Repeated Administration of Vasopressin but Not Epinephrine Maintains Coronary Perfusion Pressure After Early and Late Administration During Prolonged Cardiopulmonary Resuscitation in Pigs

Volker Wenzel, MD; Karl H. Lindner, MD; Anette C. Krismer, MD; Egfried A. Miller, BS; Wolfgang G. Voelckel, MD; Werner Lingnau, MD

Background—It is unknown whether repeated dosages of vasopressin or epinephrine given early or late during basic life support cardiopulmonary resuscitation (CPR) may be able to increase coronary perfusion pressure above a threshold between 20 and 30 mm Hg that renders defibrillation successful.

Methods and Results—After 4 minutes of cardiac arrest, followed by 3 minutes of basic life support CPR, 12 animals were randomly assigned to receive, every 5 minutes, either vasopressin (early vasopressin: 0.4, 0.4, and 0.8 U/kg, respectively; n=6) or epinephrine (early epinephrine: 45, 45, and 200 μg/kg, respectively; n=6). Another 12 animals were randomly allocated after 4 minutes of cardiac arrest, followed by 8 minutes of basic life support CPR, to receive, every 5 minutes, either vasopressin (late vasopressin: 0.4 and 0.8 U/kg, respectively; n=6), or epinephrine (late epinephrine: 45 and 200 μg/kg, respectively; n=6). Defibrillation was attempted after 22 minutes of cardiac arrest.

Mean±SEM coronary perfusion pressure was significantly higher 90 seconds after early vasopressin compared with early epinephrine (50±4 versus 34±3 mm Hg, P<0.02; 42±5 versus 15±3 mm Hg, P<0.0008; and 37±5 versus 11±3 mm Hg, P<0.002, respectively). Mean±SEM coronary perfusion pressure was significantly higher 90 seconds after late vasopressin compared with late epinephrine (40±3 versus 22±4 mm Hg, P<0.004, and 32±4 versus 15±4 mm Hg, P<0.01, respectively). All vasopressin animals survived 60 minutes, whereas no epinephrine pig had return of spontaneous circulation (P<0.05).

Conclusions—Repeated administration of vasopressin but only the first epinephrine dose given early and late during basic life support CPR maintained coronary perfusion pressure above the threshold that is needed for successful defibrillation. (Circulation. 1999;99:1379-1384.)

Key Words: cardiopulmonary resuscitation ■ vasopressin ■ epinephrine ■ perfusion ■ drugs

The role of epinephrine during cardiopulmonary resuscitation (CPR) is currently controversial. In laboratory studies, epinephrine during CPR has been associated with an increase of myocardial oxygen consumption, ventricular arrhythmias, ventilation-perfusion defect, and more severe postresuscitation myocardial dysfunction. In clinical trials, epinephrine did not result in better outcome than did saline placebo. Furthermore, high-dose epinephrine was not able to improve hospital discharge rates.

In laboratory investigations of cardiac arrest from either ventricular fibrillation or pulseless electrical activity, vasopressin provided more effective vital organ blood flow and cerebral oxygen delivery than did epinephrine. In preliminary clinical trials, vasopressin resulted in return of spontaneous circulation after unsuccessful prolonged advanced cardiac life support with epinephrine. Compared with epinephrine, vasopressin significantly improved 24-hour survival rate in a small (n=40) study of patients with ventricular fibrillation.

Although the American Heart Association and the European Resuscitation Council recommend repeated administration of epinephrine during advanced cardiac life support, it is unknown whether epinephrine given repeatedly during CPR may be effective or whether this strategy may even result in inadvertent catecholamine toxicity. Moreover, it is unknown whether repeated administration of vasopressin...
during CPR is effective and whether such a treatment regimen may result in prolonged elevated systemic vascular resistance, which may induce cardiac failure in the postresuscitation phase. Furthermore, the effects of vasopressor versus epinephrine may vary significantly when given early or late during basic life support (BLS) CPR. Accordingly, the purpose of the present investigation was to evaluate the effects of repeated administration of optimal (0.4 U/kg) and high (0.8 U/kg) dosages of vasopressor versus optimal (45 μg/kg) and high (200 μg/kg) dosages of epinephrine in a porcine cardiac arrest model simulating a short (3 minutes) and prolonged (8 minutes) duration of BLS with subsequent advanced cardiac life support.

Methods

Surgical Preparation and Measurements

This project was approved by the Austrian Federal Animal Investigation Committee, and the animals were managed in accordance with American Physiological Society and institutional guidelines. This study was performed according to Utstein-style guidelines on 24 healthy, 12- to 16-week-old swine (Tyrolean domestic pigs) of either sex weighing 30 to 40 kg. The animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (neuroleptic agent; 4 mg/kg IM) 1 hour before surgery, and anesthesia was induced with atropine (0.1 mg/kg IM) and 39.0°C.

A 7F catheter was advanced into the descending aorta via femoral cutdown for withdrawal of arterial blood samples and measurement of arterial blood pressure. A 5F pulmonary artery catheter was placed in the pulmonary artery via cutdown in the neck to measure cardiac output and to sample mixed venous blood. Cardiac output was measured with the thermodilution technique, and cardiac index was calculated by dividing cardiac output by body weight. Another 7F catheter was placed into the right atrium via femoral cutdown to measure right atrial pressure and for drug administration. Aortic, right atrial, and pulmonary artery pressures were measured with saline-filled catheters attached to pressure transducers (model 1290A, Hewlett Packard) 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). Coronary perfusion pressure (CPP) was defined as the difference between aortic and right atrial diastolic pressures. Blood gases were measured with a blood gas analyzer (Chiron Diagnostics), and end-tidal carbon dioxide was measured with an infrared absorption analyzer (Sirecust 960, Siemens).

Experimental Protocol

Fifteen minutes before cardiac arrest, 5000 U heparin IV was administered to prevent intracardiac clot formation, a single dose of 15 mg piritramide 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 pressure decreased profoundly to hydrostatic pressure, and the ECG showed ventricular fibrillation; ventilation was stopped at that point. After 4 minutes of untreated ventricular fibrillation, closed-chest CPR was performed manually, and mechanical ventilation was resumed at the same setting as before induction of cardiac arrest. Chest compression, guided by acoustical audiotones, was always performed by the same investigator at a rate of 80 compressions per minute. This investigator was blinded to hemodynamic and end-tidal carbon dioxide monitor tracings.

The first part of the study was designed to simulate administration of vasopressors after a short period of BLS CPR. Accordingly, after 4 minutes of ventricular fibrillation followed by 3 minutes of BLS CPR, 12 animals were randomly assigned to receive either vasopressin (early vasopressin group: 0.4, 0.4, and 0.8 U/kg; n=6) or epinephrine (early epinephrine group: 45, 45, and 200 μg/kg; n=6) or epinephrine (late epinephrine group: 45 and 200 μg/kg; n=6) after 3, 8 and 13 minutes of CPR, respectively (Table 1). The second part of the study was designed to simulate administration of vasopressors after a prolonged period of BLS CPR. Thus, 12 animals were randomly allocated after 4 minutes of ventricular fibrillation and 8 minutes of BLS CPR to receive either vasopressin (late vasopressin group: 0.4 and 0.8 U/kg; n=6) or epinephrine (late epinephrine group: 45 and 200 μg/kg; n=6) after 8 and 13 minutes of CPR, respectively (Table 1).

All drugs were diluted to 10 mL with normal saline and subsequently injected into the right atrium, followed by 20 mL saline flush (investigators were blinded to the drugs). Hemodynamic parameters were measured before induction of cardiac arrest, after 3 minutes of CPR, and 90 seconds and 5 minutes after each drug administration, respectively. After 22 minutes of cardiac arrest, including 18 minutes of CPR, up to 5 countershocks were administered with an energy of 3, 4, and 6 J/kg. 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 and pulse pressure of ≥40 mm Hg lasting for at least 5 minutes. In the postresuscitation period,
hemodynamic parameters were measured at 5, 15, 30, and 60 minutes after return of spontaneous circulation. After the experimental protocol was finished, the animals were killed and necropsied to verify correct positioning of the catheters and injuries to the rib cage.

### Statistical Analysis

The comparability of weight and baseline data were tested with the t test for continuous variables. One-way ANOVA was used to determine statistical significance between 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 is independent of treatment. We considered a 2-tailed value of P<0.05 statistically significant.

### Results

Before induction of ventricular fibrillation and before drug administration during CPR, there were no differences in weight, hemodynamic variables, or blood gases between groups (Table 2). When drugs were given early during BLS CPR (after 3 minutes of chest compressions), there was a strong trend toward significantly higher CPP 90 seconds after vasopressin compared with epinephrine. This trend became statistically significant between groups 5 minutes after the first vasopressin or epinephrine administration and remained significantly different for the remainder of the experiment (Figure 1).

When drugs were given late during BLS CPR (after 8 minutes of chest compressions), CPP was significantly higher after vasopressin compared with epinephrine at both 90 seconds and 5 minutes after each of 2 drug administrations (Figure 2). After 22 minutes of cardiac arrest, including 18 minutes of CPR, all pigs in the early and late vasopressin group had return of spontaneous circulation (early vasopressin group, 1.3±0.2 countershocks; late vasopressin group, 4.2±0.9 countershocks) and survived the 60-minute postresuscitation phase. In the early epinephrine group, 2 animals were defibrillated into pulseless electrical activity, and 4 animals had asystole. Necropsy confirmed appropriate catheter positions and revealed no injuries to the rib cage or intrathoracic organs in any animals.
Repeated Vasopressin vs Epinephrine During CPR

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Discussion
Repeated administration of vasopressin but only the first dose of epinephrine given early and late during BLS CPR were able to maintain CPP above the threshold between 20 and 30 mm Hg that is needed for successful defibrillation. Furthermore, these effects lasted longer after vasopressin than epinephrine, and significantly more vasopressin than epinephrine animals had return of spontaneous circulation (6 of 6 versus 0 of 6, respectively; \( P < 0.05 \)).

The present model closely simulates a short and prolonged duration of BLS followed by advanced cardiac life support. Although the 45-\( \mu \)g/kg dose of epinephrine used in our porcine study is higher than the 15-\( \mu \)g/kg dose recommended for clinical use,\(^1\),\(^2\),\(^3\) the first dosages of both vasopressin and epinephrine reflect an established optimal dose in this pig model.\(^4\),\(^5\),\(^6\) Furthermore, the high doses of 0.8 U/kg vasopressin and 200 \( \mu \)g/kg epinephrine are the maximum effective doses in swine.\(^7\),\(^8\) Interestingly, the effects of vasopressin versus epinephrine on CPP varied depending on the time of drug administration during advanced life support CPR. For example, the first vasopressin administration in the late model achieved an \( \approx 66\% \) increase in CPP over the first vasopressin injection in the early model (\( \approx 20 \) mm Hg versus 30 mm Hg). Conversely, the first epinephrine dose in the late model achieved only an \( \approx 35\% \) increase in CPP over the first epinephrine dose in the early model (\( \approx 6 \) mm Hg versus \( \approx 17 \) mm Hg). This indicates that the effects of epinephrine given late seemed to be more attenuated compared with late administration of vasopressin during BLS CPR. In fact, arteries from rats with metabolic acidosis or uremia showed selective blunting of biochemical and contractile responses to norepinephrine but not to vasopressin.\(^9\) This may suggest that after prolonged cardiac arrest and therefore fundamental global hypoxia and hypercarbic acidosis, the pressor sensitivity to vasopressin may be normal and the effects of catecholamines may be blunted.\(^10\) The underlying mechanism for a rapid and profound tachyphylaxis of epinephrine may be desensitized myocardial and peripheral adrenergic receptors.\(^11\) Accordingly, substantially elevated plasma levels of epinephrine that are endogenously released immediately after cardiac arrest before initiation of CPR may be a possible explanation for limited effectiveness of epinephrine. This may explain that in addition to endogenous epinephrine, exogenous epinephrine is necessary to increase vital organ blood flow during CPR.\(^12\)

A CPP between 20 and 30 mm Hg during CPR is one of the best predictors of return of spontaneous circulation in both animals and humans.\(^13\) The epinephrine animals reached this level only transiently 90 seconds after the first drug administration given early and late during BLS CPR, whereas CPP in the vasopressin animals was at or above this level for the entire experiment. Accordingly, all vasopressin animals in our study were successfully defibrillated after 22 minutes of cardiac arrest and survived the 60-minute postresuscitation phase, whereas all pigs resuscitated with epinephrine died. The duration of BLS and therefore of suboptimal vital organ blood flow during CPR may have a fundamental impact on resuscitability. For example, the early vasopressin pigs were successfully defibrillated with 1.3\( \pm \)0.2 countershocks, whereas the late vasopressin pigs needed 4.2\( \pm \)0.9 defibrillation attempts to achieve return of spontaneous circulation, indicating more severe cardiac ischemia. Only the first of repeated doses of epinephrine in our animals were able to increase CPP above a threshold that renders successful defibrillation likely. Subsequent doses, including a high dosage, were not able to increase CPP above a level that usually correlates with return of spontaneous circulation. This is in good agreement with a preliminary canine study showing that the first dose of epinephrine determined whether the critical CPP needed for return of spontaneous circulation was reached and the animals survived.\(^14\) In fact, with the exception of 2 animals in the early epinephrine group that we defibrillated into pulseless electrical activity, all pigs treated with epinephrine had asystole, indicating fundamental depletion of myocardial energy. This
may confirm previous results from laboratory investigations demonstrating that epinephrine fueled cardiac oxygen consumption, which subsequently resulted in a severe mismatch of cardiac oxygen delivery versus oxygen consumption during CPR. This mechanism may have been an important component in a clinical study, when a total cumulative dose of 15 mg epinephrine was found to best predict 24-hour mortality in patients with out-of-hospital cardiac arrest. In fact, the weight-adjusted total epinephrine dose given to our early epinephrine animals was almost identical to this lethal dose (≈285 μg/kg versus ≈215 μg/kg). Subsequently, no epinephrine pig had return of spontaneous circulation despite the absence of underlying disease, such as severe coronary atherosclerotic disease. Thus, if our results can be extrapolated to clinical management of cardiac arrest, they are in strong disagreement with the current guidelines of both the American Heart Association14 and the European Resuscitation Council,15 which recommend “looping” an algorithm of defibrillation–epinephrine–defibrillation while performing CPR if return of spontaneous circulation cannot be achieved.

If our explanation of the observed effects in the present experiment is correct, humans with coronary artery disease might have a greater benefit when being resuscitated with vasopressin than with epinephrine. For example, when a 33% stenosis in the mid left anterior descending coronary artery was induced in a porcine model, myocardial perfusion was not diminished during normal physiological conditions, but endocardial blood flow was significantly decreased during CPR. Given the fact that irreversible injury of ischemic myocardium was shown to develop as a transmural wave front that started in the subendocardial myocardium and moved progressively toward the subepicardial myocardium in a canine model, this mechanism may result in significant complications in the postresuscitation phase, such as fatal arrhythmias. Thus, this may indicate that during CPR in the presence of coronary artery disease, which is very common in humans suffering cardiac arrest, a relatively high CPP may be beneficial to supply appropriate perfusion to the entire myocardium. Accordingly, a vasopressin-mediated CPP that is significantly above the threshold that is actually needed to achieve return of spontaneous circulation in patients with coronary artery disease may represent an additional advantage with regard to resuscitability compared with epinephrine.

Effects of CPR management that are beneficial during the resuscitation attempt may result in potentially deleterious effects in the postresuscitation phase, which is a critical time interval between return of spontaneous circulation and long-term survival. For example, a vasopressin-mediated increased systemic vascular resistance has been shown to be an important mechanism to increase vital organ blood flow during CPR, but persisting elevated systemic vascular resistance after return of spontaneous circulation may result in cardiac failure. In fact, a reversible depressant effect on myocardial function of pigs resuscitated with vasopressin was observed compared with epinephrine; however, overall cardiovascular function was not critically or irreversibly impaired after the administration of vasopressin. Although we did not measure left ventricular pressure pattern velocity in our pigs to determine cardiac contractility after return of spontaneous circulation, cardiocirculatory parameters were stable in all animals in the postresuscitation phase. Furthermore, despite repeated administration of vasopressin during CPR, systemic vascular resistance was elevated only for ≈15 minutes after return of spontaneous circulation. Accordingly, we suggest that vasopressin may be superior to epinephrine to achieve return of spontaneous circulation, whereas catecholamines may be saved for careful titration of hemodynamic variables after successful defibrillation.

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 in pigs. In addition, we did not evaluate vasopressin plasma levels throughout the study. Furthermore, we were not able to assess whether higher return of spontaneous circulation rates as observed in the early and late vasopressin animals might have had a beneficial effect on long-term survival and neurological outcome after return of spontaneous circulation. Also, usage of potent anesthetics may have impaired cardiovascular function and autonomic control. We also used young, healthy pigs that were free of atherosclerotic disease. Furthermore, this study lacks dose-response data; therefore, we are not able to report the minimally effective vasopressin dose. Finally, we purposely omitted defibrillation attempts on starting CPR and immediately after vasopressor administration to study the hemodynamic effects of the study drugs during the resuscitation attempt.

In conclusion, repeated administration of vasopressin but only the first epinephrine dose given early and late during BLS CPR maintained CPP above a threshold that is needed for successful defibrillation.

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