Endobronchial Vasopressin Improves Survival during Cardiopulmonary Resuscitation in Pigs

Volker Wenzel, M.D.,* Karl H. Lindner, M.D.,† Andreas W. Prengel, M.D.,‡ Keith G. Lurie, M.D.,§ Hans U. Strohmenger, M.D.,†

Background: Intravenous administration of vasopressin during cardiopulmonary resuscitation (CPR) has been shown to be more effective than optimal doses of epinephrine. This study evaluated the effect of endobronchial vasopressin during CPR.

Methods: After 4 min of untreated ventricular fibrillation and 3 min of CPR, 21 pigs were randomized to be treated with 0.8 U/kg intravenous vasopressin (n = 7), 0.8 U/kg endobronchial vasopressin (n = 9), or an endobronchial placebo of normal saline (n = 5). Defibrillation was performed 5 min after drug administration to attempt return of spontaneous circulation.

Results: All animals in the intravenous and endobronchial vasopressin group were resuscitated successfully, but only two of five animals in the placebo group were. At 2 and 5 min after drug administration, coronary perfusion pressure in the intravenous and endobronchial vasopressin group was significantly higher than in the placebo group (50 ± 10, 34 ± 5 vs. 16 ± 6 mmHg, respectively; and 35 ± 10, 39 ± 10 vs. 19 ± 5 mmHg, respectively; P < 0.05).

Conclusions: Endobronchial vasopressin is absorbed during CPR, coronary perfusion pressure is increased significantly within a short period, and the chance of successful resuscitation is increased in this porcine model of CPR. Endobronchial vasopressin may be an alternative for vasopressor administration during CPR, when intravenous access is delayed or not available. (Key words: Animal model: pig. Heart: cardiopulmonary resuscitation, coronary perfusion pressure. Lung: endotracheal drug administration. Survival: return of spontaneous circulation. Vasopressor: vasopressin.)

ANNUALLY, about 100,000 persons experience fatal cardiac arrest in the United States, with a survival chance of approximately 2–25%, depending on, for example, the location of the person during cardiac arrest, past medical history, and the emergency medical system.1,2 To improve the disappointing outcome for most persons having cardiac arrest, several fundamental endocrinologic responses of the human body to cardiac arrest and cardiopulmonary resuscitation (CPR) have been investigated.3–5 Interestingly, circulating endogenous vasopressin concentrations were high in persons undergoing CPR, and levels in those who were successfully resuscitated were significantly higher than in persons who died.6

These investigations suggested that vasopressin might be an important factor in enhancing the pressure response to endogenously released epinephrine, norepinephrine, and angiotensin II. A subsequent animal model of ventricular fibrillation showed improved vital organ blood flow in animals that were resuscitated with intravenous vasopressin compared with epinephrine.7 In patients with refractory cardiac arrest, intravenous vasopressin induced an increase in blood pressure and, in some cases, return of spontaneous circulation, when standard therapy with chest compression, ventilation, defibrillation, and epinephrine had failed.8

Endobronchial administration of epinephrine is a back-up strategy during CPR, when attempts to gain intravenous access are unsuccessful or delayed.9 Achieving the hemodynamic benefit of vasopressin after endobronchial administration during CPR might be a strategic option. The purpose of the present study, therefore, was to evaluate the effect of endobronchial vasopressin...
during CPR on hemodynamic variables, blood gases, and return of spontaneous circulation.

Materials and Methods

Surgical Preparation and Measurements

This project was approved by the animal investigational committee at our institution, and the animals were managed in accordance with guidelines from the American Physiological Society. This study was performed on 21 healthy, 12- to 14-week-old domestic pigs weighing 24 - 30 kg. Before surgery, animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (a neuroleptic agent; 4 mg/kg given intramuscularly) and atropine (0.1 mg/kg given intramuscularly) 1 h before surgery. Anesthesia was induced with 15 mg/kg pentobarbital injected into an ear vein. The pigs were fixed in the dorsal recumbent position and their tracheas were intubated. They were ventilated with a volume-controlled ventilator (Servo 900; Siemens, Erlangen, Germany) with 65% nitrous oxide in oxygen at 20 breaths per minute and with a tidal volume adjusted to maintain partial pressure of carbon dioxide at 35 mmHg.

Anesthesia was maintained with a continuous infusion of pentobarbital (0.4 mg·kg⁻¹·h⁻¹) and a single dose of buprenorphine (0.015 mg/kg). Muscle paralysis was achieved by injecting 10 mg alcuronium after intubation and subsequently with pancuronium as needed. Ringer's solution (6 ml·kg⁻¹·h⁻¹) was administered continuously throughout the preparation and study period with an infusion pump (Infusomat; Braun, Melsungen, Germany). A standard lead II electrocardiograph was used to monitor cardiac rhythm.

Multiple catheters were used for hemodynamic monitoring. A 7-French catheter was advanced by femoral catheterization into the descending aorta to withdraw arterial blood samples. A 5-French pulmonary artery catheter (Swan Ganz; Baxter Edwards Laboratories, Deerfield, IL) was placed under pressure control via the external jugular vein into the pulmonary artery to measure cardiac output. Aortic pressures were measured with a micromanometer-tipped catheter (Millar, Houston, TX), and right atrial pressure was measured with a saline-filled catheter. All fluid-filled catheters were calibrated with pressure transducers (model 1290A; Hewlett Packard, Böblingen, Germany) that were calibrated to atmospheric pressure at the level of the right atrium. The fluid-filled catheters were flushed with normal saline containing 5 U/ml heparin at a rate of 3 ml/h (Intraflo II; Abbott Laboratories, North Chicago, IL) to prevent obstruction during the preparation phase. After completion of surgery and before induction of cardiac arrest, 5,000 U sodium heparin was administered intravenously to prevent intracardiac clot formation. Body temperature was recorded with a thermistor probe placed in the rectum and maintained with a heating blanket between 37.5°C and 38.5°C.

Coronary perfusion pressure during diastole was defined as the arteriovenous pressure difference (time-coincident difference between mean diastolic aortic and mean diastolic right atrial pressure) and was measured with an electronic subtraction unit. Measurements were recorded before cardiac arrest and during the period of closed-chest CPR with a monitor and a data acquisition/control unit (Analog Data Acquisition System; IFD, Mülheim/Ruhr, Germany). On-line measurements were performed at 30-s intervals before induction of cardiac arrest and after return of spontaneous circulation and at 1-s intervals during CPR. Arterial blood gases were measured with a blood gas analyzer (model ABL 520; Radiometer, Copenhagen, Denmark).

The blood concentration of arginine vasopressin was measured in duplicate by a radioimmunoassay double-antibody procedure without previous extraction of the sample, using a modification of the method described by Glick and Kagan. The cross-reactions of the arginine vasopressin antiserum determined at 50% binding are 100% for arginine vasopressin, 0.25% for lysine arginine vasopressin, 0.001% for oxytocin, and 0.001% for vasotocin. Intra- and interassay coefficients of variation were less than 7%. The method is sensitive to less than 0.8 ng/g. The normal range of plasma arginine vasopressin concentration in humans is 1 - 3 ng/g. Because this analysis technique cannot reliably measure endogenous porcine lysine vasopressin, vasopressin levels before arrest and before drug administration during CPR in all groups and throughout the experiment in the placebo group were not measured. Therefore, measured porcine vasopressin levels reflect only exogenously administered arginine vasopressin and not endogenously released porcine lysine vasopressin.

Experimental Protocol

Fifteen minutes before cardiac arrest, the inspired fraction of oxygen (FiO₂) was increased to 1.0, and 0.3 mg buprenorphine was given. Before induction of cardiopulmonary arrest, hemodynamic parameters and arterial blood gases were measured. After baseline mea-
sirements, a 50-Hz, 60-V AC current was administered via two subcutaneous needle electrodes that were applied bilaterally on the thorax in the mid-axillary line equivalent to induce ventricular fibrillation. Cardiopulmonary arrest was defined as the point at which the aortic pulse pressure decreased to zero and the electrocardiogram showed ventricular fibrillation; ventilation was stopped at that point. After 4 min of untreated cardiac arrest, closed-chest CPR was performed manually, and mechanical ventilation was resumed with ventilation parameters identical to those before cardiac arrest. The chest compression rate was 80 per minute and was always performed by the same investigator guided by 80 acoustical audiotones per minute to ensure equivalent chest compression rates in all animals. Pacing the rescuer applying chest compressions with acoustical audiotones was shown in a clinical study to correlate with consistent chest compressions, as recommended by the American Heart Association. In addition, the investigator applying chest compressions was blinded to the blood pressure and end-expiratory CO₂ monitor during CPR. The thorax was allowed to relax passively.

After 3 min of CPR, animals were randomly assigned to one of three groups. Group 1 received 0.8 U/kg commercially available vasopressin (Pitressin; Parke-Davis, Berlin, Germany) diluted with 10 ml normal saline into the right atrium and 10 ml normal saline into the endotracheal tube. Group 2 received 0.8 U/kg vasopressin diluted with 10 ml normal saline into the endotracheal tube and 10 ml normal saline into the right atrium. Group 3 received 10 ml normal saline (placebo) into the endotracheal tube and 10 ml normal saline (placebo) into the right atrium (investigators were blinded to the drugs). Endotracheal drug administration was achieved by injecting the 10-ml syringe containing either drug or placebo into the proximal aperture of the endotracheal tube, followed by five hyperinflations with a self-inflatable bag. No other drugs were administered during CPR.

Arterial blood was sampled before induction of cardiac arrest (prearrest), and then after 2, 4, 5, and 8 min of CPR and 5, 15, and 30 min after return of spontaneous circulation. Vasopressin plasma concentration were measured in the intravenous vasopressin and endobronchial vasopressin groups 90 s and 5 min after drug administration during CPR and 15 and 30 min after return of spontaneous circulation.

After 8 min of CPR, we tried to restore spontaneous circulation. Three countershocks were administered in rapid succession with an energy of 3, 4, and 6 J/kg. If ventricular fibrillation, ventricular tachycardia, asystole, or pulseless electrical activity persisted, CPR was reinitiated for an additional 90 s with up to three subsequent defibrillation attempts with 3, 4, and 6 J/kg. Successful resuscitation was defined as the presence of coordinated electrical activity, systolic blood pressure greater than 90 mmHg, and diastolic blood pressure greater than 40 mmHg for at least 5 min, during which no other resuscitative measures were applied. All animals were examined in autopsies after the experiment to check correct positioning of the catheters and to look for damage to the rib cage and internal organs.

**Statistical Analysis**

Values are expressed as mean ± SD. One-way analysis of variance was used to determine statistical significance among the three groups, followed by the Student-Newman-Keuls post hoc test. The chi-square test was used to determine statistical significance of the survival rates. Because time intervals between the first defibrillation and return of spontaneous circulation were distributed unevenly, they are expressed as medians, minimum, and maximum. For these variables, the Kruskal-Wallis test was used to determine differences among the groups. Probability values less than 0.05 were considered significant.

**Results**

After induction of ventricular fibrillation and performance of CPR, seven of seven animals in the intravenous vasopressin group, nine of nine animals in the endobronchial vasopressin group, and two of five animals in the placebo group were successfully resuscitated and survived the 30-min observation period. One animal treated with endobronchial vasopressin required another 30 s of chest compressions before defibrillation was successful. Two animals in the placebo group were defibrillated into pulseless electrical activity, and another animal in that group had severe hypotension of 50 mmHg aortic systolic pressure and therefore did not meet the definition of return of spontaneous circulation. Survival rates were significantly higher in the animals treated with intravenous or endobronchial vasopressin compared with the animals given the placebo (P = 0.05).

After removal of the last blood sample during CPR, which was followed immediately by defibrillation (i.e.,
after a total of 12 min of cardiac arrest, including 8 min of CPR), spontaneous circulation was restored within 19 s (range, 5 - 120 s) in the intravenous vasopressin group, 5 s (range, 3 - 75 s) in the endobronchial vasopressin group, and 78 s (range, 75 - 80 s) in the placebo group (P < 0.05 vs. endobronchial vasopressin). Autopsy revealed no damage to the thoracic cage or the internal organs in any of the groups.

There were no differences in hemodynamic variables before induction of ventricular fibrillation and in heart rate, mean pulmonary artery, mean right atrial, and pulmonary capillary wedge pressures after return of spontaneous circulation between groups (table 1). Significant differences between groups during the experiment were observed in coronary perfusion pressure (fig. 1), mean arterial pressure, cardiac index, and systemic vascular resistance (table 1).

Arterial blood gas analyses before cardiac arrest, during CPR, and in the postresuscitation period were not different except for lower, but not hypoxic, oxygen tension values in the animals receiving vasopressin compared with those receiving placebo at 5- and 30-min return of spontaneous circulation. Vasopressin plasma levels in the intravenous vasopressin group increased rapidly within 90 s after drug administration (P < 0.05 vs. endobronchial vasopressin); animals receiving intravenous vasopressin and those receiving endobronchial vasopressin had comparable vasopressin levels 5 min after drug administration during CPR. In the postresuscitation phase, vasopressin plasma levels in the intravenous vasopressin group decreased faster and were significantly lower than in the endobronchial vasopressin group (table 1; P < 0.05).

**Discussion**

Significantly higher levels of circulating vasopressin concentrations in patients successfully resuscitated after cardiac arrest compared with levels in patients who died suggested the possibility that exogenous vasopressin administration during CPR may be beneficial. Subsequent investigations of the nonadrenergic vasopressor vasopressin during CPR in persons and animals showed a clear benefit of vasopressin compared with epinephrine, but in all cases, vasopressin was administered either intravenously or into the right atrium. This study was designed to compare the effect of endobronchial vasopressin and placebo with intravenous vasopressin on hemodynamic variables, blood gases, and return of spontaneous circulation.

Coronary perfusion pressure is one of the best hemodynamic predictors of return of spontaneous circulation in animals and humans. We showed that within 1 min of endobronchial vasopressin during CPR, coronary perfusion pressure increased rapidly and almost doubled within 2 min, which was significantly higher than in the animals receiving placebo. A coronary perfusion pressure of 20-30 mmHg seems to be necessary for return of spontaneous circulation. One or 2 min after endobronchial administration of vasopressin, this threshold was achieved. We deliberately continued CPR for 5 min after drug administration to study the hemodynamic effects. All animals treated with either intravenous or endobronchial vasopressin were resuscitated, but only two of five animals in the placebo group (P < 0.05) were.

Administration of endobronchial drugs during CPR may be a simple and rapid alternative, when intubation is performed before intravenous cannulation, when the time interval for intravenous access is prolonged, or when attempts at intravenous access are simply unsuccessful. Thus, endobronchial drug delivery may have an advantage whenever intubation is performed before intravenous access is achieved.

Endobronchial vasopressin had a plateau effect on coronary perfusion pressure that seemed to last longer than intravenous vasopressin. The same dose of intravenous and endobronchial vasopressin resulted in the same coronary perfusion pressure 4 min after drug administration. In contrast, the equipotent endobronchial epinephrine dosage is approximately ten times greater than the intravenous epinephrine dosage during CPR.

The effect of endobronchial drugs depends on various mechanisms that may alter its effects, such as conversion or degradation by lung tissue, drug structure and permeability, ventilation-to-perfusion ratio of the lung, drug dilution with saline or water, volume of the dilution carrier, and depth of drug administration into the bronchial tree. We chose to administer vasopressin (diluted with 10 ml normal saline, equivalent to 0.4 ml/kg) into the proximal aperture of the endotracheal tube because it has been shown that subsequent hyperinflations distributed a drug as good as an injection during bronchoscopic control into the trachea and right main bronchus. Previous studies suggested that the administration of endobronchial drugs in humans with spontaneous circulation had a minor negative effect on gas exchange; however, this was not confirmed during CPR in animals. During CPR, there was no difference in arterial blood gases among the groups in this study.
Table 1. Hemodynamic Variables and Vasopressin Plasma Levels at Prearrest, during CPR, and after Return of Spontaneous Circulation (Postresuscitation Phase)

<table>
<thead>
<tr>
<th></th>
<th>Prearrest</th>
<th>Cardiopulmonary Resuscitation (min)</th>
<th>Postresuscitation Phase (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before DA</td>
<td>1.5 min after DA</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>104 ± 4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>112 ± 19</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>100 ± 26</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>104 ± 3</td>
<td>42 ± 8</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>103 ± 17</td>
<td>44 ± 7</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>99 ± 6</td>
<td>40 ± 10</td>
<td>37 ± 7,†</td>
</tr>
<tr>
<td>CI (l/min·kg⁻¹·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>135 ± 4</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>141 ± 27</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>133 ± 34</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>0 ± 1</td>
<td>12 ± 6</td>
<td>14 ± 7</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>1 ± 1</td>
<td>12 ± 5</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>1 ± 1</td>
<td>13 ± 6</td>
<td>17 ± 10</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>5 ± 1</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>5 ± 3</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>4 ± 1</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻⁵)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>2,326 ± 78</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>2,209 ± 463</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Placebo EB</td>
<td>2,446 ± 745</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Vasopressin plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin IV</td>
<td>—</td>
<td>9,919 ± 3,402*</td>
<td>5,471 ± 1,193</td>
</tr>
<tr>
<td>Vasopressin EB</td>
<td>—</td>
<td>2,258 ± 527</td>
<td>6,286 ± 742</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Analysis in the postresuscitation phase: IV vasopressin, n = 7; EB vasopressin, n = 9; EB placebo, n = 2.

Prearrest = measurements before induction of cardiac arrest; IV = intravenous; EB = endobronchial; before DA = before drug administration; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CI cardiac index; RAP = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

*P < 0.05 versus EB vasopressin.
†P < 0.05 versus IV vasopressin.

However, after return of spontaneous circulation, the animals treated with vasopressin had a lower, but not hypoxic, oxygen tension compared with the two surviving animals from the placebo group. Although we did not measure a first-pass metabolism of vasopressin in the lung, it appears that no such mechanism was present in this investigation.

Vasopressin therapy during CPR appears to work by acutely increasing systemic vascular resistance via the V₁ receptor or by potentiating the vasoconstrictor effects of endogenous catecholamines. Therefore, administration of vasopressin may cause adverse effects, such as a prolonged significantly elevated systemic vascular resistance, which in turn may contribute to heart insufficiency or subsequently even to heart failure after the resuscitation period. The animals treated with intravenous or endobronchial vasopressin had a higher systemic vascular resistance at 5 min after return of spontaneous circulation than did the animals in the placebo group; 15 min after return of spontaneous circulation,
the endobronchial vasopressin group had significantly greater systemic vascular resistance compared with the intravenous vasopressin group and a higher systemic vascular resistance than did the placebo group. This may have contributed to a lower cardiac index in the intravenous and endobronchial vasopressin group compared with the placebo group at these time points after return of spontaneous circulation.

The systemic vascular resistance observed in the endobronchial vasopressin group may confirm that vasopressin administered through the endotracheal tube during CPR may lead to a plateau effect with a prolonged length of action, as observed in investigations with endobronchial epinephrine.23,24 This profile of drug action may be reflected by corresponding vasopressin plasma levels. Both groups treated with vasopressin reached comparable drug levels during CPR immediately before defibrillation, but intravenous vasopressin reached its peak level shortly after injection, whereas endotracheal vasopressin led to a slower increase and resulted in an elevated vasopressin plasma level after resuscitation. It is important to note that mean pulmonary artery pressures in all groups were normal throughout the experiment, suggesting that pulmonary hypertension was not present in either group.

Our study is limited in several ways. In the pig, 8-lysine vasopressin (Lypressin) is secreted by the posterior pituitary gland. The hemodynamic response to arginine vasopressin in the pig may differ from that in humans, in whom arginine vasopressin is the endogenous form. Long-term survival and local tissue damage in the endobronchial tree was not determined in this study. We also used young, healthy pigs that were free from atherosclerotic disease. In addition, this study lacks dose-response data; therefore, we cannot report the minimally effective dose. Long-term outcome studies evaluating the effect of both intravenous and endobronchial vasopressin during CPR may be warranted to study this vasopressor further.

In conclusion, these experiments support the hypothesis that endobronchial vasopressin is absorbed rapidly during CPR, almost doubling coronary perfusion pressure within 2 min after drug administration and thus ensuring successful resuscitation. Endobronchial vasopressin may be a simple and rapid alternative for vasoressor administration during CPR when intravenous access is delayed or not available.

The authors thank Ursula S. Rose for ideas, support, and encouragement.

References


12. Emergency Cardiac Care Committee and Subcommittees, American Heart Association: Guidelines for cardiopulmonary resuscitation and emergency cardiac care, III: Adult advanced life support. JAMA 1992; 268:2199-241


