Evidence Favoring the Use of an \( \alpha_2 \)-Selective Vasopressor Agent for Cardiopulmonary Resuscitation

Tommaso Pellis, MD; Max Harry Weil, MD, PhD; Wanchun Tang, MD; Shijie Sun, MD; Jing Xie, MD; Lei Song, MD; Paul Checchia, MD

Background—Both \( \alpha_1 \)- and \( \beta \)-adrenergic agonists increase the severity of global myocardial ischemic injury. We hypothesized that combined \( \beta \)- and \( \alpha_2 \)-adrenergic blockade would improve initial resuscitation and postresuscitation myocardial and neurological functions. We further hypothesized that the resulting \( \alpha_2 \)-actions of relatively brief duration would favor improved functions compared with the more prolonged effect of nonadrenergic vasopressin.

Methods and Results—Three groups of 5 male domestic pigs weighing 37 \( \pm \) 3 kg were investigated. Ventricular fibrillation was untreated for 7 minutes before the start of precordial compression, mechanical ventilation, and attempted defibrillation. Animals were randomized to receive central venous injections of equipressor doses of (1) epinephrine, (2) epinephrine in which both \( \alpha_1 \)- and \( \beta \)-adrenergic effects were blocked by previous administration of prazosin and propranolol, and (3) vasopressin during CPR. All but 1 animal were successfully resuscitated. After injection of epinephrine, significantly better cardiac output and fractional area change, together with lesser increases in troponin I, were observed after \( \alpha_1 \)- and \( \beta \)-adrenergic blockade. Postresuscitation neurological function was also improved after \( \alpha_1 \)- and \( \beta \)-block in comparison with unblocked epinephrine and after vasopressin.

Conclusions—Equipressor doses of epinephrine, epinephrine after \( \alpha_1 \)- and \( \beta \)-adrenergic blockade, and vasopressin were equally effective in restoring spontaneous circulation after prolonged ventricular fibrillation. However, combined \( \alpha_1 \)- and \( \beta \)-adrenergic blockade, which represented a predominantly selective \( \alpha_2 \)-vasopressor effect, resulted in improved postresuscitation cardiac and neurological recovery. (Circulation. 2003;108:2716-2721.)

Key Words: cardiopulmonary resuscitation \( \square \) epinephrine \( \square \) receptors, adrenergic, alpha \( \square \) receptors, adrenergic, beta \( \square \) vasopressin

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of epinephrine, especially during the very-high-energy myocardium-consuming interval of VF.\textsuperscript{20,21} By minimizing global myocardial ischemic injury, we would anticipate less postresuscitation myocardial dysfunction.\textsuperscript{7} We hypothesized further that the severity of such ischemic injury may be quantified by measurements of cardiac troponin I, the structural protein that is myocyte-specific.\textsuperscript{22} Less global myocardial ischemic injury would be associated with less troponin I release into the bloodstream.

Using a porcine model of cardiac arrest, we tested our hypothesis by comparing the effects of epinephrine, epinephrine after $\alpha_1$- and $\beta$-adrenergic blockade, and arginine vasopressin in equipressor doses on postresuscitation myocardial function, troponin I release, and neurological outcomes.

Methods

The study was approved by the Animal Care and Use Committee of the Institute of Critical Care Medicine. All animals received humane care in compliance with the principles of laboratory and animal care formulated by the National Society for Medical Research and the National Institutes of Health publication 86-32 on the use of laboratory animals prepared by the Institute of Laboratory Animal Resources, as revised in 1996.

Animal Preparation

An established porcine model of cardiac arrest was used as previously described.\textsuperscript{7} Briefly, 15 healthy male Yorkshire-cross domestic pigs (Sus scrofa) weighing between 35 and 40 kg were fasted overnight except for free access to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg), completed by sodium pentobarbital (30 mg/kg), and maintained by additional doses of 8 mg/kg of sodium pentobarbital. After endotracheal intubation, animals were mechanically ventilated with a tidal volume of 15 mL/kg with the aid of a volume-controlled ventilator (model MA-1, Puritan-Bennett). End-tidal PCO$_2$ (PETCO$_2$) was monitored with an infrared mainstream analyzer (model O1R-7101A, Nihon Kohden Corp). Respiratory frequency was adjusted to maintain PETCO$_2$ between 35 and 40 mm Hg.

For measurement of aortic pressure, a fluid-filled 8F angiographic catheter (model 6523; USCI C.R. Bart Inc) was advanced into the descending thoracic aorta. For the measurement of left ventricular functions, a 5.5/7.5-MHz biplane Doppler transesophageal echocardiographic transducer with 4-way flexure (model 21366A, Hewlett-Packard Co., Medical Products Group), was used as previously described.\textsuperscript{9} For the measurements of right atrial pressure and cardiac output by the thermodilution method a 7F, pentalumen, thermodilution-tipped catheter (Abbott Critical Care 41216) was advanced flow-directed into the pulmonary artery. Conventional external pressure transducers were used (Abbott Critical Care Systems, Transpac IV). For inducing VF, a 5F pacing catheter (EP Technologies, Inc) was advanced from the right cephalic vein into the apex of the right ventricle guided by fluoroscopic image intensification. ECG electrodes were applied on the right and left upper and lower limbs. Aortic and mixed venous blood gases, hemoglobin, and oxymemoglobin were measured with a blood gas analyzer (Stat Profile Ultra C, Nova Biomedical Corp). These measurements were obtained before inducing cardiac arrest and at hourly intervals after resuscitation for a total of 4 hours. Aliquots of 1 mL of venous blood for measurements of troponin I were collected at 15 minutes before induction of VF and at 60 and 240 minutes after successful resuscitation, together with a final sample after 72 hours.

For measurement of troponin I, the blood was centrifuged at 3000 rpm for 10 minutes, and the serum was stored in liquid nitrogen at $-70^\circ$C. For immunooassay of the troponin I concentration, the Abbott Axsym System (Abbott Diagnostics) was used as described previously.\textsuperscript{23}

**Experimental Procedure**

Twenty minutes before induction of cardiac arrest, the animals were randomized by the sealed-envelope method to receive 1 of the 3 drug regimens. The experimental protocol is diagrammed in Figure 1. The vaspressor agents, the doses, and the timing of administration are summarized in Table 1. Cardiac arrest followed onset of VF after delivery of an AC current of 1 to 2 mA to the endocardium of the right ventricle. Mechanical ventilation was stopped after onset of VF. Ventricular fibrillation was untreated for 7 minutes, after which precordial compression was started with a pneumatically driven chest compressor (Thumper, model 1000, Michigan Instruments), and mechanical ventilation was resumed.\textsuperscript{7,9} At 2 minutes after the start of precordial compression, 1 of the 3 vasopressor drugs was injected into the right atrium over a 30-second interval. After an additional 4 minutes of precordial compression, a sequence of up to three 150-J biphasic electrical shocks was delivered between the conventional positive right infraclavicular electrode and the negative apical electrode with the CodeMaster XL, Smart Biphasic, defibrillator (model M1723A, Heartstream). With failure to restore spontaneous circulation, chest compression and ventilation were continued and defibrillation was again attempted, each at intervals of 1 minute. The sequence of chest compression and attempted defibrillation was continued until return of spontaneous circulation or for a total of 9 minutes of precordial compression, as shown in Figure 1. In each instance, an organized cardiac rhythm with mean aortic pressure of $>60$ mm Hg was ultimately established after electrical defibrillation except for 1 animal in group 1 in which resuscitation efforts failed after 9 minutes. Animals were monitored continuously for the ensuing 4 hours, after which spontaneous ventilation had returned. The animals were then extubated and returned to their cages.

Analogesia was administered in bolus doses of butorphanol 0.1 mg/kg by intramuscular injection as needed over the after 72 hours. After 72 hours, animals were reanesthetized with ketamine and pentobarbital, and mechanical ventilation was resumed.\textsuperscript{7,9} At 2 minutes after the start of precordial compression, 1 of the 3 vasopressor drugs was injected into the right atrium over a 30-second interval. After an additional 4 minutes of precordial compression, a sequence of up to three 150-J biphasic electrical shocks was delivered between the conventional positive right infraclavicular electrode and the negative apical electrode with the CodeMaster XL, Smart Biphasic, defibrillator (model M1723A, Heartstream). With failure to restore spontaneous circulation, chest compression and ventilation were continued and defibrillation was again attempted, each at intervals of 1 minute. The sequence of chest compression and attempted defibrillation was continued until return of spontaneous circulation or for a total of 9 minutes of precordial compression, as shown in Figure 1. In each instance, an organized cardiac rhythm with mean aortic pressure of $>60$ mm Hg was ultimately established after electrical defibrillation except for 1 animal in group 1 in which resuscitation efforts failed after 9 minutes. Animals were monitored continuously for the ensuing 4 hours, after which spontaneous ventilation had returned. The animals were then extubated and returned to their cages.

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**Table 1. Drugs, Doses, and Timing of Administration**

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>No.</th>
<th>Dose</th>
<th>Time of Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epinephrine</td>
<td>5</td>
<td>20 $\mu$g/kg</td>
<td>2 min after start of CPR</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>1</td>
<td>1 mg/kg</td>
<td>15 min before induction of VF</td>
</tr>
<tr>
<td></td>
<td>+ Prazosin</td>
<td>0.5 $\mu$g/kg</td>
<td>15 min before induction of VF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Epinephrine</td>
<td>20 $\mu$g/kg</td>
<td>2 min after start of CPR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vasopressin</td>
<td>0.4 $\mu$g/kg</td>
<td>2 min after start of CPR</td>
<td></td>
</tr>
</tbody>
</table>
Measurements

Hemodynamic data, PetCO₂, and lead II of the ECG were measured continuously and recorded on a personal computer (PC)-based data acquisition system as described previously. ECG-Doppler measurements were recorded on analog tape and time-coordinated with the PC-based data acquisition system. The CPP was digitally computed from differences in time-coincident aortic and right atrial pressures and displayed in real time. Arterial and mixed venous blood gases, hemoglobin, and oxyhemoglobin, together with arterial blood lactate, were measured in accordance with the protocol summarized in Figure 1. Troponin I was measured before and at 60 minutes, 240 minutes, and 72 hours after resuscitation.

The total number of ventricular ectopic beats was counted over an interval of 30 minutes after successful resuscitation in accord with the Lambeth Convention. A quantitative neurological alertness score developed by our group was used for evaluating neurological recovery at 24-hour intervals for a total of 72 hours.

Analyses

The study was powered to detect statistically significant differences in postresuscitation myocardial function and neurological alertness. For measurements between groups, ANOVA and Scheffé’s multi-comparison techniques were used. Comparisons between time-based measurements within each group were performed with ANOVA for repeated measurements. The outcome differences were analyzed with Fisher’s exact test. Measurements are reported as mean±SD. A value of P<0.05 was considered significant.

Results

There were no differences in baseline in hemodynamic, blood gas, or troponin I measurements between groups when measured 15 minutes before induction of VF and during CPR. Coronary perfusion pressure values during the initial 4 minutes of CPR were indistinguishable. However, CPP was significantly greater after 6 minutes of precordial compression in the vasopressin group compared with the epinephrine group (23±3 versus 14±3 mm Hg, P<0.01). Except for 1 animal that failed resuscitation attempts after treatment with epinephrine alone, spontaneous circulation was restored in each animal. A significantly larger number of electrical shocks and total energy of defibrillation was required in group 1 after epinephrine alone compared with group 2 after α₁- and β-blockade and in group 3 after vasopressin (Table 2).

The numbers of premature ventricular contractions and salvos were significantly greater in the epinephrine-treated animals. Epinephrine alone and vasopressin demonstrated an approximately equal incidence of ventricular dysrhythmias (Table 3). This contrasted with group 2 after the α₁- and β-effects of epinephrine had been blocked. Ventricular ectopy was minimized. The mean arterial pressure measured at 5 minutes after successful resuscitation was significantly greater after vasopressin compared with the other 2 groups, confirming a prolonged vasopressor action of vasopressin (Table 2). Significantly greater increases in arterial blood lactate followed epinephrine and vasopressin, and these greater increases in arterial lactate concentrations persisted for the 2-hour interval after return of spontaneous circulation (Figure 2). Most striking were increases in troponin I concentrations observed at 240 minutes in both the epinephrine (41±15 μg/mL) and vasopressin (36±14 μg/mL) groups. This contrasted with animals in which α₁- and β-adrenergic actions of epinephrine were blocked and in which troponin I remained at near baseline values (3±2 μg/mL). These differences were highly significant (P<0.01). Values of troponin I returned to baseline after 72 hours in each group (Figure 2).

The cardiac output of resuscitated animals was significantly reduced in each group. However, relatively rapid recovery over the ensuing 4 hours to near baseline values was observed in group 2 after blockade of α₁- and β-adrenergic receptors. The measurements obtained by the thermodilution and echocardiographic methods closely paralleled each other (Figure 3, A and B). Further confirmation of significantly better recovery of postresuscitation myocardial function after blockade of β- and α₁-receptors in group 2 was demonstrated by echocardiographically measured fractional area changes (Figure 3C). The neurological alertness score at 24 and 48 hours also favored animals in which α₁- and β-receptors were blocked (Figure 4). Nevertheless, no statistically significant differences in 72-hour survival were documented.

Discussion

In the setting of VF, current guidelines of advanced cardiac life support call for initial electrical defibrillation. With

<p>| TABLE 2. Number of Shocks and Total Energy of Defibrillation |
|---------------------------------|------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Shocks</th>
<th>Intervention</th>
<th>5 min</th>
<th>10 min</th>
<th>30 min</th>
<th>Mean Arterial Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6±2.8</td>
<td>Epinephrine</td>
<td>93±19†</td>
<td>99±15†</td>
<td>111±12</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.6±0.9*</td>
<td>α₁- and β-block before epinephrine</td>
<td>108±10†</td>
<td>110±10†</td>
<td>109±11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.6±0.9*</td>
<td>Vasopressin</td>
<td>134±10</td>
<td>129±15</td>
<td>104±10</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 vs Group 1; †P<0.05; ‡P<0.01 vs Group 3.

| TABLE 3. Postresuscitation Dysrhythmias |
|----------------------------------------|----------------|-----------------|-----------------|
|                                       | Premature Ventricular Contractions | Salvos | Ventricular Tachycardia, s | Episodes of Recurrent VF, n |
| Epinephrine                           | 40±13*          | 12±3‡          | 20±20           | 7                  |
| α₁- and β-block before epinephrine    | 16±7            | 3±3            | 1±0             | 1                  |
| Vasopressin                           | 39±25           | 13±10          | 169±327         | 2                  |

*P<0.05; †P<0.01 vs Blocked Epinephrine
failure to restore spontaneous circulation, the guidelines allow for intravenous administration of either epinephrine or vasopressin. The rationale for the vasopressor agent is to increase CPPs and thereby facilitate defibrillation.25 Epinephrine has remained the primary and widely used vasopressor agent for CPR, although a classic report from Redding and Pearson20 more than 40 years ago had recommended more selective α-adrenergic agonists, such as phenylephrine and methoxamine. Subsequently, Ditchey et al26 aroused concern that the β-adrenergic effect of epinephrine had adverse effects on outcomes, because it increased the severity of myocardial ischemic injury during the global ischemic interval of cardiac arrest. In their experimental studies, β-adrenergic blockade produced salutary effects. During cardiac arrest, when there is cessation of coronary blood flow, the severity of ischemic injury is magnified, and disproportionately so, because of the greatly increased myocardial oxygen demands that accompany VF.21

There is persuasive evidence that epinephrine improves the success of immediate resuscitation attempts. Yet, there is little objective documentation that epinephrine improves meaningful survival.27–28 Epinephrine increases the incidence of ventricular ectopy.7,14 A larger number of electrical shocks are required for electrical defibrillation with return of spontaneous circulation after administration of epinephrine and with the adversity of significantly greater postresuscitation myocardial dysfunction.7

In addition to β-adrenergic receptors, α1-receptors have been identified in the myocardium, and α1-agonists also have inotropic and chronotropic actions that, like β-agonists, increase oxygen demands.29 Accordingly, both β- and α1-agonists increase myocardial oxygen demands and therefore increase the severity of postresuscitation myocardial dysfunction. An additional adverse effect of α1-agonist epinephrine is coronary arterial vasoconstriction with the potential of further reductions in myocardial blood flow and therefore greater postresuscitation ischemic injury.

In contrast to α1-adrenergic receptors, no α2-adrenergic receptors have been identified in the myocardium.31 This prompted us to hypothesize that an α2-adrenergic agonist with selective peripheral vasoconstrictor actions would be a more optimal resuscitative drug. α2-Adrenergic agonists have the additional potential of increasing endothelial nitric oxide production, thereby counterbalancing α1-adrenergically induced coronary vasoconstriction.32 Experimental studies by our group with the selective α2-agonist α-methylnorepinephrine confirmed improved outcomes with fewer postresuscita-
tion arrhythmias and less postresuscitation myocardial dysfunction compared with unblocked epinephrine. When the α₁- and β-receptors of epinephrine were blocked with yohimbine, the therapeutic benefits of epinephrine for CPR were diminished. The incentive to the present study was therefore to secure the rationale for a selective α₁-agonist.

The introduction in 1993 of vasopressin for advanced life support by Linder et al addressed options for minimizing the adverse inotropic and chronotropic effects of epinephrine. Vasopressin acts directly through V₁ receptors and potentiates the vasoconstrictor effects of endogenous catecholamines. Vasopressin therefore is a potential alternative agent for increasing CPP and hence facilitates defibrillation. Although observational studies on human patients yielded promising results with vasopressin, there is as yet no proof of improved cardiac or neurological outcomes or 30-day survival in patients after in-hospital cardiac arrest. Unfortunately, no controlled human studies have been published on either epinephrine or vasopressin, although an as yet unpublished European Multicenter trial failed to demonstrate a survival benefit for vasopressin (V. Wenzel, personal communication). On the basis of currently available experimental and clinical observations, supported by the present report, vasopressin is effective for initial resuscitation but has detrimental effects on postresuscitation myocardial function. The present data support the likelihood that its half-life of 25 minutes accounts for the increased afterload, characterized by greater postresuscitation arterial pressures in association with lower cardiac output. Our findings are therefore consistent with the hypothesis that the added afterload imposed by vasopressin after successful resuscitation increases the myocardial workload of the injured heart. Consequently, it further reduces cardiac output when the contractile function of the resuscitated heart is already impaired by the global ischemic injury during the no-flow state of cardiac arrest. Coincidently observed in the present study was poor neurological recovery after vasopressin, observations that are consistent with those previously reported by Nozari et al.

The results therefore affirm our hypothesis. α₁-Adrenergic blockade in combination with nonselective β-adrenergic blockade increased CPP to levels that predicted and accomplished successful resuscitation. Moreover, both epinephrine after α₁- and β-blockade and arginine vasopressin were equally effective for initial resuscitation and especially for reestablishing a perfusing rhythm, although a significantly greater number of shocks was required with epinephrine alone. After resuscitation, the incidence of ventricular arrhythmias was significantly greater in the absence of α₁- and β-blockade. Postresuscitation myocardial dysfunction and neurological impairment were significantly decreased with blocked epinephrine compared with both unblocked epinephrine and vasopressin.

The significance of our findings was strongly supported by measurements of troponin I, a specific and sensitive marker of myocardial damage. Strikingly higher concentrations of this marker followed resuscitation with both epinephrine and vasopressin, an additional indicator of more severe myocardial injury. Conversely, the combination of α₁- and β-adrenergic blockade of epinephrine minimized myocardial injury as quantified both by measurements of myocardial function and by assay of myocardial cell injury with troponin I concentrations in the initial 4 hours after resuscitation.

The authors recognize several limitations in the interpretation of the present findings. The study was conducted on healthy pigs, and its direct application to human victims of cardiac arrest, a majority of whom have underlying heart disease, remains to be proven. Species differences in the microcirculatory effects of vasopressin and differences in vasopressin preparations have not been addressed in this experimental study. The experimental animals were anesthetized, and potentially obfuscating effects of the anesthetic agents were not excluded. Finally, pretreating of animals in group II may represent a preventive effect in that both propranolol and prazosin may have had independent prophylactic actions. Within these limitations, we conclude that when α₁-, β₁-, and β₂-adrenergic receptors are blocked, α₁-agonist actions yield pressor effects comparable to those of epinephrine alone and those produced by lysine vasopressin in pressor-equivalent bolus doses. Blocked epinephrine, unblocked epinephrine, and vasopressin were equally effective for restoring spontaneous circulation. However, under the experimental conditions of the present experiments, α₁- and β-adrenergic blockade minimized postresuscitation arrhythmias, reduced myocardial damage, decreased the severity of postresuscitation myocardial dysfunction, and improved neurological outcomes.

Acknowledgments

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References


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