

Cardiopulmonary Resuscitation During Severe Hypothermia in Pigs: Does Epinephrine or Vasopressin Increase Coronary Perfusion Pressure?

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The American Heart Association does not recommend epinephrine for management of hypothermic cardiac arrest if body core temperature is below 30°C. Furthermore, the effects of vasopressin administration during hypothermic cardiac arrest are totally unknown. This study was designed to assess the effects of vasopressin and epinephrine on coronary perfusion pressure in a porcine model during hypothermic cardiac arrest cardiopulmonary resuscitation (CPR). Pigs were surface-cooled until their body core temperature was 26°C. After 30 min of untreated cardiac arrest, followed by 3 min of basic life support CPR, 15 animals were randomly assigned to receive, at 5-min intervals, either vasopressin (0.4, 0.4, and 0.8 U/kg; $n = 5$), epinephrine (45, 45, and 200 $\mu\text{g}/\text{kg}$; $n = 5$), or saline placebo ($n = 5$). Compared with epinephrine, mean \pm SEM coronary perfusion pressure was significantly higher ($P < 0.05$) 90 s and 5 min after the first (35 ± 4 vs 22 ± 3 mm Hg and 37 ± 2 vs 16 ± 2 mm Hg) and the second vasopressin administration (40 ± 5 vs 26 ± 5 mm Hg and 36 ± 5

18 ± 2 mm Hg, respectively). After the third drug administration, coronary perfusion pressure in the epinephrine group increased dramatically and was comparable to vasopressin. In the saline placebo group, coronary perfusion pressure was significantly lower ($P < 0.05$) than in the vasopressin and epinephrine groups. Six animals treated with epinephrine or vasopressin had transient return of spontaneous circulation, whereas all placebo animals died ($P < 0.05$). During CPR in severe hypothermia, administration of both vasopressin and epinephrine resulted in significant increases in coronary perfusion pressure when compared with placebo. **Implications:** Our study was designed to assess the effects of vasopressin and epinephrine in a porcine model simulating cardiac arrest during severe hypothermia. This study demonstrates that the administration of both emergency drugs results in an increased perfusion pressure in the heart.

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The American Heart Association does not recommend epinephrine for management of hypothermic cardiac arrest if body core temperature is below 30°C (1). This recommendation is not supported

by either clinical or laboratory data. Although the effects of vasopressin during normothermic cardiac arrest are very promising, nothing is known about its action during hypothermic cardiac arrest.

Further, if epinephrine, as shown in a normothermic porcine cardiopulmonary resuscitation (CPR) model, is not able to maintain coronary perfusion pressure above a threshold that renders the return of spontaneous circulation likely (2), catecholamines may be spared when managing patients with hypothermic cardiac arrest. If laboratory (2) and clinical experience (3,4) with vasopressin during CPR and vasodilatory shock states (5,6) can be extrapolated to hypothermic CPR conditions, vasopressin may be beneficial in increasing vital organ blood flow during CPR in patients with severe hypothermia caused by exposure.

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If administration of vasopressors during hypothermic CPR increases coronary perfusion pressure, return of spontaneous circulation might be easier. The purpose of the present investigation was therefore to evaluate the effects of vasopressin compared with epinephrine and saline placebo on coronary perfusion pressure in a porcine CPR model simulating prolonged hypothermic cardiac arrest.

Methods

This project was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance with the American Physiological Society and institutional guidelines. The study was performed using Utstein-style guidelines (7) on 15 healthy, 12- to 16-wk-old Tyrolean domestic pigs of both sexes, weighing 35–45 kg. The animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (neuroleptic agent; 4 mg/kg IM) and atropine (0.1 mg/kg IM) 1 h before surgery, and anesthesia was induced with propofol (1–2 mg/kg IV). After intubation during spontaneous respiration, the pigs were ventilated with a volume-controlled ventilator (Draeger EV-A, Lübeck, Germany) with 35% O₂ at 20 breaths/min and with a tidal volume adjusted to maintain normocapnia. Anesthesia was maintained with propofol (6–8 mg · kg⁻¹ · h⁻¹) and a single dose of piritramid (30 mg). We achieved muscle paralysis with 0.2 mg/kg pancuronium after intubation and subsequently with repeated doses of 0.1 mg/kg pancuronium as required. Lactated Ringer's solution (6 mL · kg⁻¹ · h⁻¹) and a 3% gelatin solution (4 mL · kg⁻¹ · h⁻¹) were administered in the preparation and during the cooling phase before the induction of cardiac arrest to replace fluid and blood loss. A standard lead II electrocardiogram was used to monitor cardiac rhythm. Depth of anesthesia was judged according to blood pressure, heart rate, and electroencephalographic monitoring (Neurotrac; Engström, Munich, Germany). The electroencephalogram was not recorded during the experiment. If cardiovascular variables or electroencephalography indicated a reduced depth of anesthesia, we increased the propofol dose, and additional piritramid was given.

A 7F catheter was advanced into the descending aorta via a femoral cutdown for measurement of arterial blood pressure. A 5F pulmonary artery catheter was placed into the pulmonary artery via a cutdown in the neck to measure cardiac output. Another 7F catheter was placed into the right atrium via a femoral cutdown for measurement of right atrial pressure and drug administration. Aortic, right atrial, and pulmonary artery pressures were measured with saline-filled catheters attached to pressure transducers (model 1290A; Hewlett Packard, Böblingen, Germany) that

were calibrated to atmospheric pressure at the level of the right atrium; pressure tracings were recorded with a data acquisition system (Dewetron port 2000, Graz, Austria). Coronary perfusion pressure was defined as the difference between aortic and right atrial diastolic pressure.

After the preparation phase, the animals were placed on a bed of crushed ice and were covered with crushed ice. The ice was removed when body core temperature reached 26.5°C. Fifteen minutes before cardiac arrest, 5000 U of heparin was administered IV to prevent intracardiac clot formation, a single dose of 15 mg piritramid and 0.1 mg/kg pancuronium was given, and hemodynamic variables and blood gases were measured. When the body core temperature was 26°C, a 50-Hz, 60-V alternating current was applied via two subcutaneous needle electrodes to induce ventricular fibrillation. Cardiopulmonary arrest was defined as the point at which the aortic pulse pressure decreased to hydrostatic pressure, and the electrocardiogram showed ventricular fibrillation; ventilation was stopped at this point. After 30 min of untreated cardiac arrest, closed-chest CPR was performed manually, and mechanical ventilation was resumed with 100% oxygenation. Chest compression was always performed by the same investigator at a rate of 80/min guided by acoustic audio tones. This investigator was blinded to hemodynamic and end-tidal carbon dioxide monitor tracings.

After 3 min of basic life support CPR, 15 animals were randomly assigned to receive either vasopressin (0.4, 0.4, and 0.8 U/kg; *n* = 5), epinephrine (45, 45, and 200 μg/kg; *n* = 5), or saline placebo (*n* = 5) after 3, 8, and 13 min of CPR, respectively. All drugs were diluted to 10 mL with normal saline and subsequently injected into the right atrium, followed by a 20-mL saline flush (investigators were blinded to the drugs). Hemodynamic variables were measured before the induction of cardiac arrest, after 90 s of CPR, and at 90 s and 5 min after each drug administration. After 18 min of CPR, up to five 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 stopped. Return of spontaneous circulation was defined as return of ventricular complexes resulting in blood pressure. After completion of the experimental protocol, the animals were killed and autopsied to verify correct positioning of the catheters and to look for rib cage injury.

All variables are given as mean ± SEM. One-way analysis was used to determine statistical significance among the three groups. Fisher's exact test was used for analysis of return of spontaneous circulation rates. Statistical significance was considered at *P* < 0.05.

Results

Before surface cooling, at 26°C body core temperature, and before the drug administration during CPR, there were no differences in temperature and hemodynamic variables between groups. After the first and second drug administrations, there was a statistically significant ($P < 0.05$) higher mean \pm SEM coronary perfusion pressure after vasopressin than after epinephrine administration (Figure 1). After the third dose, coronary perfusion pressure 90 s and 5 min after epinephrine administration was comparable to that of vasopressin (34 ± 7 vs 38 ± 4 mm Hg, 30 ± 5 vs 26 ± 4 mm Hg, respectively). In the saline placebo group, coronary perfusion pressure was approximately 7 mm Hg during CPR and was significantly ($P < 0.05$) lower than that in the epinephrine and vasopressin groups throughout the entire experiment (Figure 1).

After 48 min of cardiac arrest, including 30 min of untreated cardiac arrest and 18 min of CPR, all animals were defibrillated up to five times. Three animals in both the epinephrine and vasopressin groups had transient return of spontaneous circulation. In two vasopressin animals, and in one epinephrine animal, return of spontaneous circulation lasted between 5 min and 1 h. The remaining animals had only a brief period of return of spontaneous circulation, lasting between 30 s and 1 min. Thus, six animals treated with vasopressors had transient return of spontaneous circulation, whereas all saline placebo pigs died ($P < 0.05$). Autopsy revealed no injuries to the rib cage or intrathoracic organs in any of the animals.

Discussion

During CPR under hypothermic conditions, the repeated administration of vasopressin maintained coronary perfusion pressure at approximately 30 mm Hg, whereas only an escalating epinephrine dose increased coronary perfusion pressure from approximately 15 to 30 mm Hg. In contrast, coronary perfusion pressure in the saline placebo group never increased above approximately 7 mm Hg.

In the present model, both the 30 minutes of cardiac arrest and the duration of basic and advanced cardiac life support reflect clinically realistic settings (8). Although the 45- μ g/kg epinephrine dose used in our porcine CPR study is higher than the 15- μ g/kg dose recommended for normothermic clinical use (1,9), the first doses of both vasopressin and epinephrine reflect an established optimal dose in this pig model (10,11). Furthermore, 0.8 U/kg vasopressin (10) and 200 μ g/kg epinephrine are the maximal effective doses in normothermic pigs (12). Therefore, the present model may be a useful tool to investigate vasopressors during hypothermic cardiac arrest.

Interestingly, in the present model of hypothermic cardiac arrest, vasopressin seemed to have a plateau-effect on coronary perfusion pressure, whereas epinephrine increased coronary perfusion pressure significantly twice and resulted in a greater increase after the third epinephrine administration using an escalating dosage. After administration of either vasopressin or epinephrine in a normothermic cardiac arrest model, peak coronary perfusion pressure during CPR reached approximately 55% and 40% of baseline values at 38.5°C (2). In our hypothermic cardiac arrest model, coronary perfusion pressure with a beating heart at 26°C was only approximately 45% of 38.5°C baseline values. This may be explained by decreased cardiac contractility and/or decreased oxygen consumption. During CPR under hypothermic conditions, coronary perfusion pressure after the first two doses of vasopressin was approximately 120% of the 26°C baseline variables, whereas only the escalating third epinephrine dose (200 μ g/kg) increased coronary perfusion pressure from approximately 60% to 120% of the 26°C baseline values. These effects may be explained by the additive effects of vasopressor administration and hypothermia-mediated vasoconstriction. Thus, mechanisms such as down-regulation of adrenoreceptors and epinephrine tachyphylaxis that have been observed under normothermic conditions (2) may simply not exist during hypothermia. Although we did not measure catecholamine plasma levels throughout the study, our results suggest that blood pressure response as a result of accumulation of epinephrine did not occur. However, we are unable to state whether this was caused by normal metabolism of study drugs or increased clearance.

Six animals treated with vasopressin or epinephrine had transient return of spontaneous circulation, whereas all saline placebo pigs died ($P < 0.05$). After return of spontaneous circulation, we withheld re-warming, vasopressor support, and additional shocks on purpose, in order to evaluate the hemodynamic effects of the study drugs. Return of spontaneous circulation was accompanied by severe bradycardia and hypotension in all but one of the epinephrine animals, which was hypotensive and tachycardic. In all animals, rebrillation occurred eventually, which seems to be a common response to hypothermia. Severe hypothermia alters myocardial electrical conduction, increases ventricular irritability and results in an increased likelihood of ventricular fibrillation (13). Accordingly, during severe hypothermia, cardiovascular complications in the postresuscitation phase, such as bradycardia, hypotension, arrhythmias, and rebrillation, may not be manageable with a single pharmacological intervention administered during CPR. Because of unstable hemodynamic function of both the

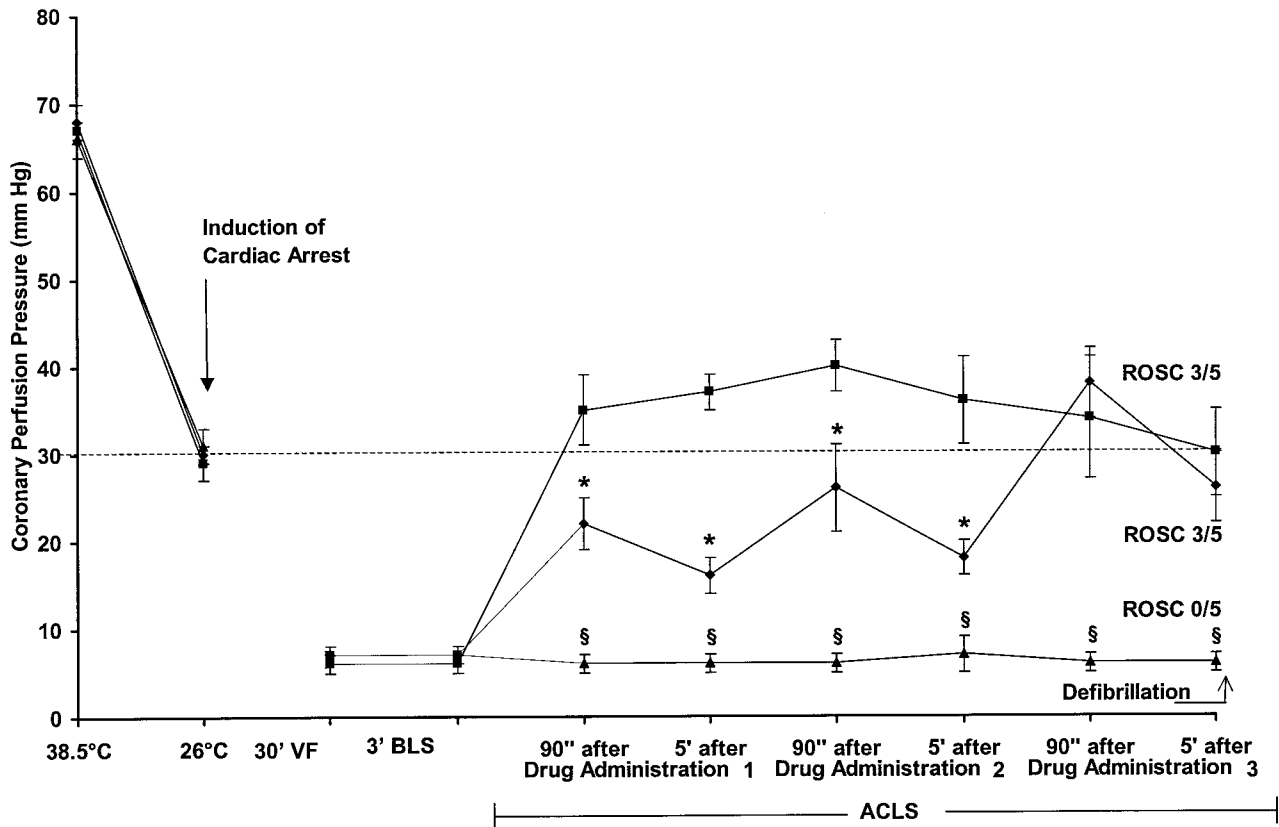


Figure 1. Administration of repeated doses of vasopressin (■), epinephrine (◆), but not saline placebo (▲) given during CPR was able to increase coronary perfusion pressure. Drug administration 1 = 0.4 U/kg vasopressin vs 45 µg/kg epinephrine vs saline placebo, Drug administration 2 = 0.4 U/kg vasopressin vs 45 µg/kg epinephrine vs saline placebo, Drug administration 3 = 0.8 U/kg vasopressin vs 45 µg/kg epinephrine vs saline placebo, 38.5°C = baseline values at 38.5°C, 26°C = baseline values at 26°C body core temperature, 30' VF = 30 min of ventricular fibrillation, 3' BLS = 3 min of basic life support, 90" after = 90 s after drug administration, 5' after = 5 min after drug administration, ACLS = advanced cardiac life support, ROSC = return of spontaneous circulation, — = 26°C coronary perfusion pressure with a beating heart. §P < 0.05 saline placebo versus epinephrine and vasopressin. *P < 0.05 vasopressin versus epinephrine.

vasopressin and epinephrine animals during the post-resuscitation phase, our study does not demonstrate an improvement in short-term survival beyond return of spontaneous circulation. Coronary perfusion pressure was not different between animals with transient return of spontaneous circulation in comparison with those without return of spontaneous circulation.

Coronary perfusion pressure is probably not the only factor that influences the return of spontaneous circulation in hypothermic cardiac arrest. Nevertheless a coronary perfusion pressure of approximately 7 mm Hg, as seen in the saline placebo group, renders the return of spontaneous circulation very unlikely. Accordingly, if our results can be extrapolated to the clinical setting, the use of vasopressor drugs during CPR of hypothermic patients may be considered when coronary perfusion pressure needs to be raised in order to make successful defibrillation more likely. This could be extremely important when rewarming with cardiopulmonary bypass is difficult or not available.

Some limitations of this study should be noted, and they include 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 we administered, may be even greater in humans when compared with pigs. The use of potent anesthetics and muscle relaxants may have affected cardiovascular function and autonomic control. Severe hypothermia may not be manageable with a single pharmacological intervention administered during CPR. Obviously, before our results can be extrapolated to the clinical setting, further investigations in animals and humans are warranted. Because we did not attempt to rewarm the animals, we are not able to assess whether the transient return of spontaneous circulation in three animals of both the vasopressin and the epinephrine groups would have been associated with long-term survival and a good neurological outcome.

In conclusion, during CPR in severe hypothermia, administration of both vasopressin and epinephrine resulted in significant increases in coronary perfusion pressure when compared with placebo.

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