Endothelin-1 Vasoconstriction During Swine Cardiopulmonary Resuscitation Improves Coronary Perfusion Pressures but Worsens Postresuscitation Outcome

Ronald W. Hilwig, DVM, PhD; Robert A. Berg, MD; Karl B. Kern, MD; Gordon A. Ewy, MD

Background—Vasoconstriction during cardiopulmonary resuscitation (CPR) improves coronary perfusion pressure (CPP) and thereby outcome. The combination of endothelin-1 (ET-1) plus epinephrine improved CPP during CPR compared with epinephrine alone in a canine cardiac arrest model. The effect of the combination on outcome variables, such as successful resuscitation and survival, has not been investigated.

Methods and Results—Twenty-seven swine were randomly provided with 1 mg epinephrine (Epi group) or 1 mg epinephrine plus 0.1 mg ET-1 (ET-1 group) during a prolonged ventricular fibrillatory cardiac arrest. ET-1 resulted in substantially superior aortic relaxation pressure and CPP during CPR. These hemodynamic improvements tended to increase initial rates of restoration of spontaneous circulation (8 of 10 versus 8 of 17, \( P = 0.12 \)). However, continued intense vasoconstriction from ET-1 led to higher aortic diastolic pressure and very narrow pulse pressure after resuscitation. The mean pulse pressure 1 hour after resuscitation was 7±8 mm Hg with ET-1 versus 24±1 mm Hg with Epi, \( P < 0.01 \). Most importantly, the postresuscitation mortality was dramatically higher in the ET-1 group (6 of 8 versus 0 of 8 in the Epi group, \( P < 0.01 \)).

Conclusions—These data establish that administration of ET-1 during CPR can result in worse postresuscitation outcome. The intense vasoconstriction from ET-1 improved CPP during CPR but had detrimental effects in the postresuscitation period. (Circulation. 2000;101:2097-2102.)

Key Words: endothelin ■ heart arrest ■ cardiopulmonary resuscitation ■ catecholamines ■ survival

Current guidelines of the American Heart Association include the administration of 1 mg epinephrine by intravenous infusion every 3 to 5 minutes during cardiopulmonary resuscitation (CPR). Intravenous epinephrine during CPR improves myocardial perfusion and thereby enhances the successful restoration of spontaneous circulation (ROSC) and survival in experimental models of fibrillatory cardiac arrest. The \( \alpha \)-adrenergic effects of epinephrine result in peripheral vasoconstriction, which raises the aortic "diastolic" (relaxation or non–chest-compression) pressure, coronary perfusion pressure (CPP), and thus myocardial perfusion. The \( \beta \)-adrenergic effects of epinephrine result in increased myocardial oxygen consumption, which may lead to adverse effects.

Endothelin-1 (ET-1), a peptide secreted by endothelial cells, is a potent vasoconstrictor that does not elicit \( \beta \)-adrenergic effects. Endothelin-1 causes vasoconstriction via a non–adrenergic-mediated increase in calcium concentration within vascular smooth muscle cells. It also has positive inotropic and chronotropic effects on the myocardium in vitro. Increased mean arterial pressure and systemic vascular resistance has followed intravenous administration of ET-1 in pigs. Interestingly, in 1 clinical study, survivors of human cardiac arrest maintained normal or elevated plasma ET-1 levels during CPR, whereas nonsurvivors had progressively reduced concentrations.

Because increased vasoconstriction and the resultant increased CPP lead to improved initial resuscitation rates from cardiac arrest, investigators have been interested in novel, powerful vasoconstrictors, such as vasopressin and ET-1. DeBehnke and associates reported that the combination of epinephrine and ET-1 significantly improved CPP in dogs compared with either agent alone. Although their findings were impressive, they studied only hemodynamics during CPR, not outcome variables. They concluded that ET-1 should be investigated further as a vasoconstrictor in cardiac arrest.

The purpose of the present study was to compare the effectiveness of standard-dose epinephrine (Epi group) versus standard-dose epinephrine plus ET-1 (ET-1 group) during CPR in a swine model of prolonged fibrillatory cardiac arrest. Outcome variables, such as ROSC, 24-hour survival, and...
neurological outcome, were evaluated, as well as hemodynamics during and after CPR.

Methods

Animal Preparation
All trials were conducted in accordance with the standards and guidelines of the American Physiological Society and with the approval of the University of Arizona Institutional Animal Care and Use Committee. Domestic swine weighing 20 to 30 kg were fasted for 18 hours and then anesthetized with isoflurane inhalation anesthetic administered by nose cone. The animals were placed on their backs and secured with ties to the surgical table. They underwent endotracheal intubation per os, and anesthesia was maintained by a mixture of 1% to 1.5% isoflurane and room air. Ventilation was provided by a rate- and volume-regulated mechanical ventilator (Harvard Medical Supplies) to maintain PETCO₂ at 40±2 mm Hg as measured continuously by an infrared capnometer (47201A, Hewlett-Packard) placed in the airway. ECG leads were attached to the limbs for continuous ECG monitoring.

The ventral neck area was prepared for sterile cutdown procedure in the standard fashion. Vascular introducer sheaths were placed via cutdown procedure into the right and left external jugular veins and right common carotid artery for placement of catheters and administration of drugs. Micromanometer-tipped catheters (MPC-500, Millar Instruments) were calibrated and inserted through the introducers into the right atrium and descending aorta.

Measurements
Right atrial pressure (RAP), aortic pressure (AoP), PETCO₂, and ECG were periodically recorded on a direct-writing recorder (Gould ES 1000) and continuously recorded on a laptop computer (Fujitsu Lifebook 530T) for decision-making during CPR and analyses of data subsequent to the trials. CPP was calculated as the difference between mid-diastolic AoP and mid-diastolic RAP.

Experimental Protocol
After collection of baseline data, a pacing electrode was positioned in the right ventricle. Isoflurane was discontinued, and VF was induced with a 60-cycle alternating current to the endocardium. VF was confirmed by the ECG waveform and precipitous decline in the AoP. Ventilation was discontinued, and the animal underwent 2 minutes of untreated cardiac arrest to simulate a typical time before initial recognition and call for help before bystander CPR. Metronome-guided manual chest compressions (100 per minute) were then begun and continued for 6 minutes (simulating bystander CPR). The animals were randomly provided with 1 mg epinephrine (Epi group) or 1 mg epinephrine plus 0.1 mg ET-1 (ET-1 group) at 8 minutes after initial VF. Ventilation with FiO₂ of 1.0 and chest compressions were provided to both groups for 10 minutes after initial drug administration (ie, a total of 18 minutes after VF induction) to mimic arrival of emergency medical services. Both groups received additional epinephrine doses at 13 and 18 minutes after VF (every 5 minutes).

Eighteen minutes after induction of VF, defibrillation was attempted with 3 J/kg for the first 2 attempts and 6 J/kg for the third and any subsequent attempts. If the 3 initial shocks were unsuccessful, 1 mg of epinephrine was administered, and CPR was continued for another minute before the next defibrillation attempt. Starting with the first defibrillation attempt, resuscitative efforts, including epinephrine, additional shocks, and lidocaine, were provided according to the American Heart Association advanced cardiac life support guidelines (except for typical swine defibrillation doses). ROSC was defined as an unassisted aortic systolic pressure >50 mm Hg and a pulse pressure >20 mm Hg for ≥1 minute. If ROSC did not occur within 20 minutes of the initial defibrillation attempt, resuscitative efforts were discontinued.

All successfully resuscitated animals were supported for 1 hour in a simulated ICU setting. Mechanical ventilation was provided with 100% oxygen and adjusted to maintain the PETCO₂ at 30 to 40 mm Hg. Dopamine and volume resuscitation were provided to maintain systolic blood pressure >80 mm Hg, and lidocaine was provided for ventricular ectopy. Recurrent cardiac arrest was treated according to American Heart Association guidelines. After the 1-hour ICU period, the animals were weaned from ventilator and pharmacological support, if any, and allowed to awaken from anesthesia. They were placed in an observation cage, monitored over the next 24 hours, and given supportive treatment if necessary.

Outcome and Neurological Evaluation
Survival and neurological outcome were evaluated at 24 hours after the initial cardiac arrest. Objective neurological evaluation included the Swine Cerebral Performance Category scale. Briefly, category 1 indicates a normal, walking, feeding, alert animal. Category 2 refers to a slightly disabled animal that is alert, walking, and feeding. Category 3 indicates a more severe disability, such as inability to stand, walk, or eat. Category 4, vegetative state or deep coma, refers to an animal with no response to its environment. Categories 1 and 2 were considered good neurological outcome. After the 24-hour evaluation, the animals were humanely euthanized by intravenous administration of phenobarbital and phenytoin.

Data Analysis
Data were analyzed at baseline, every 2 minutes during CPR, and at 1, 15, 30, 45, and 60 minutes after resuscitation in the animals with ROSC. Comparisons of the 2 experimental groups with respect to continuous variables, such as heart rate, blood pressures, and weight, were evaluated by Student’s t test and reported as mean±SEM. No correction for multiple comparisons was done. Comparisons with respect to discrete variables, such as ROSC, 1-hour survival, 24-hour survival, and good neurological outcome, were evaluated by Fisher’s exact test.

Results
The important outcome data are displayed in Tables 1 and 2. There was a trend toward higher ROSC rates among the ET-1 pigs versus epinephrine only (Epi) pigs (8 of 10 versus 8 of 17, P=0.12). However, all 8 Epi swine with ROSC survived the 1-hour intensive care unit (ICU) period versus only 3 of the 8 ET-1 swine, P=0.03. Similarly, all 8 Epi swine with ROSC survived for 24 hours versus only 2 of the 8 ET-1 swine, P<0.01. The other ET-1 animal that died after ROSC was in severe cardiorespiratory distress immediately after extubation 1 hour after ROSC and died 45 minutes later of progressive cardiorespiratory failure. The overall survival rates were higher in the Epi group (8 of 17, or 47%, versus 2 of 10, or 20%, P=0.23), but small numbers precluded statistical significance. All 24-hour survivors had good neu-

### TABLE 1. Overall Outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>1-h Survival, n (%)</th>
<th>24-h Survival, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi</td>
<td>8/17 (47)</td>
<td>8/17 (47)</td>
</tr>
<tr>
<td>ET-1</td>
<td>8/10 (80)</td>
<td>2/10 (20)</td>
</tr>
</tbody>
</table>

*P<0.05.
†P<0.01.

### TABLE 2. Outcome After Initial ROSC

<table>
<thead>
<tr>
<th>Group</th>
<th>1-h Survival, n</th>
<th>24-h Survival, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1</td>
<td>3/8</td>
<td>2/8†</td>
</tr>
<tr>
<td>Epi</td>
<td>8/8*</td>
<td>8/8†</td>
</tr>
</tbody>
</table>
end-tidal carbon dioxide concentration (PETCO₂) was significantly higher in the ET-1 group compared with the Epi group, and these differences continued throughout CPR period (Figure 1 and Table 3). Concurrently, the ventricular fibrillation [VF], aortic diastolic pressures and CPPs were significantly elevated in the ET-1 group compared with the Epi group, and these differences continued throughout CPR period until initial defibrillation attempt (18 minutes after VF). Two groups differ: *P<0.001; †P<0.01.

Death occurred 9 to 13 minutes after ROSC in all 5 ET-1 animals that died during the ICU period. Figure 4 shows typical data from 2 of these animals. All had high CPPs but very narrow pulse pressures. This led to either progressive hypotension (Figure 4A) or pulseless refractory ventricular tachycardia (Figure 4B), followed by refractory VF. Typical ECG changes of advanced myocardial ischemia (ST-segment alterations, increased T-wave amplitude, and prolonged QRS interval) were noted in all of these animals before VF, despite excellent CPPs.

After 27 animals had been treated, the data were analyzed. Our initial hypotheses were that ET-1 would improve CPP, ROSC, and 24-hour survival. If the same trends continued, adding 7 ET-1 swine or increasing the number of animals in each group to 20 would not have changed any of our statistical results. Therefore, extending the experiment was deemed neither economically sound nor humanely justified.

## Discussion

This study confirms that the addition of ET-1 to standard-dose epinephrine during CPR can substantially improve aortic relaxation pressure (“diastolic” pressure) and CPP during CPR. These improvements in myocardial hemodynamics tended to improve initial rates of ROSC. However, these data establish that greater vasoconstriction during and after CPR can have adverse effects. During CPR, ET-1 administration resulted in lower PETCO₂, presumably due to decreased cardiac output. After ROSC, the continued intense vasoconstriction from ET-1 led to higher aortic diastolic pressure and very narrow pulse pressure. More importantly, the postresuscitation mortality was significantly higher in the ET-1 group (6 of 8 versus 0 of 8 with Epi only, P<0.01).

### TABLE 3. Hemodynamics During CPR

<table>
<thead>
<tr>
<th>Time After VF Induced, min</th>
<th>Initial Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>AoD</td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>29±3</td>
</tr>
<tr>
<td>Epi</td>
<td>35±3</td>
</tr>
<tr>
<td>CPP</td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>18±4</td>
</tr>
<tr>
<td>Epi</td>
<td>24±3</td>
</tr>
<tr>
<td>PETCO₂</td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>17±1</td>
</tr>
<tr>
<td>Epi</td>
<td>21±2</td>
</tr>
</tbody>
</table>

Initial Drug indicates initial vasopressor administered at 8 minutes; AoD, aortic relaxation pressure.

*P<0.001, ET-1 vs Epi.
†P<0.01, ET-1 vs Epi.
‡P<0.05, ET-1 vs Epi.
Although it has been axiomatic that increased vasoconstriction during CPR improves CPP and thereby outcome,\textsuperscript{1,17–19} the present data indicate that excessive vasoconstriction has detrimental effects. A previous investigation from our laboratory comparing high-dose epinephrine with standard-dose epinephrine during CPR in swine demonstrated that CPP and myocardial blood flow were higher and cardiac output was lower in the high-dose group.\textsuperscript{20} The PET\textsubscript{CO2} was also lower in the high-dose epinephrine group and served as a reliable marker of cardiac output during CPR, as in other models.\textsuperscript{20 –22} Further animal investigations have established that high-dose epinephrine can lead to a toxic hyperadrenergic state, including tachycardia, severe hypertension, and ventricular ectopy, immediately after return of spontaneous circulation.\textsuperscript{23–25} In 2 randomized, controlled animal studies, high-dose epinephrine resulted in a higher mortality rate immediately after successful resuscitation than standard-dose epinephrine because of these postresuscitation hyperadrenergic effects.\textsuperscript{23,24} Studies by Ditchey and others have suggested that the adverse effects of high-dose epinephrine may be due to excess $\beta$-adrenergic stimulation.\textsuperscript{9,23–29}

The present study suggests that vasoconstriction alone can impair postresuscitation cardiac function severely enough to increase postresuscitation mortality. Five of the

**TABLE 4.** Hemodynamics After ROSC

<table>
<thead>
<tr>
<th>Time After ROSC, min</th>
<th>1</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AoS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>175±15*</td>
<td>103±8*</td>
<td>90±4</td>
<td>84±3</td>
<td>76±1</td>
</tr>
<tr>
<td>Epi</td>
<td>122±8*</td>
<td>82±3*</td>
<td>85±3</td>
<td>63±2</td>
<td>80±2</td>
</tr>
<tr>
<td><strong>AoD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>136±10†</td>
<td>92±6†</td>
<td>82±6*</td>
<td>72±5‡</td>
<td>69±8‡</td>
</tr>
<tr>
<td>Epi</td>
<td>70±10†</td>
<td>52±2†</td>
<td>61±3*</td>
<td>59±2‡</td>
<td>57±2‡</td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>39±9</td>
<td>11±2*</td>
<td>8±2†</td>
<td>12±1‡</td>
<td>7±8*</td>
</tr>
<tr>
<td>Epi</td>
<td>52±4</td>
<td>30±3*</td>
<td>24±1†</td>
<td>24±1‡</td>
<td>24±1*</td>
</tr>
</tbody>
</table>

AoS indicates aortic systolic pressure; AoD, aortic diastolic pressure; and PP, aortic pulse pressure.

*P<0.01, ET-1 vs Epi.
†P<0.001, ET-1 vs Epi.
‡P<0.05, ET-1 vs Epi.
8 ET-1 animals with ROSC died 9 to 13 minutes later, whereas all 8 Epi animals with ROSC survived for 24 hours with good neurological outcome. The high aortic diastolic pressures and low pulse pressures in the postresuscitation period are consistent with intense vasoconstriction, and the ECG changes of myocardial ischemia indicate an imbalance of myocardial oxygen supply and demand. Furthermore, the decrease in cardiac output during CPR (manifested as the lower PETCO₂) may have contributed to the postresuscitation pathophysiology.

Postresuscitation left ventricular dysfunction is a well-documented consequence of cardiac arrest. 29–34 Although administration of epinephrine during CPR improves myocardial perfusion and outcome, epinephrine can also worsen postresuscitation myocardial dysfunction. 29 It has been assumed that these adverse effects are due to myocardial energy imbalance associated with β-adrenergic effects. Data from the present study suggest that potent vasoconstriction is detrimental during the postresuscitation phase. When the stunned left ventricle is unable to tolerate the increasing systemic vascular resistance, progressive pump failure, systemic hypotension, and/or malignant ventricular arrhythmias may ensue. Interestingly, in a randomized swine study comparing vasopressin with epinephrine during CPR, the vasopressin group had higher aortic blood pressure, higher systemic vascular resistance, and worse cardiac dysfunction 15 minutes after resuscitation. 35 Powerful vasoconstricting agents with a long half-life, such as ET-1 or vasopressin, may be especially problematic, because the pharmacological effects will not resolve within a few minutes.

The dose of ET-1 administered in this study was derived from the only previous animal investigation of its use during CPR. 15 It is possible that a smaller dose of ET-1 might have produced less drastic cardiovascular alterations and improved outcomes. A dose-response study will be necessary to investigate this possibility. Moreover, all ET-1 animals also received epinephrine as in the previous animal investigation. 15 The epinephrine doses presumably contributed to the vasoconstriction during CPR and immediately after resuscitation.

In summary, this study establishes that administration of ET-1 during CPR can result in worse postresuscitation outcome. As expected, administration of ET-1 improved CPP during CPR and tended to improve initial resuscitation. However, the intense vasoconstriction was apparently a major detriment in the immediate postresuscitation period. Although adequate CPP during CPR may be necessary for successful resuscitation, too much vasoconstriction from ET-1, epinephrine, vasopressin, or other vasoconstricting agents can be harmful.

Acknowledgment
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References


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