Sodium-Hydrogen Exchange Inhibition During Ventricular Fibrillation
Beneficial Effects on Ischemic Contracture, Action Potential Duration, Reperfusion Arrhythmias, Myocardial Function, and Resuscitability

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Background—Inhibition of the sarcolemmal sodium-hydrogen exchanger isoform-1 (NHE-1) is emerging as a promising novel strategy for ameliorating myocardial injury associated with ischemia and reperfusion. We investigated whether NHE-1 inhibition (with cariporide) could minimize mechanical and electrical myocardial abnormalities that develop during ventricular fibrillation (VF) and improve outcome using a porcine model of closed-chest resuscitation.

Methods and Results—Two groups of 8 pigs each were subjected to 8 minutes of untreated VF and randomized to receive either a 3-mg/kg bolus of cariporide or 0.9% NaCl immediately before an 8-minute interval of conventional closed-chest resuscitation. Cariporide prevented progressive increases in left ventricular free-wall thickness (from 1.0 ± 0.2 to 1.5 ± 0.3 cm with NaCl, P < 0.001 versus 0.9 ± 0.1 to 1.1 ± 0.3 cm with cariporide, P = NS), maintained the coronary perfusion pressure above resuscitability thresholds (10 ± 8 versus 19 ± 3 mm Hg before attempting defibrillation, P < 0.05), and increased resuscitability (2 of 8 versus 8 of 8, P < 0.005). In 2 additional groups of 4 pigs each subjected to a briefer interval of untreated VF, cariporide ameliorated postresuscitation shortening of the action potential duration (APD) at 30%, 60%, and 90% repolarization (ie, APD90 at 2 minutes after resuscitation; 75 ± 29 versus 226 ± 16 ms, P < 0.05), minimized postresuscitation ventricular ectopic activity preventing recurrent VF, and lessened postresuscitation myocardial dysfunction.

Conclusions—NHE-1 inhibition may represent a highly potent novel strategy for resuscitation from VF that can ameliorate myocardial manifestations of ischemic injury and improve the effectiveness and outcome of closed-chest resuscitation. (Circulation. 2003;107:1804-1809.)

Key Words: action potentials • cardiopulmonary resuscitation • defibrillation • ischemia • myocardium

Strategies to improve resuscitability from ventricular fibrillation (VF) have traditionally centered on means to enhance the delivery of oxygen and energy substrates while limiting injury related to the resuscitation process itself. Yet, the possibility that improved resuscitability could result from targeting specific pathogenic mechanisms activated during ischemia and reperfusion has been largely unexplored.

We have identified activation of the sarcolemmal sodium-hydrogen exchanger isoform-1 (NHE-1) as a potentially important pathogenic target1 and demonstrated, in rat models of VF and resuscitation, that NHE-1 inhibition can ameliorate myocardial abnormalities relevant to cardiac resuscitation.2 In these models, NHE-1 inhibition reduced ischemic contracture during VF (improving the hemodynamic efficacy of chest compression), minimized postresuscitation ventricular ectopic activity (preventing recurrent VF), and lessened postresuscitation myocardial dysfunction.2 Contemporary to our studies, Wirth et al1 reported, in a swine model of regional coronary occlusion, similar antiarrhythmic effects of NHE-1 inhibition associated with preservation of the action potential duration (APD).

In the present studies, using a clinically more relevant porcine model of VF, we investigated the capability of NHE-1 inhibition to ameliorate the aforementioned myocardial abnormalities and to facilitate closed-chest resuscitation. The effects on ischemic contracture were investigated by use...
of transesophageal echocardiography (TEE). The effects on APD and ventricular ectopic activity were investigated by use of a monophasic action potential (MAP) recording/pacing catheter.\textsuperscript{4,5}

**Methods**

These studies were approved by our Research and Development Committee and conducted according to institutional guidelines.

**Animal Preparation**

Male domestic pigs (30 to 42 kg; Oak Hill Genetics, Ewing, Ill) were sedated with ketamine (30 mg/kg IM) and anesthetized with pentobarbital (30 mg/kg IV for induction and 8 mg/kg IV every 30 minutes for maintenance). Ventilation was provided through an orotracheal tube with a volume-controlled ventilator (Bear 1000; Bear Medical Systems, Inc) set to deliver a tidal volume of 10 mL/kg, peak flow of 40 L/min, and FiO\textsubscript{2} of 0.4. The respiratory rate was adjusted to maintain an end-expired P\textsubscript{CO\textsubscript{2}} between 35 and 45 mm Hg. Rectal temperature was maintained between 36.5°C and 37.5°C with a servocontrolled water-circulated blanket. A lead II ECG was recorded through skin electrodes, and 2 self-adhesive conductive gel pads were positioned on the chest for electrical defibrillation.

In an initial series, a 5F pacing electrode was advanced through the right cephalic vein into the right ventricle for induction of VF. A 7F angiographic catheter was advanced through the right femoral artery into the left ventricular cavity, and its tip was positioned against the endocardium for measuring MAP stroke output (Edwards Critical Care Explorer, Baxter Healthcare Corp) along with right atrial and pulmonary artery pressures. A 7F high-fidelity Micro-Tip pressure-transducer pigtail-catheter (model SPC-474A, Millar Instruments) was advanced from the right carotid artery into the descending thoracic aorta for pressure measurements. A 5.0-MHz transesophageal echocardiography system (128XP/10, Acuson) was advanced into the midesophagus for measuring left ventricular cavity size and wall thickness.

In a subsequent series, a 7F MAP recording/pacing contact catheter (EP Technology) was advanced under fluoroscopy from the right femoral artery into the left ventricular cavity, and its tip was positioned against the anterolateral ventricular wall endocardium. Stable endocardial contact was verified by MAP morphology.\textsuperscript{6} The catheter was used for inducing VF and recording MAPs. The left ventricular catheter, right ventricular electrode, and TEE probe were omitted.

**Measurements**

For TEE measurements, the esophageal probe, set in transverse plane orientation with maximal leftward (~30°) and anterior (~45°) deflections, provided an adequate long-axis view of the left-side chambers. Although in many instances, chest compression precluded complete imaging of the left ventricular cavity, the anterolateral left ventricular free wall was consistently well visualized. Images were recorded on S-VHS tapes and analyzed by use of a viewing station (Micronsonics Imageview). Simultaneous ECG recordings served to identify diastole (onset of QRS) and systole (end of T wave). Myocardial thickness was measured at the base of the anterolateral papillary muscle insertion. Ventricular area was estimated by electronic integration after manual endocardial tracking. Ejection fraction was calculated as the difference between the end-diastolic and end-systolic areas divided by the end-diastolic area.

Cardiac output was determined by thermodilution in triplicate after bolus injection of 10 mL of ice-cold 0.9% NaCl solution into the right atrium. Cardiac output was normalized to body surface area (BSA) on the basis of the Kelly equation: BSA (m\textsuperscript{2})=0.073×weight\textsuperscript{0.45} (kg). Coronary perfusion pressure corresponded to the aortic minus right atrial pressures at the end of diastole during spontaneous circulation and at the end of chest relaxation during chest compression.

For MAP analysis, a line parallel to the baseline that passed through the crest of the action potential plateau was first drawn to determine its maximal amplitude and then used to identify repolarization at 30%, 60%, and 90% of the action potential amplitude.\textsuperscript{6} The APD at each of these amplitudes (APD\textsubscript{30}, APD\textsubscript{60}, and APD\textsubscript{90}) was measured relative to the fast initial MAP stroke.

For NHE-1 inhibition, cariporide (4-isopropyl-methylsulfonyl-benzoyl-guanidine methanesulfonate; Aventis Pharma Deutschland GmbH) was used in a bolus dose of 3 mg/kg.\textsuperscript{3}

**Experimental Protocol**

Initial experiments (series 1) were conducted in pigs instrumented for TEE. VF was induced by an alternating current (1 to 5 mA) delivered to the right ventricular endocardium, and mechanical ventilation was discontinued. Pigs were randomized to receive a bolus of either cariporide (n=8) or 0.9% NaCl (n=8) into the right atrium at 7 minutes and 45 seconds of untreated VF. Chest compression and ventilation with 100% oxygen were initiated 15 seconds later with a pneumatically driven chest compressor/ventilator (Thumper model 1007, Michigan Instruments) set to deliver 80 compressions per minute and 1 breath every 6 compressions. The force of compression was gradually increased in an attempt to generate within 3 minutes a coronary perfusion pressure above the minimal resuscitability threshold of 10 mm Hg in pigs.\textsuperscript{8} This requirement was met in 8 of 12 pigs randomized to NaCl and in 8 of 13 pigs randomized to cariporide. Only pigs that met this criterion are reported here. Defibrillation was attempted after 8 minutes of chest compression with a biphasic waveform defibrillator (Smart Biphasic Heartstream XL M4735A, Agilent Technologies) and an escalating energy protocol of 50, 100, 150, and 200 J. Up to 2 shocks were delivered within each energy level. If VF persisted or an organized rhythm with a mean aortic pressure ≤25 mm Hg ensued, chest compression was resumed for 30 seconds. The compression-defibrillation sequence was repeated for a maximum of 4 additional cycles, increasing the energy of individual shocks to the next level in instances of refractory VF. Spontaneous circulation was defined as an organized cardiac activity with a mean aortic pressure ≥60 mm Hg. Recurrent VF prompted 100-J shocks without additional chest compressions. Resuscitated pigs were monitored for 120 minutes and then euthanized with pentobarbital (150 mg/kg IV). Subsequent experiments (series 2) were conducted in pigs instrumented for MAP recordings. The protocol was identical to series 1 except that untreated VF was shortened to 6 minutes (to increase resuscitability) and pigs were euthanized at 60 minutes after resuscitation.

**Statistical Analysis**

Continuous variables were analyzed between groups by 1-way ANOVA and within groups by repeated-measures ANOVA and Dunnett’s test for multicomparisons relative to baseline. Categorical variables were analyzed by Fisher’s exact test. Equivalent nonparametric tests were substituted when tests for normality or equal variance failed. The data are presented as mean±SD unless otherwise stated. A 2-tail probability value of P<0.05 was considered significant.

**Results**

**Series 1**

VF halted left ventricular contractions, establishing cavity diameters and wall thickness comparable to those present at the end of mechanical diastole. These dimensions remained largely unchanged during untreated VF. However, during the ensuing 8 minutes of chest compression, the left ventricular wall thickness increased progressively in control pigs from 1.0±0.2 to 1.5±0.3 cm (P<0.001). In contrast, the wall thickness in cariporide-treated pigs exhibited only negligible and statistically insignificant increases, from 0.9±0.1 to 1.1±0.3 cm. Representative TEE images are shown in Figure
1. The aggregate data (Figure 2) demonstrated significant differences between groups from the second minute of chest compression on. During this interval, the end-of-relaxation left ventricular pressures remained largely unchanged in NaCl- and cariporide-treated pigs (ie, 5±3 and 5±3 mm Hg at 2 minutes and 6±2 and 7±3 mm Hg at 6 minutes of chest compression, *P=*NS).

During the initial 3 minutes of chest compression, the coronary perfusion pressure increased to ~18 mm Hg in both groups (Figure 2). Thereafter, the coronary perfusion pressure declined in control pigs despite maximal force of compression but remained stable in cariporide-treated pigs, attaining an almost 2-fold difference immediately before defibrillation was attempted (10±8 versus 19±3 mm Hg, *P*<0.05).

All 8 cariporide-treated pigs were defibrillated successfully, with return of spontaneous circulation after 4.6±2.8 electrical shocks (438±453 J) and had minimal postresuscitation ventricular ectopic activity, with no episodes of recurrent VF (Table 1). In contrast, 4 of the 8 NaCl-treated pigs failed the initial resuscitation attempt: 2 had refractory VF and 2 developed pulseless electrical activity. Spontaneous circulation was restored in the remaining 4 pigs after the initial defibrillation attempts, requiring 6.4±3.1 electrical shocks (744±522 J; *P=*NS versus cariporide). These pigs, however, developed intense ventricular ectopic activity, with frequent episodes of recurrent VF requiring additional electrical shocks (Table 1). Spontaneous circulation was restored in 2 of these 4 pigs after 9.5±0.7 additional electrical shocks (950±71 J), whereas 2 failed the postresuscitation defibrillation attempts. Thus, all 8 cariporide- but only 2 NaCl-treated pigs were resuscitated successfully and survived the postresuscitation interval (*P*<0.005).

After resuscitation, cariporide-treated pigs had myocardial wall thickness comparable to baseline but decreased left ventricular ejection fraction, cardiac index, and mean aortic pressure that partially reversed during the ensuing postresuscitation interval. Surviving control pigs had prominent myocardial wall thickness and worse myocardial dysfunction (Figure 2 and Table 2).

**Series 2**

The shorter duration of untreated VF allowed successful resuscitation in each instance. Control pigs (n=4) again displayed intense postresuscitation ventricular ectopic activity, with frequent episodes of recurrent VF (Table 1) coincident with marked shortening of the APD and changes in morphology to a more triangular shape. These abnormalities subsided within 10 minutes. In contrast, pigs treated with cariporide (n=4) had their APD preserved with morphology similar to baseline (Figures 3 and 4). In addition, cariporide-treated pigs had significantly less postresuscitation ventricular
Ischemic contracture refers to the progressive myocardial dysfunction that results from severe ischemia. Onset of ischemic contracture is associated with decreases in ATP to levels <10% of normal. Ischemic contracture of varying severity has been reported during cardiac arrest to compromise resuscitability in animal models and in human victims of cardiac arrest.

In our studies, ischemic contracture developed in control pigs duringVF, but only during the interval of low-flow coronary perfusion promoted by chest compression. These observations, along with previous reports in isolated rat heart models of VF and isolated cardiac myocytes, suggests that reperfusion and reoxygenation could play an important precipitating role. Ischemic contracture occurred with essentially no changes in end-of-chest-relaxation left ventricular pressures, confirming reductions in myocardial compliance.

### Discussion

NHE-1 inhibition during VF (1) attenuated the development of ischemic contracture; (2) reduced postresuscitation ventricular ectopic activity in association with preservation of APD, preventing episodes of recurrent VF; and (3) ameliorated postresuscitation myocardial dysfunction. These effects enhanced the hemodynamic effectiveness of closed-chest resuscitation and facilitated successful resuscitation and survival.

### Ischemic Contracture

Ischemic contracture refers to the progressive myocardial wall thickening with reductions in ventricular cavity that ectopic activity and significantly less postresuscitation myocardial dysfunction (Table 1, Figure 5).

### Table 1. Ventricular Ectopic Activity During the Initial 5 Minutes After Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Singles, n</th>
<th>Bigeminy, n</th>
<th>Salvos, n</th>
<th>Episodes of VT, n</th>
<th>Episodes of VF, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Series 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=4)</td>
<td>34.8±25.1</td>
<td>17.5±26.8</td>
<td>5.5±6.5</td>
<td>0.0±0.0</td>
<td>4.0±2.9</td>
</tr>
<tr>
<td>Cariporide (n=8)</td>
<td>6.3±9.1†</td>
<td>0.0±0.0†</td>
<td>1.3±3.5</td>
<td>0.1±0.4</td>
<td>0.0±0.0‡</td>
</tr>
<tr>
<td><strong>Series 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=4)</td>
<td>41.5±23.6</td>
<td>12.5±8.2</td>
<td>6.3±6.7</td>
<td>2.5±2.4</td>
<td>2.5±2.1</td>
</tr>
<tr>
<td>Cariporide (n=4)</td>
<td>5.3±9.2†</td>
<td>0.0±0.0†</td>
<td>0.0±0.0†</td>
<td>0.0±0.0†</td>
<td>0.0±0.0</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia.

*Only pigs that restored spontaneous circulation after the initial resuscitation attempt were included in this analysis; 2 of these 4 pigs subsequently succumbed to recurrent VF (see text for details).

†P<0.05; ‡P<0.005 vs NaCl by 1-way ANOVA.

### Table 2. Myocardial Function (Series 1)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (−10 min)</th>
<th>Minutes After Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>15</td>
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<tr>
<td>LV end-diastolic area, cm²</td>
<td></td>
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<tr>
<td>NaCl (n=8)</td>
<td>9.3±2.8</td>
<td>4.9±1.0</td>
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<tr>
<td>Cariporide (n=8)</td>
<td>9.1±2.0</td>
<td>8.6±2.8</td>
</tr>
<tr>
<td>LV end-systolic area, cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=8)</td>
<td>3.7±1.1</td>
<td>2.6±0.6</td>
</tr>
<tr>
<td>Cariporide (n=8)</td>
<td>3.7±0.7</td>
<td>5.4±2.7</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=8)</td>
<td>60±6</td>
<td>47±1</td>
</tr>
<tr>
<td>Cariporide (n=8)</td>
<td>58±7</td>
<td>40±14†</td>
</tr>
<tr>
<td>AoP (mean), mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>NaCl (n=8)</td>
<td>107±15</td>
<td>63±25</td>
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<tr>
<td>Cariporide (n=8)</td>
<td>126±8</td>
<td>102±11†§</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=8)</td>
<td>5±1</td>
<td>7±4</td>
</tr>
<tr>
<td>Cariporide (n=8)</td>
<td>5±1</td>
<td>9±4†</td>
</tr>
<tr>
<td>Cl, L·min⁻¹·m⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl (n=8)</td>
<td>6.3±1.1</td>
<td>3.6±1.6</td>
</tr>
<tr>
<td>Cariporide (n=8)</td>
<td>7.2±1.2</td>
<td>4.4±0.6†</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; AoP, aortic pressure; PAOP, pulmonary artery occlusive pressure; and CI, cardiac index.

*Only 2 successfully resuscitated NaCl-treated pigs provided postresuscitation data.

†P<0.05 vs baseline by repeated-measures ANOVA and Dunnett’s multicomparison test.

‡P<0.05, §P<0.01 vs NaCl by 1-way ANOVA.
NHE-1 inhibition using the potent and selective inhibitor cariporide prevented ischemic contracture and enabled chest compression to maintain a coronary perfusion pressure above resuscitability thresholds. In a limited number of experiments in which the left ventricle was well visualized during chest compression, cariporide attenuated reductions in left ventricular cavity size. Thus, preservation of end-of-chest-relaxation ventricular volumes with enhanced forward blood flow probably explained these favorable effects of NHE-1 inhibition. In our second series, statistically insignificant higher coronary perfusion pressures also favored cariporide (16/1100 mm Hg before defibrillation was attempted). The shorter duration of untreated VF most likely explained greater ease of maintaining coronary perfusion pressures above resuscitability thresholds in control pigs.

**Postresuscitation Ventricular Arrhythmias and APD**

Electrical instability with recurrent VF commonly occurs after cardiac resuscitation and may contribute to the nearly 30% incidence of early postresuscitation deaths. Ventricular arrhythmias probably share mechanisms common to those present during reperfusion after coronary occlusion. In this setting, prominent repolarization abnormalities occur that are characterized by shortening of the APD and change to a more triangular shape, decreased amplitude, APD alternans, and afterdepolarizations. APD shortening is partly explained by opening of sarcolemmal K_ATP channels. However, recent evidence also implicates NHE-1 activation.

Prominent APD shortening occurred in control pigs during the interval of maximal postresuscitation ventricular ectopic activity. These abnormalities were similar but quantitatively more prominent than those reported by Wirth and coworkers after regional ischemia in pigs. NHE-1 inhibition was remarkably effective in limiting APD shortening, reducing postresuscitation ventricular dysrhythmias, and preventing recurrent VF and arrhythmic deaths.

**Postresuscitation Myocardial Dysfunction**

Reversible diastolic and systolic dysfunction of varying severity occurs after cardiac resuscitation. The present experiments provide insights on mechanisms. The 2 control pigs successfully resuscitated in series 1 had persistent left ventricular wall thickening (Figure 2) along with numerical reductions in end-diastolic cavity size, suggesting that ischemic contracture and postresuscitation diastolic dysfunction share common pathogenic mechanisms. In contrast, wall thickness and cavity size were unaffected in pigs treated with cariporide, which had no demonstrable ischemic contracture. Both groups, however, had systolic dysfunction manifested by reductions in left ventricular ejection fraction, cardiac index, and mean aortic pressure despite increases in pulmonary artery occlusive pressure. In series 2, with all pigs being successfully resuscitated, beneficial effects of NHE-1 inhibition on postresuscitation myocardial function were more evident. Cariporide prevented statistically significant reductions in postresuscitation cardiac index and left ventricular stroke work index (Figure 5).
Mechanisms of Protective Action

Excellent reviews have been published on the pathogenic mechanisms of NHE-1 activation and the protective actions of NHE-1 inhibition.17,18 Yet, the application of these concepts to the cardiac arrest setting is novel.1,2 The intense intracellular acidosis that develops during VF after cessation of coronary blood flow is believed to activate the sarcolemmal NHE-1, leading to a proton-driven sarcolemmal Na⁺ influx with progressive cytosolic Na⁺ accumulation as the Na⁺-K⁺ pump fails to extrude Na⁺ during ischemia.19 Cytosolic Na⁺ overload becomes a “substrate” for ischemia and reperfusion injury.20 During closed-chest resuscitation, the coronary blood flow rarely exceeds 20% of normal, failing to reverse ischemia21 but allowing normoacidoic blood to perfuse the coronary circuit. Unremitting ischemia with a large transsarcolemmal proton gradient creates optimal conditions for NHE-1 to remain active throughout chest compression and probably the early minutes after return of spontaneous circulation.

NHE-1 inhibition reduces sarcolemmal Na⁺ entry and the detrimental downstream effects on cell physiology. Less cytosolic Na⁺ overload is thought to spare ATP use by the Na⁺-K⁺ pump, retarding its intracellular depletion and the consequent ischemic contracture.22 Reduced cytosolic Na⁺ overload may also attenuate mitochondrial injury by limiting Na⁺-induced membrane depolarization, mitochondrial swelling, cytochrome c release and by preserving oxidative phosphorylation.23 Less cytosolic Na⁺ overload could also attenuate Na⁺-induced reverse-mode operation of the Na⁺-Ca²⁺ exchanger and the ensuing outward (repolarizing) current, presumably responsible for APD shortening. Less cytosolic Ca²⁺ overload could also favor postresuscitation electrical stability and myocardial function.24

Clinical Implications

The effects of NHE-1 inhibition reported here are similar to those previously reported in isolated heart and intact rat models of VF.2 In addition, comparable myocardial protective actions have been reported in settings of regional and global myocardial ischemia in nonfibrillating hearts from different species.17,18 Sarcolemmal NHE-1 is expressed in human myocardium,25 and clinical trials have demonstrated myocardial benefits derived from NHE-1 inhibition in subsets of patients undergoing emergent coronary revascularization.26 Thus, effects similar to those reported here in pigs may also apply to humans and facilitate closed-chest resuscitation from VF. Clinical studies on NHE-1 inhibition during cardiac resuscitation are eagerly awaited.

Acknowledgments

This work was supported by a VA Merit Review Grant titled Myocardial Protection during Ventricular Fibrillation, a bridge fund from the Finch University of Health Sciences/The Chicago Medical School, and a grant from Aventis Pharma Deutschland GmbH, Frankfurt, Germany. The authors wish to acknowledge the valuable support provided by Biomedical Engineering; Pharmacy Services; and the Supply, Processing, and Distribution Center at the North Chicago VA Medical Center.

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Circulation. 2003;107:1804-1809; originally published online March 24, 2003; doi: 10.1161/01.CIR.0000058704.45646.0D

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

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