Developing a Vasopressor Combination in a Pig Model of Adult Asphyxial Cardiac Arrest

Viktoria D. Mayr, MD; Volker Wenzel, MD; Wolfgang G. Voelckel, MD; Anette C. Krismer, MD; Tilko Mueller, BS; Keith G. Lurie, MD; Karl H. Lindner, MD

Background—The purpose of this study was to investigate the effects of vasopressin versus epinephrine, and both drugs combined, in a porcine model of simulated adult asphyxial cardiac arrest.

Methods and Results—At ≈7 minutes after the endotracheal tube had been clamped, cardiac arrest was present in 24 pigs and remained untreated for another 8 minutes. After 4 minutes of basic life support cardiopulmonary resuscitation, pigs were randomly assigned to receive, every 5 minutes, either epinephrine (45, 200, or 200 μg/kg; n=6); vasopressin (0.4, 0.8, or 0.8 U/kg; n=6); or epinephrine combined with vasopressin (high-dose epinephrine/vasopressin combination, μg/kg and U/kg: 45/0.4, 200/0.8, or 200/0.8; n=6; optimal-dose epinephrine/vasopressin combination, 45/0.4, 45/0.8, or 45/0.8; n=6). Mean±SEM coronary perfusion pressure was significantly (P<0.05) higher 90 seconds after high- or optimal-dose epinephrine/vasopressin combinations versus vasopressin alone and versus epinephrine alone (37±10 versus 25±7 versus 19±8 versus 6±3 mm Hg; 42±6 versus 40±5 versus 21±5 versus 14±6 mm Hg; and 39±6 versus 37±4 versus 9±3 versus 12±4 mm Hg, respectively). Six of 6 high-dose, 6 of 6 optimal-dose vasopressin/epinephrine combination, 0 of 6 vasopressin, and 1 of 6 epinephrine pigs had return of spontaneous circulation (P<0.05).

Conclusions—Epinephrine combined with vasopressin, but not epinephrine or vasopressin alone, maintained elevated coronary perfusion pressure during cardiopulmonary resuscitation and resulted in significantly higher survival rates in this adult porcine asphyxial model. (Circulation. 2001;104:1651-1656.)

Key Words: heart arrest ■ vasoconstriction ■ epinephrine ■ ventilation ■ cardiopulmonary resuscitation

The American Heart Association and the European Resuscitation Council recommend 10 μg/kg epinephrine for pediatric cardiopulmonary resuscitation (CPR) regardless of the presenting rhythm, such as ventricular fibrillation, pulseless electrical activity, and asystole; in adults, 40 U vasopressin or 1 mg epinephrine is recommended for patients presenting with ventricular fibrillation and 1 mg epinephrine for patients presenting with pulseless electrical activity or asystole.1-2 This CPR strategy of a universal pharmacological approach may be too simplistic, because metabolic status, endogenous stress hormone levels, and therefore vasopressor response of the vasculature may be fundamentally different during sudden ventricular fibrillation, pulseless electrical activity, or asystole subsequent to progressively deteriorating respiratory function with severe global acidosis, hypoxia, and hypercarbia. Thus, if pharmacological CPR strategies could be identified that better reflect the underlying cause of cardiac arrest, CPR outcome in both the adult and pediatric setting might be improved.

In adult porcine CPR preparations with ventricular fibrillation3 or postcountershock pulseless electrical activity,4 vasopressin improved vital organ blood flow during CPR,5 cerebral oxygen delivery,6 resuscitability,7 and neurological recovery8 better than did epinephrine. Surprisingly, these beneficial effects of vasopressin could not be extrapolated to a model of pediatric asphyxial cardiac arrest, in which epinephrine was clearly superior to vasopressin with respect to improving vital-organ blood flow.9 This may indicate different efficiencies of vasopressors in pediatric versus adult preparations and that different effects of dysrhythmic versus asphyxial cardiac arrest may be of significant importance for vasopressor efficiency. In a model of pediatric ventricular fibrillation, we found that a combination of vasopressin and epinephrine increased both myocardial and cerebral blood flow during CPR better than either vasopressin alone or epinephrine alone (unpublished observations). To assess whether the beneficial effects of this drug combination were due to the type of model used or the drug combination itself,
it was necessary to repeat the experiment in an adult porcine asphyxia preparation. Thus, the purpose of this study was to apply either vasopressin or epinephrine or both drugs combined during simulated adult asphyxial cardiac arrest and to assess their effect on coronary perfusion pressure and return of spontaneous circulation in a porcine model. Our hypothesis was that there would be no differences in study end points between groups.

Methods

Surgical Preparation and Measurements

This investigation was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance with American Physiological Society, institutional, and Utstein-style guidelines.10 Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care. Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted in our swine, which were of either sex and weighed 40 to 50 kg (~16 weeks old, indicating sexual maturity). Before surgery, pigs were premedicated with azaperone (4 mg/kg IM) and atropine (0.1 mg/kg IM); anesthesia was induced with ketamine (20 mg/kg IM), propofol (1 to 2 mg/kg IV), and piritramid (30 mg IV).11 followed by endotracheal intubation. Ventilation was performed with a volume-controlled ventilator (Draeger EV-A) with 21% O2 at 15 breaths per minute and with a tidal volume adjusted to maintain normocapnia. Anesthesia was maintained with propofol (6 to 8 mg·kg\(^{-1}\)·h\(^{-1}\)); muscle relaxation was provided by a continuous infusion of pancuronium (0.2 mg·kg\(^{-1}\)·h\(^{-1}\)). Ringer’s solution (6 mL·kg\(^{-1}\)·h\(^{-1}\)) and 3% gelatin solution (4 mL·kg\(^{-1}\)·h\(^{-1}\)) were infused during the preparation phase; body temperature was maintained between 38.0°C and 39.0°C. Depth of anesthesia was judged according to blood pressure, heart rate, and electroencephalography (Neurotrac, Engström). If cardiovascular variables or electroencephalography indicated a reduced depth of anesthesia, additional propofol and piritramid were given. Cardiac rhythm was monitored with a standard lead II ECG. One 7F saline-filled catheter was advanced into the right atrium for measurement of right atrial pressure and for drug administration; another catheter was advanced into the thoracic aorta for measurement of aortic blood pressure. A 7.5F pulmonary artery catheter was inserted into the pulmonary artery to measure pulmonary artery pressure, cardiac output, and core temperature. The intravascular catheters were attached to pressure transducers (model 1290A, Hewlett Packard) that were aligned at the level of the right atrium; all pressure tracings were recorded with a data acquisition system (Dewetron port 2000).

Experimental Protocol

After preparation, the animals were paralyzed with 8 mg/kg pancuronium to avoid gasping, 15 mg piritramid was given, and 5000 U heparin IV was administered to prevent intracardiac clot formation. Asphyxial cardiac arrest was then induced by clamping of the endotracheal tube, and cardiac arrest was determined by loss of aortic pulsations, defined as an aortic pulse pressure <2 mm Hg.12 After 8 minutes of untreated cardiac arrest, mechanical ventilation was resumed with 100% oxygen, and manual closed-chest CPR was initiated. Chest compressions were performed by the same investigator in all animals at a rate of 100 compressions/min guided by acoustic audiometers; this investigator was blinded to hemodynamic and end-tidal carbon dioxide monitor tracings throughout the experiment. After 4 minutes of basic life support CPR, 24 pigs were randomly assigned to receive either epinephrine (epinephrine group; 45, 200, or 200 μg/kg, n=6), vasopressin (vasopressin group; 0.4, 0.8, or 0.8 U/kg, n=6), epinephrine combined with vasopressin (high-dose vasopressin/epinephrine combination; μg/kg and U/kg; 45 and 0.4, 200 and 0.8, or 200 and 0.8, n=6), or epinephrine combined with vasopressin (optimal-dose vasopressin/epinephrine combination; μg/kg and U/kg; 45 and 0.4, 45 and 0.8, or 45 and 0.8, n=6). All drugs were diluted to 10 mL with normal saline and injected separately intravenously at 5-minute intervals followed by a 20-mL saline flush (all investigators were blinded to the drugs). Hemodynamic parameters measured were obtained before induction of cardiac arrest, after 90 seconds of CPR, and at 90 seconds and 5 minutes after each drug administration (Table).

Seventeen minutes after initiation of CPR, up to 3 countershocks were administered with an energy of 3, 4, and 6 J/kg, respectively. If asystole or pulseless electrical activity was present after defibrillation, the experiment was terminated. Return of spontaneous circulation was defined as an unassisted pulse with a systolic arterial pressure of ≥80 mm Hg for ≥5 minutes. When indicated, surviving animals received infusions of dopamine, phenylephrine, and lidocaine. In the postresuscitation period, hemodynamic parameters were measured after 5, 15, 30, and 60 minutes. After the experimental protocol was finished, the animals were euthanized with an overdose of potassium chloride and fentanyl; all pigs were then necropsied to check correct positioning of the catheters, damage to the rib cage, and internal organs.

Statistical Analysis

Baseline data were tested with the t test for continuous variables; 1-way ANOVA was used to determine statistical significance between the vasopressin and epinephrine as well as between the combination groups and was corrected for multiple comparisons by the Bonferroni method. Using Fisher’s exact test, we tested the null hypothesis that the number of surviving animals was independent of treatment; a 2-tailed value of P<0.05 was considered statistically significant.

Results

Before cardiac arrest and drug administration, there were no statistically significant differences in study end points between groups. The duration of asphyxia between clamping of the tube and cardiac arrest ranged in all groups between 7 and 8 minutes (P=NS between groups). During the subsequent 8 minutes of the nonintervention cardiac arrest interval, spontaneous ventricular fibrillation occurred in 9 of 24 animals, pulseless electrical activity in 9 of 24, and asystole in 6 of 24 (P=NS between groups). Coronary perfusion pressure was significantly (P<0.05) higher 90 seconds after each of 3 injections of high-dose and optimal-dose epinephrine/vasopressin combination versus vasopressin alone versus epinephrine alone (Figures 1 and 2). None of 6 vasopressin and only 1 of 6 epinephrine pigs had return of spontaneous circulation, whereas 6 of 6 high-dose epinephrine/vasopressin combination and 6 of 6 optimal-dose epinephrine/vasopressin combination swine could be successfully resuscitated and survived for 60 minutes, when the experiment was terminated (P<0.05 high-dose and optimal-dose epinephrine/vasopressin combination versus epinephrine alone and vasopressin alone). Necropsy confirmed appropriate catheter positions and revealed no injuries of the rib cage or intrathoracic organs in any animal.

Discussion

In this model of adult porcine asphyxia CPR, only high-dose and optimal-dose epinephrine/vasopressin combinations improved coronary perfusion pressure to levels of ~35 to 45 mm Hg, whereas either vasopressin alone or epinephrine alone improved coronary perfusion pressure only moderately, to ~15 to 20 mm Hg. Accordingly, none of 6 vasopressin and
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**Hemodynamic Variables Before Arrest and After Return of Spontaneous Circulation (Postresuscitation Phase)**

<table>
<thead>
<tr>
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<th>Before Arrest</th>
<th>Postresuscitation Phase, min</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
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<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td>102±5</td>
<td>252</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>101±4</td>
<td></td>
</tr>
<tr>
<td>High-dose combination</td>
<td>103±4</td>
<td>216±18</td>
</tr>
<tr>
<td>Optimal-dose combinaiton</td>
<td>101±3</td>
<td>200±13</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td>92±4</td>
<td>98</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>91±5</td>
<td></td>
</tr>
<tr>
<td>High-dose combination</td>
<td>93±3</td>
<td>165±7</td>
</tr>
<tr>
<td>Optimal-dose combinaiton</td>
<td>93±3</td>
<td>147±9</td>
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<tr>
<td>MPAP, mm Hg</td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td>21±2</td>
<td>30</td>
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<tr>
<td>Vasopressin</td>
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<tr>
<td>High-dose combination</td>
<td>22±1</td>
<td>37±3</td>
</tr>
<tr>
<td>Optimal-dose combinaiton</td>
<td>18±1</td>
<td>32±2</td>
</tr>
<tr>
<td>CI, mL · kg⁻¹ · min⁻¹</td>
<td></td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td>159±14</td>
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<tr>
<td>Vasopressin</td>
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<tr>
<td>High-dose combination</td>
<td>157±9</td>
<td>99±12</td>
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<tr>
<td>Optimal-dose combinaiton</td>
<td>167±4</td>
<td>91±10</td>
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<tr>
<td>SVR, dyne · s · cm⁻⁵</td>
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<td></td>
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<tr>
<td>Epinephrine</td>
<td>1242±197</td>
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<tr>
<td>Vasopressin</td>
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<tr>
<td>High-dose combination</td>
<td>1206±128</td>
<td>3180±242</td>
</tr>
<tr>
<td>Optimal-dose combinaiton</td>
<td>1303±109</td>
<td>3576±397</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. HR indicates heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; and SVR, systemic vascular resistance. Epinephrine was at 45, 200, and 200 μg/kg; vasopressin, 0.4, 0.8, and 0.8 U/kg; high-dose combination (μg/kg and U/kg), 45/0.4, 200/0.8, and 200/0.8; optimal-dose combination (μg/kg and U/kg), 45/0.4, 45/0.8, and 45/0.8.

*P<0.05 vs optimal-dose combination.

only 1 of 6 epinephrine pigs had return of spontaneous circulation, whereas 6 of 6 high-dose and 6 of 6 optimal-dose epinephrine/vasopressin combination swine could be successfully resuscitated and survived for 60 minutes (P<0.05).

Asphyxial cardiac arrest differs pathophysiologically from ventricular fibrillation, because the progression to complete ischemia is sudden in ventricular fibrillation and gradual in asphyxia. Furthermore, because global hypoxia and hypercarbia are fully developed during asphyxia even before resuscitation efforts are initiated, cellular energy stores are fundamentally depleted. Thus, the degree of ischemia after asphyxia is likely to be considerably greater than after ventricular fibrillation cardiac arrest. The observation that ischemic brain injury after asphyxial cardiac arrest and subsequent resuscitation appears more severe and more widespread than after ventricular fibrillation of the same duration supports this assumption. Therefore, cardiac arrest due to asphyxiation must be considered and treated in a fundamentally different manner from that after cardiac arrhythmia. Accordingly, immediate restoration of ventilation with supplemented oxygen is the most important therapy in asphyxial cardiac arrest; if restoration of oxygenation and chest compressions fail to restart the arrested heart, epinephrine is recommended.

We used a validated model for asphyxiation by clamping the endotracheal tube in the presence of room-air ventilation with full muscle paralysis, which reliably prevents any form of gasping that would be a severe confounding variable in an asphyxia model. Also, pilot studies showed that after asphyxial cardiac arrest, a period of 8 minutes without intervention is absolutely necessary to avoid successful resuscitation with ventilation and chest compressions alone, which would prevent our studying the effects of vasopressor drugs. The 45- and 200-μg/kg epinephrine doses have been shown to induce an optimal and maximum hemodynamic effect in pigs; furthermore, the 0.4- and 0.8-U/kg vasopressin dosages are considered to be optimal and high doses, respectively, reflecting a clinically realistic setting of asphyxial cardiac arrest to study advanced cardiac life support drugs.
The observation that vasopressin alone was unable to improve coronary perfusion pressure is surprising and in strong contrast to earlier results.\textsuperscript{3–8} In fact, this may be the first laboratory cardiac arrest setting in which CPR efforts with epinephrine alone, as well as with vasopressin alone, were unsuccessful. Also, this observation is in strong contrast to previous investigations reporting a good vasopressor response to epinephrine during asphyxial cardiac arrest. On critical review of earlier asphyxia CPR studies, it is likely that our model represented a significantly greater degree of hypoxia (prearrest ventilation with 21% versus 100% oxygen)\textsuperscript{19} and longer total low/no flow duration (19 versus 7 versus 5 versus 2 minutes, respectively).\textsuperscript{20–24} Thus, it is possible that the degree of ischemia in our model simply determined whether or not vasopressin or epinephrine alone was effective. This is only partially in agreement with in vitro measurements,\textsuperscript{25} however, when only vasopressin, but not epinephrine, resulted in a vasopressor response during severe acidosis. The most likely explanation may be that the interactions between vasopressin and epinephrine depend on the presence of each other more than previously thought. For example, during CPR with vasopressin in pigs, substantial endogenous epinephrine levels of \(\approx 100,000 \text{ pg/mL}\) were present,\textsuperscript{26} and vasopressin improved coronary perfusion pressure easily from \(\approx 15\) to \(\approx 50 \text{ mm Hg}\). Although we did not measure endogenous epinephrine plasma levels in the present experiment, it is obvious that after clamping of the endotracheal tube, high amounts of endogenous epinephrine were immediately discharged in an effort to maintain cardiocirculatory homeostasis until cardiac arrest finally occurred \(\approx 8\) minutes after induction of asphyxia. Thus, it is possible that endogenous epinephrine plasma levels were depleted 19 minutes after clamping of the tube, when vasopressin alone was injected, with no vasopressor response thereafter. This indicates that vasopressin effects are most effective in the presence of high endogenous or exogenously induced epinephrine plasma levels.

It is surprising that identical combinations of vasopressin and epinephrine were definitely superior to vasopressin alone or epinephrine alone in this asphyxia model, but not in a model with postcountershock pulseless electrical activity.\textsuperscript{27} Interestingly, the duration of no/low flow in both models before drug administration was almost identical (19 versus 18 minutes), indicating that the underlying pathophysiology of cardiac arrest may have a more important effect on vasopressor drugs than previously thought. In fact, if these results can be extrapolated to humans, it may even be advisable to combine vasopressors such as vasopressin and epinephrine once it is determined that initial CPR management does not result in return of spontaneous circulation. This concept would be entirely new but is in full agreement with previous lifesaving observations in 8 in-hospital CPR patients who did not respond to advanced cardiac life support with \(\approx 2\) to 15 mg epinephrine during prolonged (\(\approx\) 15 to 25 minutes) resuscitation efforts but had return of spontaneous circulation after subsequent injection of 40 U vasopressin.\textsuperscript{28} Similarly, 4 of 10 patients undergoing prolonged CPR efforts (\(\approx 40\) minutes) with \(\approx 18\) mg epinephrine had return of spontaneous circulation after subsequent injection of 1 U/kg vasopressin.\textsuperscript{29} These clinical experiences are in full agreement with our laboratory study and may be of fundamental importance in improving pharmacological CPR management. In a similar manner, results of an in-hospital CPR study that used a single vasopressin dosage followed by epinephrine\textsuperscript{30} are in full agreement with our laboratory experience. In that clinical study and in our laboratory, both vasopressin and epinephrine were almost equally potent when the cardiac arrest duration was very short and therefore the degree of ischemia only moderate.\textsuperscript{30} As such, it is possible that a combination of epinephrine and vasopressin is especially effective when CPR is prolonged and/or global ischemia is marked. Our asphyxial cardiac arrest model would be simply a tool to determine a different response of the organism when advanced cardiac life support drugs are given either late during CPR or during severe ischemia.
Some limitations of this study should be noted, including different vasopressin receptors in pigs (lysine vasopressin) and humans (arginine vasopressin), which may result in a different hemodynamic response to exogenously administered arginine vasopressin. The circulatory effects of arginine vasopressin as administered in the present investigation, however, may be even greater in humans than in pigs. Also, use of potent anesthetics may have impaired cardiovascular function and autonomic control in our pigs. Moreover, we purposely omitted defibrillation attempts on starting CPR and immediately after vasopressor administration to determine the hemodynamic effects of the study drugs during the resuscitation attempt. Finally, we are unable to determine whether this result of a porcine study can be extrapolated to CPR in humans.

In conclusion, the combination of epinephrine with vasopressin, but not epinephrine or vasopressin alone, maintained elevated coronary perfusion pressure during prolonged CPR and resulted in significantly higher survival rates in this model of an adult porcine asphyxia model.

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