Milrinone Facilitates Resuscitation From Cardiac Arrest and Attenuates Postresuscitation Myocardial Dysfunction

James T. Niemann, MD; Daniel Garner, MS; Emaid Khaleeli, MD; Roger J. Lewis, MD, PhD

Background—Left ventricular (LV) dysfunction with a low cardiac index after successful CPR contributes to early death attributable to multiorgan failure, and an effective treatment has not been identified. The purpose of this study was to investigate the use of milrinone, a selective phosphodiesterase III inhibitor, as treatment for LV dysfunction after resuscitation.

Methods and Results—Ventricular fibrillation (VF) was induced electrically in 32 swine. After 5 minutes of VF, CPR was initiated and animals were randomized to receive either saline (control group, n=16) or a bolus and infusion of milrinone 50 μg/kg as a bolus and then 0.5 μg/kg per min for 60 minutes (treatment group, n=16). After 2 minutes of CPR (total VF time, 7 minutes), countershocks were given. Coronary perfusion pressures during CPR were similar for the groups (24±2 versus 21±4 mm Hg). All animals were defibrillated; 6 of 16 control animals developed refractory postcountershock pulseless electrical activity compared with 0 of 16 treated animals (P=0.018). At 30 minutes after restoration of spontaneous circulation, stroke volume (16±3 versus 26±7 mL, P<0.01) and LV dp/dt (793±197 versus 1108±316 mm Hg/s, P<0.02) were higher in the treatment group. Similar differences were observed 60 minutes after restoration of spontaneous circulation. Significant differences in heart rates between groups were not observed, and peripheral vascular resistance was significantly greater in the control group 30 and 60 minutes after resuscitation.

Conclusions—Milrinone facilitates resuscitation from prolonged VF and attenuates LV dysfunction after resuscitation without worsening major determinants of myocardial oxygen demand. (Circulation. 2003;108:3031-3035.)

Key Words: heart arrest ■ cardiopulmonary resuscitation ■ drugs ■ contractility
beneficial in the management of postresuscitation ventricular dysfunction. The purpose of this study was to determine if milrinone, a selective PDE III, could prevent or attenuate the decrease in myocardial contractility observed early after resuscitation from cardiac arrest attributable to VF.

Methods

This investigation was approved by the Animal Care and Utilization Review Committee of our institution and conformed to the position of the American Heart Association on research animal use. Male and female domestic swine (30 to 55 kg; Irish Farms, San Bernardino, Calif) were premedicated with intramuscular telazol (4 mg/kg) or ketamine (20 mg/kg) and xylazine (2 mg/kg). General anesthesia was induced with isoflurane via nose cone and, after endotracheal intubation, maintained with inhaled isoflurane (MAC 0.5% to 1.5%) and nitrous oxide in a 1 to 1 mixture with oxygen. Minute ventilation was adjusted to maintain an arterial Pco2 of 35 to 45 mm Hg and pH of 7.40 to 7.50, and standard lead II was monitored continuously. Self-adhesive defibrillation electrodes (Quick-Combo, Medtronic Physio-Control Corporation) were applied to the lateral aspects of the shaved thorax.

A carotid artery, both external jugular veins, and a femoral artery were surgically exposed, and micromanometer-tipped catheters (Mil- lar Instruments) were inserted and positioned in right atrium, left ventricle (LV), and aortic (Ao) arch. The tip of a bipolar pacing catheter was positioned in contact with the right ventricular endocardium. A thermodilution catheter was positioned in a branch of the pulmonary artery for cardiac output (CO) measurements.

After instrumentation, heart rate, systolic and diastolic Ao pressure, mean Ao pressure (MAP), LV end-diastolic pressure, LV systolic (max) and diastolic (min) dP/dt, CO, and stroke volume were recorded or calculated and arterial blood was analyzed. Peripheral vascular resistance (PVR) was derived using a standard formula. VF was then induced with a brief 60-Hz AC current pulse delivered to the right ventricular endocardium. Animals were randomized via permuted block design to 1 of 2 treatment groups. After 5 minutes of untreated VF, manual closed-chest compressions were begun in both groups. At the time compressions were initiated, group 1 animals (control group, n=16) were given a 2-mL intravenous bolus of normal saline, and chest compressions were continued for 2 minutes before the first countershock was administered. In group 2 animals (treatment group, n=16), 50 μg/kg of milrinone (approximately 2-mL volume) was given as an intravenous bolus at the time chest compressions were initiated. Countershock was performed 2 minutes later. After restoration of spontaneous circulation (ROSC), group 1 animals received normal saline at a rate of 100 mL/h. The investigators were blinded to treatment groups.

Chest compressions were performed with the animal in the supine position and administered by a single investigator at a rate 100 to 120 per minute with force sufficient to depress the sternum 1.5 to 2.0 inches. Ventilation was not performed during the 2-minute interval preceding the first countershock. After 2 minutes, defibrillation was attempted with a monophasic damped sine waveform (Medtronic Physio-Control Corporation, LifePak 12). Three shocks were administered with an escalating energy sequence (100 J to 200 to 300 J), if necessary. Strength-duration curves for delivered voltage and current were measured during the first shock, and mean transthoracic impedance was calculated. The postshock rhythm and Ao pressure were recorded and analyzed for a minimum of 10 seconds after each shock. If 1 of the first 3 countershocks terminated VF but resulted in a nonperfusing spontaneous cardiac rhythm, ie, asystole or pulseless electrical activity (PEA), or ifVF persisted after the first 3 shocks, chest compressions were restarted and positive pressure ventilations (FIO2 1.0) at a rate of 10 to 12 per minute were begun at a tidal volume equal to that of the prearrest period. Chest compressions were not interrupted during ventilations. CPR was continued in those animals with postshock asystole or PEA until spontaneous cardiac activity was associated with systolic arterial pressure pulse exceeding 60 mm Hg. IfVF persisted after the first 3 shocks, CPR was performed as described above and countershock was attempted 60 to 90 seconds later with up to 3 additional 360-J shocks. This CPR-defibrillation sequence continued until termination of VF or for 10 minutes. Animals not resuscitated within 10 minutes of the first shock because of countershock refractory VF or persistent postshock asystole or PEA were considered resuscitation failures. No drugs other than milrinone were administered during resuscitation efforts. Animals that achieved ROSC were observed for 60 minutes. Other than the continuous infusion of milrinone given to group 2 animals, no other drugs were given during this post-ROSC observation period. Volume loading was not performed in response to hemodynamic changes. Hemodynamic measurements were made at 15-minute intervals.

The following variables were measured and compared between groups: number of shocks required to terminate VF, defined as termination of VF for at least 5 seconds after the shock; total energy delivered; recurrent VF episodes; rate of ROSC; and hemodynamic variables 15, 30, and 60 minutes after VF termination in those animals that developed a spontaneous perfusing rhythm within 10 minutes of the first shock.

Data were analyzed using SigmaStat (SPSS Inc, version 2.0). Continuous variables were compared between groups using the Student’s t test or Mann-Whitney rank-sum test. One-way repeated-

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**TABLE 1. Resuscitation Variables for Study Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Milrinone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary perfusion pressure</td>
<td>21±6</td>
<td>20±4</td>
<td>0.597</td>
</tr>
<tr>
<td>Transthoracic impedance</td>
<td>42±5</td>
<td>42±8</td>
<td>0.936</td>
</tr>
<tr>
<td>Defibrillation success</td>
<td>16/16</td>
<td>16/16</td>
<td>1.00</td>
</tr>
<tr>
<td>No. of countershocks</td>
<td>3.0±1.2</td>
<td>2.1±1.2</td>
<td>0.083</td>
</tr>
<tr>
<td>Total joules</td>
<td>629±401</td>
<td>421±365</td>
<td>0.136</td>
</tr>
<tr>
<td>Refibrillation episodes</td>
<td>1.4±2.3</td>
<td>0.5±1.1</td>
<td>0.144</td>
</tr>
<tr>
<td>ROSC</td>
<td>10/16</td>
<td>16/16</td>
<td>0.018</td>
</tr>
</tbody>
</table>

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Figure 1. Left ventricular contractility after resuscitation. Systolic dp/dt (+) is shown in the top panel and diastolic dp/dt (−) in the bottom panel. Values are mean±SEM. *P<0.05, **P<0.01 control vs milrinone group.
measures ANOVA and Tukey's t test were used to determine difference over time within groups. Proportions were compared using Fisher's exact test. A P value of 0.05 was considered statistically significant.

**Results**

Hemodynamic data for the study groups are shown in Table 1 and Figures 1 and 2. Significant differences in hemodynamic variables between study groups were not observed during the prearrest period. Data related to resuscitation outcome are shown in Table 2. Coronary perfusion pressure, defined as the Ao-right atrium pressure difference measured at the mid point of the chest relaxation phase of CPR and measured after 2 minutes of chest compressions, was not significantly different between control and treatment groups. All animals were successfully defibrillated with 1 or more countershocks, and the transthoracic impedance, number of countershocks, and total joules required for defibrillation were not different between groups. Ten of 16 control animals developed postshock PEA that did not respond to CPR within 10 minutes of the first shock, and these animals were considered resuscitation failures. All treated animals achieved restoration of spontaneous circulation. The difference in rate of ROSC was statistically significant. Recurrent VF after ROSC was more frequently observed in control animals than in treated animals, but this difference was not statistically significant. If only resuscitated animals are considered, the difference in total joules required for defibrillation remained insignificant (control, 430±189 J; treatment group, 421±365 J).

During the 60-minute postresuscitation observation period, hemodynamic variables were measured or calculated at 15, 30, and 60 minutes after ROSC. Data for the study groups are shown in Table 1 and Figure 1. Six control animals were not resuscitated and are not included in the analysis. One animal in the treatment group inadvertently received 10 times the study infusion dose of milrinone and was excluded from the analysis. Cardiac output, stroke volume, and LV systolic +dp/dt and LV diastolic −dp/dt progressively decreased in the control group, reached a nadir at 30 minutes after ROSC, and did not return to control values. A similar but less severe decline was observed in the treatment group. Statistically significant differences between the 2 groups were observed at each measurement interval. Indices of left ventricular contractility favoring milrinone treatment were most pronounced at 30 and 60 minutes after ROSC. Mean arterial pressure and peripheral vascular resistance for the study groups are shown in Figure 2. MAP in the control group was dependent on a marked and sustained increase in afterload compared with the milrinone-treated group.

**Discussion**

The findings of this study indicate that milrinone, a selective phosphodiesterase III inhibitor, lessens the degree of postresuscitation left ventricular contractile function typically observed in the early postresuscitation period. The observed improvements in left ventricular contractility and cardiac output compared with the placebo group were not accompanied by an increase in heart rate over that observed before induction of VF, nor was heart rate different from that
observed in control animals. The increase in peripheral vascular resistance observed in the control group during the postresuscitation period was prevented by a continuous infusion of milrinone at a fixed dose. Therefore, milrinone improved cardiac contractile function without increasing these determinants of myocardial oxygen demand.

Regulation of myocardial contractility by inotropic agents is achieved by 1 of 3 mechanisms: (1) an increase in intracellular calcium mobilization (upstream mechanism); (2) an increase in calcium binding affinity to troponin C (central mechanism); or (3) facilitation of the process subsequent to calcium binding to troponin C (downstream mechanism). Milrinone and other selective phosphodiesterase III inhibitors are not receptor-dependent and act on 1 of 3 isozymes to increase cAMP and increase contractility by upstream and central mechanisms. cAMP may also play a role in increasing myofilament sensitivity to calcium. The selective PDE III inhibitors also decrease coronary and peripheral vascular resistance, presumably via alteration in calcium efflux and influx. These combined properties would seem ideal in treating depressed ventricular contractility after resuscitation from cardiac arrest. In this study, contractility (dP/dt max) was maintained throughout the postresuscitation period in milrinone-treated animals, and dP/dt, cardiac output, and stroke volumes exceeded control values. Milrinone also prevented the increase in peripheral vascular resistance observed in control animals.

Although extensively studied in the research laboratory, the frequency, severity, and duration of myocardial dysfunction after resuscitation in the clinical population is not well established. In addition, frequency of cardiac dysfunction as the primary cause of in-hospital death after successful initial resuscitation is not well defined. Only 2 clinical studies have reported serial measurements of indices of cardiac function. Laurent et al reported that 44% of patients admitted after cardiac arrest. In this study, contractility (dP/dt max) was maintained throughout the postresuscitation period in milrinone-treated animals, and dP/dt, cardiac output, and stroke volumes exceeded control values. Milrinone also prevented the increase in peripheral vascular resistance observed in control animals.

The management of postresuscitation ventricular dysfunction has not been extensively studied in in vivo models of cardiac arrest. One approach has been to minimize the degree of dysfunction by altering interventions used during resuscitation efforts. The adverse effects of epinephrine have been established, and vasopressin is now recommended as an alternative for the management of countershock refractory VF. Lower current biphasic defibrillation waveforms have been shown to be more effective than monophasic waveforms for VF termination and, in selected instances, to be associated with less-pronounced alterations in cardiac contractility. Once established, few studies have addressed the management of postresuscitation ventricular dysfunction. Dobutamine is the only drug that has been systematically evaluated in in vivo animal models of cardiac arrest and resuscitation. Dobutamine is a synthetic catecholamine that has been shown to augment myocardial contractility via β1-adrenergic receptor stimulation with minimal chronotropic effect. At usual doses, dobutamine also has balanced β2- and α1-receptor agonist actions and therefore little net effect on the systemic vasculature. In a swine model of postresuscitation contractile dysfunction, dobutamine at a selected infusion dose of 10 μg/kg per min significantly improved indices of systolic and diastolic function after resuscitation from a 10-minute period of untreated cardiac arrest. However, a persistent and significant increase in heart rate over that recorded during the prearrest period was observed. This sustained increase in heart rate was interpreted to represent an increase in cardiac work and oxygen demand, offsetting the observed benefits on contractility and left ventricular end-diastolic pressure.

In the present study, milrinone produced directionally similar improvement of indices of myocardial function as those observed with dobutamine but was not associated with a significant increase in heart rate. Although the PDE III inhibitors, unlike dobutamine, may be arrhythmogenic, no difference in the recurrence rate of VF was observed between the study groups and no animal in either group developed sustained conduction defects.

Limitations

Although the anatomy of the coronary circulation of swine resembles that of humans, the typical patient resuscitated from cardiac arrest has extensive atherosclerotic coronary disease, which may not only impact the severity of ventricular dysfunction after resuscitation but also the response to administered pharmacologic agents. Only a single dose of milrinone, administered as a bolus and a continuous infusion, was studied. Although the degree of cardiac dysfunction was less in treated animals, complete resolution was not observed at all time points. Earlier return to prearrest values may have been observed at titrated doses. Milrinone and dobutamine were not directly compared in the present study. However, existing data suggest that PDE III inhibitors, specifically milrinone and olprinone, offer substantial advantages over dobutamine in selected cardiac preparations.

Repeated high-energy shocks, typically in excess of those used clinically, have been shown to produce myocardial injury. The present investigation evaluated left ventricular
function after defibrillation using a monophasic damped sine waveform. Lower-energy, biphasic truncated exponential waveform shocks have been shown to be associated with less echocardiographic evidence of postresuscitation cardiac dysfunction compared with monophasic waveform shocks in porcine models with low transthoracic impedance. The degree of cardiac dysfunction observed in the present study may not have been as severe if biphasic shocks had been used during resuscitation.

The duration of cardiac arrest was 7 minutes, and the magnitude of the observed hemodynamic effects of milrinone may not be as pronounced if studied after a longer period of untreated cardiac arrest. Postresuscitation LV function was monitored for only 60 minutes after resuscitation. Prior laboratory work by others suggests that indices of LV function reach a nadir at 30 to 60 minutes after ROSC, when VF duration is of 4- to 10-minute duration, remains relatively constant during the ensuing 4 to 6 hours, and returns to prearrest values 24 to 72 hours after resuscitation. It is likely that the postresuscitation ventricular dysfunction observed in the present study would have resolved spontaneously and without treatment if the observation period had been longer. However, the decline in arterial pressure and cardiac output observed in the control group (Table 2 and Figure 2) during the first hour after restoration of circulation would prompt intervention if encountered in the clinical setting.

Conclusions
Milrinone, a selective phosphodiesterase III inhibitor, given at a standard mid-range dose, can lessen the degree of left ventricular dysfunction occurring early (within 60 minutes) after resuscitation from global myocardial ischemia accompanying cardiac arrest. It also appears to decrease the incidence of refractory postshock pulseless electrical activity.

Acknowledgments
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References
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