Successful Ventricular Defibrillation by the Selective Sodium-Hydrogen Exchanger Isoform-1 Inhibitor Cariporide

Raúl J. Gazmuri, MD, PhD; Iyad M. Ayoub, MS; Elizabeth Hoffner, MS; Julieta D. Kolarova, MD

**Background**—Sodium-hydrogen exchanger isoform-1 (NHE-1) activation worsens functional myocardial abnormalities associated with ischemia and reperfusion. We hypothesize that these abnormalities may limit cardiac resuscitation from ventricular fibrillation (VF) and investigated whether NHE-1 inhibition with the benzoylguanidine derivative cariporide could improve resuscitability, postresuscitation myocardial function, and short-term survival in isolated heart and intact rat models of VF.

**Methods and Results**—In the isolated rat heart, VF was induced for 25 minutes. Perfusion was interrupted for the initial 10 minutes and restarted at 10% of baseline flow for the remaining 15 minutes (simulating chest compression). Cariporide ameliorated ischemic contracture, prevented postresuscitation diastolic dysfunction, and favored earlier return of contractile function. In the intact rat, cariporide, injected into the right atrium before chest compression was started (after 6 minutes of untreated VF), prompted spontaneous defibrillation between minutes 7 and 9 of chest compression in 6 of 8 rats. In contrast, electrical defibrillation was required in each of 8 control rats after completion of a predetermined 16-minute interval of VF. After resuscitation, cariporide-treated rats had less ventricular ectopic activity and normalized their hemodynamic function faster. Electrical defibrillation was then timed in control rats to match the time when spontaneous defibrillation occurred in cariporide-treated rats. With comparable VF duration, postresuscitation hemodynamic dysfunction was ameliorated by cariporide, but only when more severe ischemia was modeled by prolongation of the interval of untreated VF from 6 to 10 minutes.

**Conclusion**—NHE-1 inhibition may represent a novel and remarkably effective intervention for resuscitation from VF. (Circulation. 2001;104:234-239.)

**Key Words:** cardiopulmonary resuscitation • fibrillation • ischemia • sodium-hydrogen antiporter • cariporide
Isolated Rat Heart

A model of VF and ischemia previously developed in adult Sprague-Dawley rats was used.13,14 Hearts were harvested from 511- to 642-g rats according to the classic Langendorff technique, except that perfusion was started in situ (to minimize preconditioning) with a bicarbonate-buffered solution containing (in mmol/L) NaCl 118, KCl 4.7, CaCl₂ 1.25, MgSO₄ 1.2, NaHCO₃ 25, KH₂PO₄ 1.2, glucose 5, and Na pyruvate 2 and equilibrated with 95% oxygen (PO₂ 253±23 mm Hg) and 5% CO₂ (PCO₂, 30±2.2 mm Hg; pH 7.48±0.04). A latex balloon with an unstressed volume of 500 μL was positioned in the left ventricle. A thermistor (TSD102A, BIOPAC Systems, Inc.) and an electrode (to induce VF) were advanced into the right ventricle. The heart was immersed in a water-circulated chamber filled with perfusate, and the myocardial temperature was maintained at 37±0.3°C. After stabilization, the perfusate flow was increased to 20 mL/min, and the balloon was distended to an end-diastolic pressure of 10 mm Hg.

End-diastolic pressure-volume curves were obtained by 20-μL balloon decrements from an end-diastolic pressure >50 mm Hg to an end-diastolic pressure <10 mm Hg. The residual balloon volume was added to obtain absolute values, and the data were fitted to a 3-constant exponential function by the nonlinear Levenberg-Marquardt method according to the equation P(V)=A×V⁻ᵃ×e⁻ᵇ×V, in which P(V) is pressure as a function of volume, a is the slope of this relationship, and A and C are parameters of the equation. By use of the fitted equation, volumes corresponding to arbitrarily selected end-diastolic pressures ranging from 15 to 50 mm Hg were obtained. With this approach, the data variability was limited to the volume axis, facilitating statistical analysis and graphic rendition. Coronary vascular resistance corresponded to the mean perfusion pressure divided by the perfusate flow. Left ventricular water content was determined from wet and dry weights.14

VF was induced by a 0.5-mA alternating current delivered for 3 minutes to the right ventricular endocardium. Additional 30-second intervals of current were delivered whenever spontaneous defibrillation occurred, securing a 25-minute interval of uninterrupted VF. The perfusate flow was stopped during the initial 10 minutes (simulating untreated VF) and resumed at 10% of baseline flow for the remaining 15 minutes (simulating chest compression). The perfusate flow was then increased to baseline levels, and defibrillation was attempted with 0.1-J monophasic epicardial shocks delivered at 1-minute intervals.

The selective and potent NHE-1 inhibitor cariporide (4-isopropylmethylsulfonylbenezoyl-guanidine methanesulfonate, Aventis Pharma Deutschland GmbH) was administered during the interval of low-flow perfusion and the initial 5 minutes after defibrillation (n=8). A 100-μmol/L solution prepared in 0.9% NaCl was infused into the aortic cannula at 10% of the perfusate flow to yield a 10-μmol/L concentration in the coronary circuit. This concentration was shown to fully inhibit the exchanger in rat cardiac myocytes without effects on the Na⁺-Ca⁺ exchanger and fast Na⁺ current and to cause negligible effects on nonactivating Na⁺ currents.15 Control hearts received 0.9% NaCl (n=8).

Intact Rat

Adult Sprague-Dawley rats (438 to 545 g) were anesthetized by intraperitoneal injection of sodium pentobarbital (45 mg/kg) supplemented with 10 mg/kg at 30-minute intervals. Core temperature was maintained between 36.5°C and 37.5°C by use of an infrared heating lamp. A 5F catheter was orally advanced into the trachea and used subsequently for mechanical ventilation. Placement was verified with an infrared CO₂ analyzer (CO₂SMO model 7100, Novametrix Medical Systems, Inc). PE50 catheters were advanced into the abdominal aorta and the right atrium for pressure measurements and blood sampling. Through the right jugular vein, a 3F catheter (C-PUM-301J, Cook) was advanced into the right atrium, and a precurved guidewire was advanced through its lumen into the right ventricle. It was subsequently used to induce VF.

Ventricular ectopic activity was analyzed during the initial 4 minutes after resuscitation. Premature wide-QRS complexes were classified as singlets, bigemini, salvos, and nonsustained wide-complex tachycardia defined as ≥4 consecutive complexes lasting 120 seconds. Coronary perfusion pressure corresponded to the aortic minus the right atrial pressure at the end of diastole during spontaneous circulation and at the end of chest relaxation during chest compression.

VF was induced by a 60-Hz alternating current delivered to the right ventricular endocardium (0.10 to 0.70 mA) for 3 minutes.16 Fifteen seconds before completion of a predetermined interval of untreated VF, a 1-mg/kg bolus of cariporide or 0.9% NaCl solution (control) was injected into the right atrium. The dose was chosen because it significantly reduced the incidence of ventricular arrhythmias after coronary occlusion and reperfusion in rats without adverse effects on heart rate, blood pressure, and QT interval.17 Positive pressure ventilation with 100% oxygen was then initiated with a pneumatic valve (R-481, Clipper Instrument Laboratory Inc) set to deliver 0.39 mL/100 g body wt at 100 breaths per minute. Concomitant chest compression was provided with a pneumatically driven compressor (CJ-80623, CJ Enterprises) synchronized to delivered 2 compressions per 1 breath (200 compressions per minute). The depth of compression was adjusted to promote a coronary perfusion pressure exceeding the 20 mm Hg threshold required for successful resuscitation.16,18 The maximum piston travel provided estimates of compression depth. At a predetermined interval, electrical defibrillation was attempted by a maximum of two 2-J DC monophasic transthoracic countershocks (LifePak 9P, Physio-Control). If VF persisted or an organized electric rhythm with a mean arterial pressure of ≤25 mm Hg ensued, chest compression was resumed for 30 seconds. The defibrillation-compression sequence was repeated for a maximum of 3 additional cycles, increasing the energy of individual shocks to 4 and then to 8 J for the last 2 cycles. After successful resuscitation, ventilation was continued with a volume-controlled ventilator (683, Harvard Apparatus) using 100% oxygen for the initial 15 minutes and 50% oxygen for the remaining interval.

Three series of 16 experiments each (8 cariporide and 8 controls) were conducted. In the first series, VF remained untreated for 6 minutes, and electrical defibrillation was attempted after an additional 10 minutes of chest compression. Because spontaneous defibrillation occurred in cariporide-treated rats (shortening the duration of VF), 2 additional series were conducted in which electrical defibrillation was timed in control rats to match the time of spontaneous defibrillation in cariporide-treated rats. For these 2 series, the dose of cariporide was increased to 3 mg/kg, the interval of untreated VF corresponded to 6 and 10 minutes, and the postresuscitation interval was increased to 180 minutes.

Statistical Analysis

Continuous variables were analyzed between groups by 1-way or 2-way ANOVA. Categorical variables were analyzed by Fisher’s exact test. Equivalent nonparametric tests were substituted when tests for normality or equal variance failed. Multiple regression was used to assess the effects of drug treatment and other intervening variables on selected postresuscitation outcomes. The data are presented as mean±SD unless otherwise stated. A value of P<0.05 was considered significant.

Results

Isolated Rat Heart

Ischemic contracture developed during the 15-minute interval of low-flow perfusion and VF, increasing the ventricular pressure by 24±11 mm Hg in control hearts but only by 5±5 mm Hg (P<0.005) in cariporide-treated hearts (Figure 1, bottom). Cariporide also attenuated increases in coronary vascular resistance (Figure 1, top). After resuscitation, hearts treated with cariporide had normal end-diastolic pressure-volume relationships (Figure 2) despite no effects on left ventricular water content (83.3±0.6% in control hearts versus 82.9±0.6% in cariporide-treated hearts, P=NS). In addition,
contractile function normalized earlier in hearts treated with cariporide (Figure 3).

**Intact Rat**

**First Series (6 Minutes Untreated VF, Unmatched Defibrillation)**

During VF, the depth of chest compression necessary to attain comparable coronary perfusion pressure was less in cariporide-treated rats (Table 1). Unexpectedly, spontaneous defibrillation with return of a perfusing rhythm occurred between minutes 7 and 9 of chest compression in 6 of 8 rats treated with cariporide but in none of 8 controls. A representative experiment is shown in Figure 4. Spontaneous defibrillation was associated with restoration of spontaneous circulation 145 seconds earlier and the need for fewer electrical shocks with less cumulative energy (Table 1). After restoration of spontaneous circulation, cariporide-treated rats had less ventricular ectopic activity (Table 2), higher mean aortic pressure, and more rapidly normalized arrest-induced increases in arterial lactate (Figure 5). Each cariporide-treated rat survived 120 minutes, whereas 3 control rats died displaying progressive hypotension.

**Second Series (6 Minutes Untreated VF, Matched Defibrillation)**

As in the preceding series, a lesser depth of chest compression and spontaneous defibrillation were observed in cariporide-treated rats (Table 1). Despite matched defibrillation times, cariporide-treated rats restored spontaneous circulation 28 seconds earlier ($P<0.05$ vs BL within each group by 1-way repeated-measures ANOVA).

**Third Series (10 Minutes Untreated VF, Matched Defibrillation)**

As in the 2 preceding series, spontaneous defibrillation occurred only in cariporide-treated rats. This again prompted fewer electrical shocks and return of spontaneous circulation 29 seconds earlier ($P=NS$) because no additional defibrillation-compression cycles were required (Table 1). Again, less postresuscitation ventricular ectopic activity occurred in cariporide-treated rats (Table 2). In contrast to the preceding series, indices of hemodynamic function were not different between the 2 groups (Figure 6). Seven cariporide-treated rats and 6 control rats survived the postresuscitation interval.

Figure 1. Isolated perfused heart. Solid bars represent perfusate flow, duration of VF, and duration of cariporide or NaCl infusion. LVP indicates left ventricular end-diastolic pressure during sinus rhythm and "arrest" pressure during VF; CVR, coronary vascular resistance. Values are mean±SEM. ● indicates NaCl (n=8); ○, cariporide (n=8). Differences in LVP and CVR between treatment groups were significant ($P<0.0001$ by 2-way ANOVA for treatment effect). $^{*}P<0.05$, †$P<0.01$, ‡$P<0.001$ vs NaCl by 1-way ANOVA.

cariporide-treated rats (Table 1). Despite matched defibrillation times, cariporide-treated rats restored spontaneous circulation 28 seconds earlier ($P=NS$) because no additional defibrillation-compression cycles were required (Table 1). Again, less postresuscitation ventricular ectopic activity occurred in cariporide-treated rats (Table 2). In contrast to the preceding series, indices of hemodynamic function were not different between the 2 groups (Figure 6). Seven cariporide-treated rats and 6 control rats survived the postresuscitation interval.

Figure 2. Left ventricular end-diastolic pressure (LVEDP)–volume (LVEDV) curves. Circles indicate baseline; squares, 10 minutes postresuscitation; and triangles, 30 minutes postresuscitation. Solid symbols represent NaCl (n=8); open symbols, cariporide (n=8). Values are mean±SEM. $^{*}P<0.05$ vs baseline curves by 2-way repeated-measures ANOVA for time effect; $^{†}P<0.0001$ vs corresponding curve in hearts treated with cariporide by 2-way ANOVA for treatment effect.

Figure 3. Maximal rate of left ventricular pressure rise (dP/dt\(_{max}\)). BL indicates baseline; PR, postresuscitation. Solid bars represent NaCl (n=8); open bars, cariporide (n=8). $^{*}P<0.05$ vs BL within each group by 1-way repeated-measures ANOVA.

cariporide-treated rats (Table 1). Despite matched defibrillation times, cariporide-treated rats restored spontaneous circulation 28 seconds earlier ($P=NS$) because no additional defibrillation-compression cycles were required (Table 1). Again, less postresuscitation ventricular ectopic activity occurred in cariporide-treated rats (Table 2). In contrast to the preceding series, indices of hemodynamic function were not different between the 2 groups (Figure 6). Seven cariporide-treated rats and 6 control rats survived the postresuscitation interval.

Figure 4. Intact rat experiment demonstrating spontaneous defibrillation. LV indicates left ventricular pressure; Ao, aortic pressure; RA, right atrial pressure; and EKG, ECG. A bolus of cariporide was injected into right atrium after 5 minutes and 45 seconds of untreated VF. Chest compression (CC) was started after 6 minutes of untreated VF. Spontaneous defibrillation occurred during minute 8 of CC, with rapid return to baseline (BL) hemodynamic conditions. Artifacts caused by CC were removed from VF signal with a high-pass digital filter (10-Hz cutoff frequency).
In the quiescent (nonfibrillating) heart. The role of NHE-1 in the development of ischemic contracture has been documented in intact porcine models of VF and in patients suffering out-of-hospital cardiac arrest. Ischemic contracture limits the left ventricular filling volumes, causing progressive reductions in stroke volume and coronary perfusion pressure and increasing myocardial energy requirements.

**Discussion**

There is compelling evidence that NHE-1 inhibition ameliorates the severity of regional and global myocardial ischemia in the quiescent (nonfibrillating) heart. The role of NHE-1 inhibition when VF accompanies ischemia, however, is unclear. Although VF may worsen ischemia by intensifying the myocardial energy requirements, VF may also promote additional Na\(^+\) influx, potentially circumventing the benefits associated with NHE-1 inhibition. In previous studies using an isolated rat heart preparation, we documented intramyocardial Na\(^+\) increases from 11.5\(\pm\)0.8 (baseline) to 15.1\(\pm\)1.7 mmol/kg wet tissue after 25 minutes of ischemia in the absence of VF and to 20.2\(\pm\)2.1 mmol/kg in the presence of VF. Interventions limiting sarcolemmal Na\(^+\) entry (cariporide and/or perfusion with HEPES-substituted buffer) reduced intracellular Na\(^+\) to 17.6\(\pm\)2.3 mmol/kg and attenuated the development of ischemic contracture by a magnitude comparable to that observed in the present experiments.

In the present studies, we demonstrate that NHE-1 inhibition in the setting of VF-induced cardiac arrest ameliorates myocardial abnormalities previously shown to compromise resuscitability and survival.

**Ischemic Contracture**

Development of ischemic contracture has been documented in intact porcine models of VF and in patients suffering out-of-hospital cardiac arrest. Ischemic contracture limits the left ventricular filling volumes, causing progressive reductions in stroke volume and coronary perfusion pressure and increasing myocardial energy requirements.

### TABLE 1. Resuscitation Effort in the Intact Rat

<table>
<thead>
<tr>
<th></th>
<th>CPP, mm Hg</th>
<th>Depth of Compression, mm</th>
<th>Spontaneous Defibrillation, n</th>
<th>Shocks, n</th>
<th>Cumulative Energy, J</th>
<th>Time to ROSC, s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC min 4</td>
<td>CC min 8</td>
<td></td>
<td></td>
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<tr>
<td>Untreated VF 6 min (unmatched defibrillation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>26(\pm)4</td>
<td>27(\pm)5</td>
<td>15.3(\pm)1.9</td>
<td>0/8</td>
<td>2.6(\pm)1.3</td>
<td>6.5(\pm)3.3</td>
</tr>
<tr>
<td>Cariporide</td>
<td>28(\pm)4</td>
<td>24(\pm)7 [4]</td>
<td>13.4(\pm)1.4*</td>
<td>6/8†</td>
<td>0.4(\pm)0.7†</td>
<td>0.8(\pm)1.5†</td>
</tr>
<tr>
<td>Untreated VF 6 min (matched defibrillation)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>24(\pm)2</td>
<td>24(\pm)3 [7]</td>
<td>16.3(\pm)0.9</td>
<td>0/8</td>
<td>2.6(\pm)1.5</td>
<td>7.0(\pm)4.7</td>
</tr>
<tr>
<td>Cariporide</td>
<td>26(\pm)3</td>
<td>23(\pm)2 [7]</td>
<td>14.1(\pm)1.7†</td>
<td>4/8</td>
<td>0.6(\pm)0.7†</td>
<td>1.3(\pm)1.5†</td>
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<td>Untreated VF 10 min (matched defibrillation)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>24(\pm)4</td>
<td>25(\pm)3 [5]</td>
<td>15.8(\pm)1.7</td>
<td>0/8</td>
<td>2.9(\pm)1.7</td>
<td>9.1(\pm)8.8</td>
</tr>
<tr>
<td>Cariporide</td>
<td>21(\pm)4</td>
<td>25(\pm)2 [5]</td>
<td>14.8(\pm)2.5</td>
<td>7/8†</td>
<td>0.3(\pm)0.4†</td>
<td>0.5(\pm)1.4†</td>
</tr>
</tbody>
</table>

Time to ROSC indicates time to restoration of spontaneous circulation after start of chest compression (CC); CPP, coronary perfusion pressure.

*P<0.05; †P<0.01; ‡P<0.001 vs control.

**TABLE 2. Postresuscitation Ventricular Ectopic Activity**

<table>
<thead>
<tr>
<th></th>
<th>Singlets, n</th>
<th>Bigemini, n</th>
<th>Salvos, n</th>
<th>Episodes of VT, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated VF 6 min (unmatched defibrillation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>17.4(\pm)11.0</td>
<td>15.8(\pm)12.0</td>
<td>24.8(\pm)36.0</td>
<td>6.9(\pm)11.2</td>
</tr>
<tr>
<td>Cariporide</td>
<td>6.8(\pm)8.0*</td>
<td>4.1(\pm)4.5*</td>
<td>0.8(\pm)0.7†</td>
<td>0.9(\pm)1.0*</td>
</tr>
<tr>
<td>Untreated VF 6 min (matched defibrillation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>53.5(\pm)52.1</td>
<td>58.0(\pm)47.1</td>
<td>22.5(\pm)32.2</td>
<td>3.3(\pm)4.5</td>
</tr>
<tr>
<td>Cariporide</td>
<td>5.5(\pm)4.5*</td>
<td>7.4(\pm)11.5†</td>
<td>2.6(\pm)4.7†</td>
<td>1.3(\pm)1.2</td>
</tr>
<tr>
<td>Untreated VF 10 min (matched defibrillation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>33.4(\pm)37.4</td>
<td>59.7(\pm)73.0</td>
<td>9.7(\pm)7.7</td>
<td>1.1(\pm)1.8</td>
</tr>
<tr>
<td>Cariporide</td>
<td>14.5(\pm)10.7</td>
<td>17.8(\pm)41.4</td>
<td>2.3(\pm)3.5*</td>
<td>0.6(\pm)0.7</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia.

*P<0.05; †P<0.01 vs control.
ultimately compromising resuscitability. In the isolated heart, cariporide markedly attenuated the magnitude of ischemic contracture and lessened the increases in coronary vascular resistance. In the intact rat, the depth of compression necessary to achieve comparable hemodynamic effects averaged 12% less in cariporide-treated rats. This effect is consistent with attenuation of ischemic contracture, allowing larger ventricular volumes to be maintained before each chest compression. It also suggests that increasing the depth of compression after administration of cariporide could result in larger systemic blood flows.

Spontaneous Defibrillation
Small hearts have a tendency to spontaneously defibrillate. Sustained VF, however, can be induced after 3 minutes of uninterrupted electrical stimulation in both the isolated13 and the intact 16 rat heart. Subsequent defibrillation typically requires restoration of coronary perfusion and electrical shocks. In the present intact rat experiments, however, cariporide promoted spontaneous defibrillation in 70% of the instances after 8 minutes of chest compression, hence obviating the need for electrical shocks. It is likely that spontaneous defibrillation was the result of a metabolic rather than hemodynamic effect, because the end-tidal PCO₂ and the coronary perfusion pressure (surrogate measurements of systemic and coronary blood flow)16 were comparable in control and cariporide-treated rats. Additional work is necessary to elucidate the mechanisms of spontaneous defibrillation and to determine whether this effect could lower the energy requirements for successful electrical defibrillation in larger animals that do not autodefibrillate.

Postresuscitation Ectopic Activity
Significantly less ventricular ectopic activity occurred in cariporide-treated rats. The multiple regression analyses identified cariporide as the main factor responsible for the decreased incidence of singlets, bigemini, and salvos. The smaller number of episodes of ventricular tachycardia was probably related to the lower energy delivered as a result of spontaneous defibrillation.

Reperfusion arrhythmias have been linked to Ca²⁺ overload and cytosolic Ca²⁺ oscillations.22 Thus, amelioration of reperfusion arrhythmias after administration of cariporide is consistent with the postulated mechanism of NHE-1 inhibition; namely, reduction in Na⁺-induced cytosolic Ca²⁺ overload. Consistent with these observations, pretreatment with cariporide has been shown to prevent the development of VF and other ventricular ectopic rhythms in rats after coronary artery ligation.23

Postresuscitation Myocardial Dysfunction
In the isolated heart, cariporide prevented postresuscitation diastolic dysfunction and prompted earlier return of contrac-

<table>
<thead>
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<th>TABLE 3. Multiple Regression Models</th>
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<tr>
<td>Drug treatment</td>
</tr>
<tr>
<td>No. of shocks</td>
</tr>
<tr>
<td>Total energy delivered</td>
</tr>
<tr>
<td>Time to ROSC</td>
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</table>

VT indicates ventricular tachycardia. Multiple regression models constructed by forward stepwise selection were used to assess the predictive value of drug treatment, number of shocks, total energy delivered, and time to restoration of spontaneous circulation (ROSC) on mean aortic pressure (MAP) at 5 minutes after resuscitation and ventricular ectopic activity during the initial 4 minutes after resuscitation. Only values of P<0.05 are listed, and they denote when statistically significant contributions of the predictive variables were present.
tile function. In the first intact rat series, cariporide was associated with improved postresuscitation hemodynamic function and faster normalization of arrest-induced lactate increases. No postresuscitation benefits were observed in the second series, however, when the defibrillation times were matched despite a slightly earlier return of spontaneous circulation (≈30 seconds) and fewer electrical shocks. Yet, when the duration of untreated VF was increased to 10 minutes, causing more severe postresuscitation hemodynamic dysfunction, cariporide had a beneficial effect manifested by a significantly higher mean aortic pressure during the initial 30 minutes after resuscitation. This effect, however, did not influence postresuscitation lactate changes, suggesting that the differences observed in the first series reflected the longer duration of cardiac arrest in control rats.

The multiple regression analyses identified drug effect and the time to restoration of spontaneous circulation as significant determinants of postresuscitation hemodynamic function. Postresuscitation hemodynamic benefits could have derived from preservation of diastolic function and faster recovery of systolic function, as suggested by the studies in the isolated rat heart preparation. Improved hemodynamic stability was associated with significant increases in survival.

Clinical Relevance
The effects of cariporide were examined in adult rats only; however, the cellular effects associated with NHE-1 activation may not be subject to large interspecies and age variation. Similar benefits, including improved myocardial function, preservation of cellular ultrastructure, and reduced incidence of arrhythmias after NHE-1 inhibition, have been confirmed in different experimental models and different species.24

In clinical settings, electrical defibrillation is typically attempted earlier after onset of VF. Yet, previous experiments in dogs25 and more recent clinical data26 suggest that efforts to improve the myocardial metabolic conditions before delivering electrical shocks may be warranted in instances of prolonged untreated VF. Our experimental protocols were designed to best characterize the myocardial effects of cariporide and therefore purposely planned electrical defibrillation 10 minutes after administration of cariporide. Although spontaneous defibrillation occurred after ≈8 minutes, clinical protocols would most likely include earlier defibrillation attempts. Currently, some patients are successfully resuscitated within 5 to 10 minutes of advanced cardiac life support, yet many others require multiple electrical shocks and continued resuscitation efforts exceeding 10 minutes. For these patients, interventions that ameliorate the ischemic process, like the one proposed here, may be instrumental to securing successful resuscitation.

Acknowledgments
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References
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