Vasopressin Combined With Epinephrine Decreases Cerebral Perfusion Compared With Vasopressin Alone During Cardiopulmonary Resuscitation in Pigs

Volker Wenzel, MD; Karl H. Lindner, MD; Sven Augenstein; Andreas W. Prengel, MD; Hans U. Strohmenger, MD

Background and Purpose—It is unknown whether a combination of vasopressin and epinephrine may be superior to vasopressin alone by targeting both nonadrenergic and adrenergic receptors.

Methods—After 15 minutes of cardiac arrest (13 minutes of ventricular fibrillation and 2 minutes of pulseless electrical activity) and 3 minutes of chest compressions, 16 animals were randomly treated with either 0.8 U/kg vasopressin (n=8) or 0.8 U/kg vasopressin combined with 200 μg/kg epinephrine (n=8).

Results—Comparison of vasopressin with vasopressin and epinephrine at 90 seconds and 5 minutes after drug administration resulted in comparable mean (±SEM) coronary perfusion pressure (54±3 versus 57±5 and 36±4 versus 35±4 mm Hg, respectively), cerebral perfusion pressure (59±6 versus 65±8 and 40±6 versus 39±6 mm Hg, respectively), and median (25th to 75th percentiles) left ventricular myocardial blood flow [116 (81 to 143) versus 108 (97 to 125) and 44 (35 to 81) versus 62 (42 to 74) mL·min⁻¹·100 g⁻¹, respectively], but significantly increased (P<0.05) total cerebral blood flow [81 (77 to 95) versus 39 (34 to 58) and 50 (43 to 52) versus 28 (16 to 35) mL·min⁻¹·100 g⁻¹, respectively]. Return of spontaneous circulation rates in both groups were comparable (vasopressin, 7 of 8; vasopressin and epinephrine, 6 of 8).

Conclusions—Comparison of vasopressin with vasopressin and epinephrine resulted in comparable left ventricular myocardial blood flow but significantly increased cerebral perfusion. (Stroke. 1998;29:1462-1468.)

Key Words: cardiopulmonary resuscitation ■ cerebral blood flow ■ epinephrine ■ heart arrest ■ vasopressin ■ pigs

Laboratory investigations demonstrated that vasopressin increased vital organ blood flow¹ and cerebral oxygen delivery² in comparison with epinephrine, indicating that vasopressin may be a promising alternative vasopressor during cardiopulmonary resuscitation (CPR). In clinical studies, when standard advanced cardiac life support had failed, vasopressin administration resulted in an increased coronary perfusion pressure³ and even in return of spontaneous circulation in some patients.⁴ Although vasopressin administration seemed to be the underlying mechanism for successful defibrillation in the short-term survivors, all patients received large epinephrine dosages until shortly before being enrolled in the vasopressin investigations. Thus, we were unable to determine what impact increased epinephrine plasma levels had on the effects of vasopressin administered during CPR.

In a small (n=40) trial of vasopressin versus epinephrine as first-line therapy in out-of-hospital patients with cardiac arrest, patients treated with vasopressin had significantly higher 24-hour survival rates but hospital discharge rate was comparable.⁵ It is unknown whether simultaneous coad-
study was performed according to Utstein-style guidelines on 16 healthy, 12- to 16-week-old swine (crossbred between Belgian and German domestic pigs) of either gender, weighing 30 to 40 kg. The animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (4 mg/kg IM) and atropine (0.1 mg/kg IM) 1 hour before surgery, and anesthesia was induced with pentobarbital (15 mg/kg IV). After intubation during spontaneous respiration, the pigs were ventilated with a volume-controlled ventilator (Servo 900, Siemens), with 65% N2O in O2 at 20 breaths per minute and a tidal volume adjusted to maintain normocapnia. Anesthesia was maintained with pentobarbital (0.4 mg · kg⁻¹ · min⁻¹) and a single dose of buprenorphine (0.015 mg/kg). Muscle paralysis was achieved with 10 mg alcuronium after intubation and subsequently with pancuronium as needed. Ringer's solution (6 mL · kg⁻¹ · h⁻¹) and a 3% gelatin solution (4 mL · kg⁻¹ · h⁻¹) were administered continuously throughout the preparation and study period. A standard lead II ECG was used to monitor cardiac rhythm; depth of anesthesia was judged according to blood pressure, heart rate, and ECG (Neurotrac, Engström). If physiological signs or ECG indicated a lessening of anesthesia, the pentobarbital dose was increased and additional buprenorphine was given. In our experience, the pigs do not respond to painful or auditory stimuli under this anesthetic regimen when the paralyzing agent is withheld and the loading dose of pentobarbital subsides. Body temperature was maintained with a heating blanket between 37.5°C and 38.5°C. A 7F catheter was advanced into the descending aorta for withdrawal of arterial blood samples and measurement of arterial blood pressure, and a 7F pigtail catheter was placed into the left ventricle to inject radiouclide microspheres. Reference blood samples for measurement of organ blood flow were withdrawn from a 5F catheter placed in the descending aorta. A 5F pulmonary artery was placed in the pulmonary artery to measure cardiac output and sample mixed venous blood; another 5F catheter was placed in the right atrium to measure right atrial pressure and for drug administration. Before trepanation, 5 mL local anesthetic (bupivacaine 0.5%, Curasan) was infiltrated into the skull overlying the skull to provide additional anesthesia. For sampling of cerebral venous blood and measurement of intracranial pressure, a burr hole was drilled into the skull over the midline and a catheter was placed into the sagittal sinus. All catheters were flushed with normal saline containing 5 U/mL heparin at a rate of 3 mL/h to prevent obstruction during the preparation phase. Aortic, right atrial, pulmonary, and intracranial pressures were measured with normal saline-filled catheters with pressure transducers (model 1290A, Hewlett Packard) calibrated to atmospheric pressure at the level of the right atrium; pressure tracings were recorded with a data acquisition system (Dewetron Port 2000). Coronary perfusion pressure was defined as the difference between aortic and right atrial diastolic pressure. Blood gases were measured with a blood gas analyzer (Nova Biomedical Stat Profile Ultra) and end-tidal carbon dioxide with an infrared absorption analyzer (Capnomac Ultima, Datex). After 90 seconds of CPR as well as 90 seconds and 5 minutes after drug administration, blood flow was measured with radioactively labeled microspheres according to the technique described by Heymann et al and as previously described in validation studies of the microsphere technique.

**Experimental Protocol**

Fifteen minutes before cardiac arrest, 5000 U heparin IV was administered to prevent intracardiac clot formation, the FiO2, was increased to 1.0, a single dose of 0.3 mg buprenorphine and 8 mg pancuronium was given, and hemodynamic parameters as well as blood gases were measured. A 50-Hz, 60-V alternating current was then applied via 2 subcutaneous needle electrodes to induce ventricular fibrillation. Cardiopulmonary arrest was defined as the point at which the aortic pulse pressure decreased to zero and the ECG showed ventricular fibrillation; ventilation was stopped at that point. After 13 minutes of untreated ventricular fibrillation, countershocks were administered with a defibrillator (Lilipak 6, Physio Control) in rapid succession with an energy of 1, 2, and 3 J/kg, respectively, to convert ventricular fibrillation into pulseless electrical activity. Pulseless electrical activity was defined as the presence of organized ECG complexes with an aortic pulse pressure of <2 mm Hg. After an additional 2 minutes of pulseless electrical activity (total cardiac arrest time, 15 minutes), closed-chest CPR was performed manually, and mechanical ventilation was resumed with identical ventilation parameters as before cardiac arrest. Chest compression (at a rate of 80 compressions per minute) was always performed by the same investigator, guided by acoustical audio tones, who was blinded to hemodynamic and end-tidal carbon dioxide tracings. After 3 minutes of CPR, animals were randomly assigned to receive either 0.8 U/kg vasopressin (Pitressin, Parke-Davis) or 0.8 U/kg vasopressin combined with 200 μg/kg epinephrine diluted to 10 mL normal saline into the right atrium, which was followed by 20 mL saline flush (investigators were blinded to the drugs). Blood was sampled before induction of cardiac arrest, after 90 seconds of CPR, and 90 seconds and 5 minutes after drug administration. After 23.5 minutes of cardiac arrest, including 8.5 minutes of CPR, up to 3 countershocks were administered with an energy of 3, 4, and 6 J/kg, respectively, when ventricular fibrillation occurred; if asystole or pulseless electrical activity was present, the experiment was terminated. Return of spontaneous circulation was defined, as described in a CPR investigation with a cardiac arrest interval identical to that in the present report, as an unassisted pulse with a systolic arterial pressure of ≥50 mm Hg and pulse pressure of ≥20 mm Hg lasting for at least 1 minute. After finishing the experimental protocol, the animals were euthanized and autopsied to check correct positioning of the catheters and damage to the rib cage and internal organs and to harvest the internal organs.

**Statistical Analysis**

One-way analysis of variance was used to determine statistical significance of hemodynamic variables and blood gases between the 2 groups; values are expressed as mean±SEM. The Mann-Whitney U test was used to determine differences of vital organ blood flow between the 2 groups; results are given as median (25th to 75th percentiles). Fisher’s exact test was used to test statistical significance of return of spontaneous circulation rates. Statistical significance was considered at P<0.05.

**Results**

Before induction of ventricular fibrillation and before drug administration during CPR, there were no differences between groups (Table 1). After 13 minutes of untreated ventricular fibrillation, pulseless electrical activity was achieved with 2.4±0.6 shocks in the vasopressin and 3.0±0.5 shocks in the vasopressin and epinephrine group. Heart rate during pulseless electrical activity was 56±8/min in the vasopressin and 68±3/min in the combination animals. At both 90 seconds and 5 minutes after drug administration, mean arterial pressure, coronary perfusion pressure, and cerebral perfusion pressure were comparable in the vasopressin group when compared with the combination pigs (Table 1). Arterial, mixed venous, and sagittal sinus pH were comparable between groups throughout the experiment. At both 90 seconds and 5 minutes after drug administration, sagittal sinus Pco₂ was significantly higher in the vasopressin and epinephrine animals when compared with the vasopressin group (P<0.05; Table 1). Arterial, mixed venous, and sagittal sinus Pco₂ were comparable between groups during the entire experiment.

Ninety seconds and 5 minutes after drug administration, myocardial blood flow was comparable between groups (Table 2). At the same points in time, cerebral blood flow was
significantly higher in animals treated with vasopressin compared with vasopressin and epinephrine–treated pigs \( (P<0.05; \text{Table 3}) \). After removal of the final blood sample during CPR (ie, after a total of 23.5 minutes of arrest, including 8.5 minutes of CPR), ventricular fibrillation was present in all animals; defibrillation resulted in spontaneous circulation in 7 of 8 animals in the vasopressin group and in 6 of 8 animals in the combination group.

### TABLE 2. Regional Left Ventricular Blood Flow During CPR

<table>
<thead>
<tr>
<th>Variable</th>
<th>90-CPR</th>
<th>90-DA</th>
<th>5-DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium, mL ( \cdot ) min (^{-1} ) \cdot 100 g (^{-1} )</td>
<td>7 (6–13)</td>
<td>137 (93–145)</td>
<td>58 (51–73)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>5 (5–16)</td>
<td>123 (100–158)</td>
<td>81 (67–88)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>9 (2–13)</td>
<td>122 (47–157)</td>
<td>42 (31–63)</td>
</tr>
<tr>
<td>Mesocardium, mL ( \cdot ) min (^{-1} ) \cdot 100 g (^{-1} )</td>
<td>6 (2–19)</td>
<td>109 (89–153)</td>
<td>63 (30–84)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>6 (2–12)</td>
<td>91 (63–139)</td>
<td>32 (23–44)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>5 (5–13)</td>
<td>76 (57–120)</td>
<td>47 (29–68)</td>
</tr>
<tr>
<td>Endocardium, mL ( \cdot ) min (^{-1} ) \cdot 100 g (^{-1} )</td>
<td>9 (4–13)</td>
<td>116 (81–143)</td>
<td>44 (35–81)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>5 (4–16)</td>
<td>108 (97–125)</td>
<td>62 (42–74)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>1.01 (0.90–1.08)</td>
<td>.74 (0.54–1.03)</td>
<td>.55 (0.36–0.83)</td>
</tr>
<tr>
<td>Endocardial/epicardial ratio</td>
<td>1.00 (0.83–1.00)</td>
<td>.68 (0.40–1.17)</td>
<td>.55 (0.40–0.86)</td>
</tr>
</tbody>
</table>

Values are given as median (25th to 75th percentiles). CPR indicates cardiopulmonary resuscitation; 90-CPR, after 90 seconds of chest compressions; 90-DA, 90 seconds after drug administration; and 5-DA, 5 minutes after drug administration. *\( P<0.05 \) vs vasopressin.
TABLE 3. Regional Cerebral Blood Flow During CPR

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90-CPR</td>
</tr>
<tr>
<td>Left cerebral cortex, mL·min⁻¹·100 g⁻¹</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>6 (4–7)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>4 (4–8)</td>
</tr>
<tr>
<td>Right cerebral cortex, mL·min⁻¹·100 g⁻¹</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>4 (3–8)</td>
</tr>
<tr>
<td>Cerebellum, mL·min⁻¹·100 g⁻¹</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>11 (8–12)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>10 (9–13)</td>
</tr>
<tr>
<td>Medulla oblongata, mL·min⁻¹·100 g⁻¹</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>16 (12–21)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>14 (9–16)</td>
</tr>
<tr>
<td>Total cerebral blood flow, mL·min⁻¹·100 g⁻¹</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>9 (7–12)</td>
</tr>
<tr>
<td>Vasopressin + epinephrine</td>
<td>7 (6–12)</td>
</tr>
</tbody>
</table>

Values are given as median (25th to 75th percentiles). CPR indicates cardiopulmonary resuscitation; 90-CPR, after 90 seconds of chest compressions; 90-DA, 90 seconds after drug administration; and 5-DA, 5 minutes after drug administration.

Discussion

Because vasopressin was shown to be beneficial in both laboratory and clinical investigations of ventricular fibrillation cardiac arrest,1–5 we hypothesized that these favorable effects could be extrapolated to treatment of pulseless electrical activity. Further, combining vasopressin and epinephrine, and therefore targeting nonadrenergic and adrenergic receptors, seems promising. To simulate fundamental cardiac ischemia in the present porcine model, we chose 15 minutes of cardiac arrest (13 minutes ventricular fibrillation and 2 minutes’ pulseless electrical activity), followed by chest compressions and drug therapy after 18 minutes. Our model may actually closely reflect results of a large out-of-hospital study, in which the interval between collapse and the arrival of paramedics was about 13 minutes and that between collapse and initial drug therapy was approximately 20 minutes.12 Moreover, due to the prolonged cardiac arrest, we decided to evaluate a combination of the maximum effective porcine dosages of 0.8 U/kg vasopressin1 and 200 μg/kg epinephrine13 in comparison with 0.8 U/kg vasopressin alone.

Based on a vasopressor-induced increased systemic vascular resistance,14 we observed a marked peripheral vasoconstriction after drug administration, which may shift blood toward the myocardium and brain. Interestingly, the combination therapy of both vasopressin and epinephrine did not improve myocardial blood flow compared with vasopressin alone, but cerebral perfusion was significantly lower. Although vasopressin and epinephrine combined yielded a significantly higher cerebral blood flow during CPR than after epinephrine alone in another laboratory investigation,15 our data indicate that when combining these vasopressors during CPR, epinephrine may diminish the vasodilating effect of vasopressin on the cerebral vasculature significantly. Interestingly, a similar observation was reported in a porcine model with only 4 minutes’ ventricular fibrillation cardiac arrest and a different drug combination (0.3 U/kg vasopressin and 40 μg/kg epinephrine).16

In both experimental groups in our study, cerebral perfusion pressure was comparable during CPR, which suggests that another mechanism, such as cerebral artery resistance, may be responsible for different cerebral perfusion. In a canine study, vasopressin dilated the basilar artery via specific V1 receptors; when the dogs received in addition the nitric oxide inhibitor NG-monomethyl-L-arginine, the vasopressin-mediated vasodilatory response was suppressed. This suggested that vasopressin dilates the cerebral vasculature via the release of nitric oxide from both the intraluminal and extraluminal sides.17 The binding of both vasopressin and epinephrine to its receptors causes characteristic changes such as intracellular concentration of phosphatidylinositol and calcium.18,19 In fact, a rodent study20 evaluating administration of vasopressin, norepinephrine, and a combination of vasopressin and norepinephrine showed that V1 and α-adrenergic receptors saturated the same intracellular transduction pathway. Although speculative, this mechanism may have hampered nitric oxide release in the cerebral vasculature induced by vasopressin, and therefore suppressed cerebral perfusion in our animals receiving a combination of vasopressin and epinephrine. These results are striking, because epinephrine selectively spares the cerebral circulation from vasoconstriction when administered during CPR alone.21 Accordingly, significantly lower cerebral perfusion in our vasopressin and epinephrine animals compared with the vasopressin group, and possibly higher carbon dioxide production due to excessive β-adrenergic stimulation,22 may be the mechanism that resulted in the combination animals into...
a significantly higher sagittal sinus PCO₂ compared with the vasopressin group. The observation of lower brain perfusion when combining vasopressors raises several important issues for future investigations studying vasopressors during CPR. Preliminary clinical experience suggests that in both trials with large epinephrine dosages and subsequent vasopressin administration and studies with either epinephrine or vasopressin injection, vasopressin during CPR was beneficial with regard to of neurological outcome.4,5

Seven of 8 vasopressin and 6 of 8 combination animals were resuscitated into a supraventricular rhythm, showing that our strategy to combine vasopressors did not necessarily result in higher return of spontaneous circulation rates. As such, the question arises: Does this investigation show improved survival with either vasopressor? First, this laboratory study was designed not to evaluate survival rates beyond immediate return of spontaneous circulation but rather to evaluate vital organ blood flow during CPR. Second, a porcine investigation with an identical cardiac arrest interval evaluating 24-hour survival rate11 showed that aggressive intensive care treatment was necessary for 2 hours immediately after return of spontaneous circulation, which included administration of lidocaine, atropine, bretylium, dopamine, additional epinephrine, and additional shocks. This indicates that after a major myocardial injury as in the present model, cardiovascular complications in the postresuscitation phase (such as hypotension, arrhythmias, fibrillation, or acidosis) may not be manageable with a single pharmacological intervention administered during CPR, but instead, for example, with a multiagent, multi-intervention, intensive-care protocol12 or continuous drug infusion immediately after return of spontaneous circulation.21

Epinephrine therapy during CPR has been associated with an increase of myocardial oxygen consumption,24 ventricular arrhythmias,25 ventilation-perfusion defect,26 and postresuscitation myocardial dysfunction.27 Given these potential adverse effects, the fact that a combination of vasopressin and epinephrine in the present study did not result in increased vital organ blood flow during CPR, and a higher rate of return of spontaneous circulation compared with vasopressin alone, we suggest that vasopressin may be the superior drug for successful defibrillation, whereas epinephrine and other adrenergic vasopressors may be spared for careful titration of cardiac function after return of spontaneous circulation in the postresuscitation phase.

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. However, the circulatory effects of arginine vasopressin, as administered in the present investigation, may be even greater in humans than pigs. Additionally, we did not evaluate vasopressin plasma levels throughout the study and are therefore unable to answer the question of whether inappropriate vasopressin dynamics result from an impaired baroreflex-mediated vasopressin secretion or from a fundamental depletion of pituitary vasopressin stores.28 We are unable to assess whether a higher total cerebral blood flow might have had a beneficial effect on long-term survival and neurological outcome after return of spontaneous circulation. Accordingly, since we were unable to measure vital organ blood flow using radioactive microspheres in the postresuscitation phase due to limitations posed by government regulations, we cannot comment on effects of drugs given during CPR on organ perfusion after successful defibrillation. We also used young, healthy pigs that were free from atherosclerotic disease. Furthermore, this study lacks dose-response data; therefore, we are unable to report whether different drug combinations would have yielded better results. Long-term outcome studies evaluating the effect of vasopressin during CPR may be warranted to further examine this vasopressor. Finally, investigations to further evaluate saturation of a common intracellular transduction pathway of V₁₄ and α-adrenergic agonists may be necessary.

In conclusion, comparison of vasopressin with vasopressin and epinephrine resulted in comparable left ventricular myocardial blood flow but significantly increased cerebral perfusion.

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References


Editorial Comment

Ideally, vasopressor therapy during CPR is designed to increase coronary blood flow sufficient for rapid defibrillation while restoring cerebral blood flow sufficient for preserving neuronal viability. Epinephrine, the drug of choice for many years, slows arterial runoff after each chest compression and increases perfusion pressure for the heart and brain by producing profound peripheral vasoconstriction while selectively sparing the coronary and cerebral vascular beds. However, because the rate of successful resuscitation with good neurological outcome after cardiac arrest remains low, the search for improved resuscitation strategies remains a high priority.

Arginine vasopressin has received considerable interest as an alternative to epinephrine in recent years because it is less likely to stimulate myocardial and cerebral oxygen demand than epinephrine while generating a similar pattern of selective peripheral vasoconstriction. Indeed, previous work from the laboratory of Lindner and associates indicates that bolus administration of vasopressin during CPR after 4 minutes of cardiac arrest in pigs increases cerebral blood flow more than epinephrine administration at comparable increases in perfusion pressure. Thus, vasopressin administration appears to permit additional cerebral vasodilation compared with epinephrine administration at the subnormal perfusion pressures generated during CPR after a period of complete cerebral ischemia.

In the present study by Wenzel et al, the authors evaluated whether the combination of epinephrine and vasopressin injection is superior to vasopressin injection alone during CPR after 15 minutes of cardiac arrest in pigs. The increase in perfusion pressure was similar with the 2 treatment regimens, suggesting that peripheral vasoconstriction is all-ready maximal with vasopressin administration alone. Left ventricular myocardial blood flow, which is extremely low during CPR with no vasoconstrictor therapy, increased markedly to similar levels with the 2 treatment regimens. Thus, the coadministration of epinephrine did not appear to produce a significant increase in coronary α-adrenergic tone beyond that which may occur from endogenous catecholamines. In contrast, combined treatment resulted in lower cerebral blood flow than vasopressin alone. This result indicates that combined treatment is not superior to vasopressin treatment alone and that the large increase in plasma epinephrine concentration limits cerebral vasodilation. This result is surprising, because permeability of the blood-brain barrier to the small tracer molecule, aminoisobutyric acid, is not increased during CPR, even after 15 minutes of cardiac arrest. Thus, one would not expect epinephrine to have access to cerebrovascular smooth muscle and cause α-adrenergic constriction. However, access of plasma catecholamines may be limited by endothelial monoamine oxidase activity. It is possible that tissue hypoxia associated with the initially poor reflow during CPR after 15 minutes of complete ischemia reduces oxygen-dependent activity of this enzyme. A compromised functional barrier to catecholamines at the moment that the bolus injection of epinephrine produces extremely high plasma concentrations could result in cerebral vasconstriction and limit reflow at subnormal perfusion pressure.

Two other aspects of the results were remarkable. By extending the duration of cardiac arrest from 4 minutes in the previous study to 15 minutes in the present study, cerebral blood flow after vasopressin injection remained very high (eg, 81 mL · min⁻¹ · 100 g⁻¹). Ordinarily, extending the duration of cardiac arrest enhances the no-reflow phenome-
non at subnormal perfusion pressures during CPR.\textsuperscript{6,7} Assuming that the increase in flow was homogenous at the microcirculatory level, vasopressin administration may act to overcome the no-reflow phenomenon. Whether this degree of improved reflow before defibrillation has a substantial impact on neurological outcome after 15 minutes of complete ischemia remains to be determined.

Second, the ability to successfully resuscitate the heart in large, healthy animals typically decreases when the duration of arrest extends to 15 minutes. The rather high success rate with vasopressin alone (7 of 8 pigs) after 15 minutes of arrest is impressive. Whether this translates to more rapid resuscitation in patients with diseased hearts remains to be determined in a large clinical trial.

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References
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