation of sodium. These acids are used experimentally to produce uncoupling in cardiac preparations (37,38,41, 45). The suppressant effect of cariporide indicates that this drug might antagonize cellular uncoupling; it is conceivably due to the reduction in sodium overload (8).

**Effects on Isolated Hearts**

In isolated working rat hearts subjected to ischemia and reperfusion [regional ischemia induced by a 15-min clamp of the left anterior descending coronary artery (LAD)], the release of lactate, lactate dehydrogenase, and creatine kinase was reduced during ischemia in the presence of cariporide at concentrations from 0.01 μmol (48). In the preischemic period, the drug had no effect. The incidence of ventricular fibrillation in cariporide-treated hearts was significantly decreased. After reperfusion, the tissue content of ATP, glycogen, and creatine phosphate was higher in cariporide-treated hearts. After 30 min of
regional ischemia, rabbit hearts treated with 1 μM cariporide had higher ATP concentrations than did untreated hearts (8).

The reported antiarrhythmic activity of cariporide in dogs and rats (56) has been investigated in more detail by Dhein et al. (8). NHE inhibition may lead to a stronger intracellular acidification and, thus, to a larger electrically silent area, reduced energy consumption, and consequently lower arrhythmogenicity. This concept was tested in isolated rabbit hearts subjected to regional ischemia (30 min) followed by 30-min reperfusion. The electrically silent zone was not expanded by cariporide, but the ischemia-induced elevation of the ST-segment in the epicardial electrocardiograms (an indicator of ischemic damage) was attenuated by the drug. The loss of ATP was reduced, and there was a lesser increase in end-diastolic pressure in cariporide-treated than in control animals. The drug reduced the incidence of ventricular fibrillation and antagonized the increase in the dispersion of action potential duration. Dispersion is characterized by the occurrence of short- and long-action potentials next to each other; it is usually viewed as a risk factor for the initiation of reentrant arrhythmia. It is the consequence of local heterogeneity of action potential duration in the ischemic center and border zone and is due to gap-junction uncoupling. It was concluded that the antiarrhythmic activity of cariporide is due to several factors: reduction of dispersion, slower recovery of action potential duration (which may also lead to mitigation of local differences in the potential duration and give more time for the assimilation between the reperfused and normal zone), cardioprotection due to reduction of ATP loss, and prevention of cellular uncoupling (8). The hypothesis that prevention of sodium overload may be an important factor in cardioprotection is supported by Eng et al. (11). These investigators used isolated perfused hearts (submitted to 30 min of ischemia and reperfusion) to compare the effects of cariporide and tetrodotoxin on sodium entry blockade. Both treatments improved ventricular performance, and the authors concluded that sodium entry may play a crucial role in the pathophysiology of cardiac ischemia.

In isolated rat hearts, 5 μmol of cariporide attenuated and delayed the decrease in left ventricular pressure and the elevation of left ventricular end-diastolic pressure induced by 150 to 200 μmol of hydrogen peroxide. The effects of purine and xanthine oxidase were not antagonized by cariporide (18). The H$_2$O$_2$-induced loss of high-energy phosphates was also reduced. The authors concluded that the Na$^+$/H$^+$ antiporter is somehow involved in the cardiotoxicity of hydrogen peroxide. Subsequently, Hoque et al. (17) showed that cariporide, at 5 μmol, antagonized the cardiac depressant effect of lysophosphatidylcholine (an activator of NHE) in rat hearts. Lysophosphatidylcholine also activates protein kinase C (39), an enzyme that is also involved in the regulation of NHE, so that protein kinase C-dependent activation of NHE may be viewed as a contributory factor to myocardial hypoxia (19).

Cariporide significantly improved the cardiac performance of isolated rat hearts perfused with carbonate-buffered saline and exposed to global low-flow ischemia (42). Isolated rat hearts subjected to hypoxia (40 min) and reoxygenation (90 min) developed marked myocardial edema (20), which was antagonized by 6.7 μmol of cariporide. This effect of cariporide was intensified by perfusion with HCO$_3^-$-free medium and concomitant inhibition of Na$^+$/HCO$_3^-$-symport by 4,4’-dibenzamidostilbene-2,2’-disulfonic acid.

Chakrabarti et al. (5) evaluated the concept that ischemia may induce apoptosis and that NHE may contribute to the pathophysiology of ischemia-induced cardiac depression.
These investigators used rat hearts exposed to global zero-flow ischemia (10- to 30-min duration) with or without reperfusion (5). Cariporide significantly reduced the number of apoptotic cells in ischemic and reperfused hearts, indicating an involvement of NHE in the pathophysiology of ischemia-induced apoptosis. This antiapoptotic effect of cariporide may also be involved in the mechanism of its cardioprotective action.

Although the precise mechanism of the cardioprotective effect of preconditioning is still unclear, there is general agreement that preconditioning attenuates the intracellular acidosis that develops during the subsequent ischemia. An involvement of NHE has been proposed, but 1 μM cariporide did not reduce the efficacy of preconditioning (51). This might be of clinical relevance if the drug is used in the therapy of unstable angina pectoris.

The effects of cariporide on cardiac performance after normothermic cardioplegia were investigated in a rat model (54). Cardioplegia led to a marked myocardial edema. Myocardial water content was significantly lower in hearts receiving cariporide for the duration of the experiment or only during cardioplegia. If the drug was administered during reperfusion only, it had no effect on myocardial edema. The functional recovery of left ventricular pressure after cardioplegia was enhanced by cariporide. The most important in vitro data are summarized in Table 1.

### Effects in Vivo

Cariporide was administered to anesthetized rats at 0.01, 0.1, and 1 mg/kg i.v. 5 min prior to ligation of the LAD (48). The drug reduced all types of cardiac arrhythmias, especially ventricular fibrillation and ventricular tachycardia. Cariporide was also effective orally at doses of 0.1 mg/kg or higher.

In anesthetized pigs subjected to occlusion of the LAD for 55 min, followed by 5 h of reperfusion (14), pretreatment with cariporide reduced rigor and hypercontracture, diminished infarct size, and attenuated arrhythmias. By intracoronary administration into the area at risk, cariporide suppressed reperfusion arrhythmias but did not reduce infarct size. By systemic administration prior to reperfusion, cariporide had no effect. To be effective, it appears that cariporide must reach the area at risk prior to reperfusion, preferably before ischemia. It is noteworthy that cariporide (3 mg/kg; peak plasma concentration, 6.7 μmol

### Table 1. Summary of in vitro data on cariporide

| Formula | C_{13}H_{21}N_{3}O_{6}S_{2} (cariporide-mesilate) |
| Molecular weight | 284 (cariporide mesilate) |
| Solubility | in 1% DMSO |
| Potassium affinity (K_{i}) for NHE-1 | 0.05 μmol/L |
| Potassium affinity (K_{i}) for NHE-2 | 3 μmol/L |
| Potassium affinity (K_{i}) for NHE-3 | 1000 μmol/L |
| Effective concentrations (in vitro experiments) | 0.1–5.0 μmol/L |
| Main findings | Slowing of pH recovery (NH_{4}Cl prepulse, metabolic inhibition) antiarrhythmic reduced increase in dispersion reduced infarct size (given prior to occlusion) limits ATP loss no effect on action potential morphology |

Abbreviations: DMSO, dimethyl sulfoxide; NHE, Na^{+}/H^{+} exchanger with subtype 1 (NHE-1), subtype 2 (NHE-2), and subtype 3 (NHE-3).
at 5 min after injection with an exponential decay over 240 min with 1.7 μmol after 90 min) did not alter heart rate, aortic pressure, or coronary blood flow. In the same study, cariporide had no effect on platelet count, thromboplastin time, blood pH, or blood gases.

The antiarrhythmic properties of cariporide have also been examined in vivo in dogs and rats (1,56). Xue et al. (56) showed that 1 mg/kg of cariporide significantly suppressed the incidence of ventricular fibrillation in a dog model of coronary occlusion (30 min) and reperfusion. Ventricular premature beats and ventricular tachycardia during ischemia were, however, not suppressed by the drug. As in other studies, the heart rate, blood pressure, and QT-duration were not changed by cariporide. After bolus administration of the drug, plasma concentrations of cariporide exhibited a double exponential decay fitting a two-compartment model. In rats, Aye et al. (1) systematically investigated the antiarrhythmic effects of cariporide with regard to the minimal dosage required. Three types of treatment were used: pretreatment (i.e., 5 min prior to occlusion); posttreatment (i.e., 3 min after the start of the occlusion period); and reperfusion-treatment. Ventricular tachycardia, ventricular fibrillation, and mortality were effectively reduced by cariporide at doses ≥0.1 mg/kg in the pretreatment protocol. In the posttreatment protocol, ventricular tachycardia was suppressed by cariporide only at 1 mg/kg, while ventricular fibrillation and mortality were reduced at doses ≥0.1 mg/kg. Given with reperfusion, cariporide failed to reduce ventricular tachycardia or mortality, although the incidence of ventricular fibrillation was somewhat diminished.

Cariporide also reduced infarct size in rabbits subjected to 30-min LAD occlusion and 3-h reperfusion (34). The drug was effective at 0.6 mg/kg, given 10 min before ischemia; it reduced the infarct size from 55% in the control group to 26% in the cariporide-treated group. Cariporide was ineffective, however, when administered at 5 min prior to reperfusion. The effect of cariporide was not altered by protein kinase C inhibition.

The cardioprotective effects of cariporide were also confirmed by Linz et al. (31) in rabbits submitted to 30-min occlusion of a branch of the left coronary artery and 2-h reperfusion. Infarct size was reduced, and ventricular function was improved by cariporide at doses >0.03 mg/kg, when administered 10 min before occlusion; if administered 5 minutes before reperfusion, the drug was considerably less effective.

Cariporide, 1 mg/kg, was found to reduce the infarct size in pigs (26). In this study, cariporide was administered not before but at 15 min after induction of ischemia, which lasted for 60 min and was followed by 24 h of reperfusion. The ischemia was, however, not complete in this study. A residual blood flow (3 ml/min) to the ischemic area was maintained during the entire ischemic period.

In another study, sheep (open-chest model) were subjected to graded hypoxia with or without treatment with an intravenous bolus injection of cariporide, 2 mg/kg, at 20 min prior to the induction of hypoxia. In control animals, the myocardial intracellular pH remained unchanged or only slightly decreased during hypoxia, while in cariporide-treated animals, there was a significant drop in myocardial pH. The loss of energy-rich phosphates was more pronounced in cariporide-treated animals than in controls. These results appear contradictory to other findings, but one has to keep in mind that graded global hypoxia is a completely different pathophysiological model. In regional ischemia, local effects may be important, and an increased local sodium influx may enhance ATP consumption. In a graded global hypoxia, the maintenance of body pH and the release of catecholamines play an important role (44). The exact mechanism of cariporide action in
graded hypoxia is, however, still unknown. On the basis of available pharmacological studies, the use of cariporide in global systemic hypoxia, such as asphyxia, cannot be recommended.

Under normoxic conditions, the infusion of cariporide did not alter hemodynamic parameters, intracellular pH, or the myocardial level of energy-rich phosphates (44). To explore the possible use of cariporide in cardiac surgery, Kim et al. (24,25) investigated the effect of the drug on cardiac preservation. Cariporide improved cardiac function in hearts (stored for 4 h) from brain-dead or normal donor dogs (25). Addition of cariporide to the cardioplegic solution improved myocardial compliance in donor hearts for 24 h (25).

It can be concluded from the present experimental evidence that cariporide is potentially useful in the treatment of cardiac ischemia and unstable angina pectoris and as an additive to cardioplegic solution to reduce damage to transplant hearts during transportation. The main in vivo data are summarized in Table 2. The putative mechanism of action of cariporide is depicted in Fig. 2.

**CLINICAL PHARMACOLOGY OF CARIPORIDE**

At present, there are no published data on the human pharmacokinetics or clinical trials of cariporide, although Phase I and Phase II clinical studies have been performed. Preliminary results of an ongoing clinical trial (the GUARDIAN Trial; GUAR During Ischemia Against Necrosis) were presented at the 1999 Annual Meeting of the American College of Cardiology. In this trial, the efficacy of cariporide during unstable angina pectoris was evaluated in 11,500 patients. Cariporide was added to the existing treatment of high-risk patients suffering from unstable angina pectoris and those undergoing percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting. Preliminary data indicated a favorable safety profile for cariporide in these patients. The composite endpoint of death or myocardial infarction did not show an overall statistically significant benefit of the drug. However, a detailed subgroup analysis is still lacking.

Most pharmacological studies indicated that cariporide is effective in reducing infarct size when given prior to the infarct. Thus, the drug should be expected to prevent or to reduce the severity of the myocardial infarct if used as a preventive therapy. The effectiveness of a drug can also depend on the site of occlusion in the coronary vascular bed. It is conceivable that cariporide would prevent or reduce myocardial infarcts due to

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<th>Time to peak concentration after bolus injection</th>
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<td>antiarrhythmic</td>
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<td>reduced infarct size (given prior to occlusion)</td>
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<td>no effect on heart rate, QT-time, blood pressure</td>
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<td>no effect on blood gases</td>
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**TABLE 2. Summary of in vivo data on cariporide**
occlusion only at a certain site of the coronary vascular tree. Proper selection of patients for clinical trials can, therefore, be critical for the successful evaluation of a drug. Cariporide may not reduce the incidence of infarction in patients with unstable angina pectoris, but it may limit the severity of the infarct if the occlusion occurs at the same site as in animal experiments. Pharmacological data also indicate that patients with global myocardial ischemia should not be treated with cariporide.

Cariporide was also studied in patients undergoing coronary angioplasty for acute anterior myocardial infarction (10). The drug was administered at 40 mg by infusion over a 10-min period prior to angioplasty. The study involved 100 patients randomized to receive either placebo \( (n = 51) \) or cariporide \( (n = 49) \). Prior to angioplasty the left ventricular dysfunction did not differ between the groups of patients. When tested at 18 to 22 days after angioplasty, the ejection fraction in patients treated with cariporide was improved by 5.4%, regional wall motion abnormalities were significantly reduced, and the end-systolic volume was decreased. The creatine kinase (myocard-bound) (CK-MB) area under the curve was significantly smaller in cariporide-treated patients. This study supports the hypothesis that NHE inhibition can attenuate reperfusion injury and improve

**FIG. 2.** Mechanism of action of cariporide. Intracellular pH is controlled by \( \text{Na}^+ / \text{H}^+ \) exchange (NHE) and by \( \text{Na}^+ / \text{HCO}_3^- \) symport as well as \( \text{HCO}_3^- / \text{Cl}^- \) antiport (the latter is not shown). Reduction in intracellular pH can activate NHE and, in the presence of \( \text{HCO}_3^- \), the \( \text{Na}^+ / \text{HCO}_3^- \) symport (symp.). The resulting increase in intracellular \( \text{Na}^+ \) will activate both \( \text{Na}^+ / \text{K}^+ \)-ATPase and, as long as the pH is not too low, \( \text{Na}^+ / \text{Ca}^{2+} \)-exchanger (exch.), since low pH can inhibit sodium-calcium exchange (9). The increase in the intracellular \( \text{Na}^+ \) can also lead to sodium overload, an increase in ATP consumption, and possibly calcium overload. Calcium overload can be assumed to occur especially upon reperfusion, when the intracellular pH begins to normalize and the exchanger is no longer inhibited.
ventricular function if the drug is administered prior to reperfusion. However, this finding must be confirmed by large clinical trials, such as the ongoing GUARDIAN Trial.

At present, on the basis of pharmacological studies, it can be concluded that NHE inhibitors, such as cariporide, may conceivably be useful in the treatment of unstable angina pectoris, in balloon angioplasty (PTCA) for acute myocardial infarction, in the preservation of transplant hearts for cardiac surgery, and in cardioplegia. A final evaluation of this new therapeutic principle will be possible when the results of more clinical placebo-controlled studies are available.

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