Vasopressin Improves Survival After Cardiac Arrest in Hypovolemic Shock

Wolfgang G. Voelckel, MD*†, Keith G. Lurie, MD*, Karl H. Lindner, MD†, Todd Zielinski, MS*, Scott McKnite, BS*, Anette C. Krismer, MD†, and Volker Wenzel, MD†

*Cardiac Arrhythmia Center, Cardiovascular Division, Department of Medicine at the University of Minnesota, Minneapolis, Minnesota; and †Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens-University of Innsbruck, Innsbruck, Austria

Survival after hypovolemic shock and cardiac arrest is dismal with current therapies. We evaluated the potential benefits of vasopressin versus large-dose epinephrine in hemorrhagic shock and cardiac arrest on vital organ perfusion, and the likelihood of resuscitation. In 18 pigs, 35% of the estimated blood volume was withdrawn over 15 min and ventricular fibrillation was induced 5 min later. After 4 min of cardiac arrest and 4 min of standard cardiopulmonary resuscitation, a bolus dose of either 200 μg/kg epinephrine ($n = 7$), 0.8 unit/kg vasopressin ($n = 7$), or saline placebo ($n = 4$) was administered in a blinded, randomized manner. Defibrillation was attempted 2.5 min after drug administration, and all animals were subsequently observed for 1 h without further intervention. Spontaneous circulation was restored in 7 of 7 vasopressin animals, in 6 of 7 epinephrine pigs, and in 0 of 4 placebo swine. At 5 and 30 min after return of spontaneous circulation, median (minimum and maximum) renal blood flow after epinephrine was 2 (0–31), and 2 (0–48) mL · 100 g^{-1} · min^{-1}, respectively; and after vasopressin 96 (12–161), and 44 (16–105) mL · 100 g^{-1} · min^{-1}, respectively ($P < .01$ between groups). Epinephrine animals developed a profound metabolic acidosis by 15 min after return of spontaneous circulation (mean arterial pH, 7.11 ± 0.01), and by 60 min all epinephrine-treated animals had died. The vasopressin pigs had ($P = 0.015$) less acidosis (pH = 7.26±0.04) at corresponding time points, and all survived ≥55 min ($P < 0.01$). In conclusion, treatment of hypovolemic cardiac arrest with vasopressin, but not with large-dose epinephrine or saline placebo, resulted in sustained vital organ perfusion, less metabolic acidosis, and prolonged survival. Based on these findings, clinical evaluation of vasopressin during hypovolemic cardiac arrest may be warranted.

(Anesth Analg 2000;91:627–34)

Trauma is the principal cause of death among Americans between the ages of 1 and 38 yr (1). Unfortunately, the chances for survival after trauma and subsequent cardiac arrest have not significantly improved for decades (2–4). The role of external cardiac compressions in hemorrhagic shock is poorly understood, and not well studied. Moreover, current pharmacotherapy for cardiac arrest is often ineffective. Although the American Heart Association and the European Resuscitation Council recommend the administration of epinephrine during advanced cardiac life support (5,6), it is unknown whether epinephrine is sufficiently effective to increase systemic vascular resistance, and therefore, vital organ blood flow during cardiopulmonary resuscitation (CPR) and hemorrhagic shock. Furthermore, when on-scene treatment may be limited, such as in a battlefield scenario, a single drug therapy may be the only option to gain time for transport, control bleeding, and replace fluids.

Vasopressin is a promising alternative to epinephrine (7) for resuscitation in cardiac arrest victims (8), and hemodynamic stabilization in septic shock patients (9). In hypovolemic, anesthetized animals, vasopressin increased cardiac output, mean aortic and central venous pressure, and subsequently, organ blood flow values to the heart, and intestinal organs (10). Furthermore, vasopressin appears to be a uniquely effective vasopressor in the irreversible phase of hemorrhagic shock unresponsive to volume replacement and catecholamine vasopressors (11).

Supported, in part, by the Cardiac Arrhythmia Center, University of Minnesota, Minneapolis, MN, and the Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens-University of Innsbruck, Austria.

Presented, in part, as an abstract at the 72nd Scientific Sessions of the American Heart Association, Atlanta, Georgia, November 1999.

Accepted for publication May 8, 2000.

Address correspondence and reprint requests to Keith G. Lurie, MD, Department of Medicine, Cardiac Arrhythmia Center, Cardiovascular Division, University of Minnesota, Box 508, Mayo, 420 Delaware St. SE, Minneapolis, MN 55455. Address e-mail to lurie002@maroon.tc.umn.edu.

0003-2999/00

Cardiac arrest during hypovolemic shock can result from the development of ventricular fibrillation, pulseless electrical activity, and asystole. Vasopressin given during cardiac arrest and hemorrhagic shock may improve vital organ blood flow during CPR, and stabilize cardiocirculatory function after successful resuscitation. Accordingly, the purpose of the present investigation was to test the effects of vasopressin versus epinephrine in a porcine model of volume-controlled hemorrhagic shock on return of spontaneous circulation and vital organ blood flow in the postresuscitation phase. We designed this study to focus particularly on the first critical 60-minute phase after successful resuscitation, when adjunctive pharmacological therapies may be most effective in the absence of available fluid replacement.

Methods

The Committee on Animal Experimentation approved this project at the University of Minnesota, and the animals were managed in accordance with the American Physiological Society, institutional guidelines, and Position of the American Heart Association on Research Animal Use, as adopted on November 11, 1984. Animal care and use was performed by qualified individuals, supervised by veterinarians, and all facilities and transportation comply with current legal requirements and guidelines. Anesthesia was used in all surgical interventions. All unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care.

The study was performed according to Utstein-style guidelines (12) on 18 healthy, 12 to 16-wk-old female domestic farm pigs weighing 28–34 kg. The pigs were anesthetized with a single bolus dose of 20 mg/kg IM ketamine, a 15 mg/kg IV bolus of pentobarbital followed by a 15 $mg \cdot kg^{-1} \cdot h^{-1}$ IV infusion, and a 2 mg bolus of morphine given via an ear vein. The pigs were intubated during spontaneous respiration with a 7.5-mm cuffed endotracheal tube, and mechanically ventilated at a volume-controlled setting of 20 mL/kg. During the preparation time, respiratory frequency was adjusted at 10–12 breaths/min according to end-tidal and arterial carbon dioxide partial pressure values to maintain the mean arterial carbon dioxide partial pressure at 35 mm Hg; inspiratory oxygen concentration was 21%. Total fluid management consisted of 1000–1200 mL IV normal saline solution throughout the 3-h preparation period to maintain a diastolic right atrial pressure level of 3 to 5 mm Hg.

Left ventricular and ascending aortic arch blood pressures were monitored by using a single high fidelity micromanometer-tipped catheter. This luminal aorto-left-ventricular micromanometer catheter was positioned under fluoroscopic guidance by femoral cutdown, and used for injection of radiolabeled microspheres. To monitor right atrial pressures and administer the study drugs, another micromanometer catheter was inserted through a right jugular vein sheath. Reference blood samples for measurement of organ blood flow were withdrawn from a 5F catheter placed in the descending aorta by femoral cutdown. For the measurement of body temperature, a thermistor probe was placed in the rectum. Body temperature was maintained with a heating blanket between 38.0°C and 39.0°C.

Pressure tracings obtained from the high-fidelity micromanometer catheters were continuously monitored with a data acquisition and recording system. Digitized data were analyzed electronically to provide hemodynamic measurements. Heart rate was determined from a simultaneously recorded electrocardiogram signal. Coronary perfusion pressure calculated during diastole (relaxation) was defined as the arteriovenous pressure difference (time-coincident difference between aortic and right atrial pressure). Arterial blood gases were analyzed every 30 min to ensure adequate acid base status and oxygenation. Organ blood flow was assessed with radiolabeled microspheres according to the method described by Heymann et al (13).

Microspheres used in this study were radioactively labeled with ^{141}Ce, ^{95}Nb, ^{51}Cr, and ^{113}Sr (New England Nuclear, Du Pont, Boston, MA). Each microsphere vial was placed in a water bath and subjected to ultrasonic vibration for 1 min before injection. Approximately 5×10^6 microspheres were then immediately injected into the left ventricle through the lumen of the Millar catheter. The syringe and catheter were flushed with 10 mL of heparinized saline. With an automatic pump, arterial blood was continuously withdrawn from the descending aorta at a rate of 6 mL/min just before the microspheres injection and up to 4 min thereafter. At the end of the experiment, the entire heart, the cerebrum, the adrenal glands, both kidneys, and the pancreas were removed. The left ventricular free wall was sectioned into three layers. Aliquots of each tissue were weighed and placed into vials. Radioactivities from tissues and blood were measured with a γ scintillation spectrometer, and blood flow values were subsequently calculated.

The experimental protocol is demonstrated in Table 1. After assessing baseline organ blood flow, 35% of total blood volume according to normal physiological values for swine (14), was withdrawn via an arterial catheter over 15 min with an automatic driven pump. Organ blood flow was subsequently assessed again under the conditions of acute hemorrhagic shock. Ventricular fibrillation was induced with a single 5-s

Table 1. Flow Chart of the Experimental Protocol

Preparation (min)		Exsanguination (min)		VF (min)		Cardiopulmonary resuscitation (min)			Postresuscitation phase (min)			
0	180[a,b]	0	15[a,b]	0[a]	4	0	4	6.5	0	5[a,b]	30[a,b]	60[a]
							↑ Drug Administration	↑ Defibrillation				

VF = ventricular fibrillation, Drug Administration = central venous injection of 0.8 U/kg vasopressin vs. 200 μg/kg epinephrine vs. saline placebo, Defibrillation = defibrillation with 200 joule.
[a] Sampling of arterial and mixed venous blood gases.
[b] Measurement of vital organ blood flow with radiolabeled microspheres.

administration of alternating current via an indwelling bipolar pacing catheter, and ventilation was discontinued. After 4 min of untreated ventricular fibrillation, closed-chest standard CPR was performed with a pneumatically driven automatic piston device for CPR (15) and ventilation was performed by manual bag valve ventilation with 10 L/min oxygen and a 5:1 compression-ventilation ratio. After 4 min of CPR, animals were randomly assigned to receive a central venous bolus of either 200 μg/kg epinephrine versus 0.8 unit/kg vasopressin versus saline placebo; investigators were blinded to the drugs. At 2.5 min after drug administration, up to three countershocks (200 joules each) were administered with a defibrillator. If ventricular fibrillation, pulseless electrical activity, or asystole was observed, CPR was resumed for 2 min and an additional dose of either 200 μg/kg epinephrine, or 0.8 unit/kg IV vasopressin, or saline placebo was given; defibrillation (200-joule shock) was performed again at 2.5 min after drug administration. Return of spontaneous circulation was defined as an unassisted pulse with a mean arterial pressure ≥ baseline values before exsanguination, lasting for at least 5 min. The saline infusion was started at 3 $mL \cdot kg^{-1} \cdot h^{-1}$ to replace further fluid loss, and maintained during the postresuscitation period. No additional intervention was performed during the postresuscitation phase. Hemodynamic variables and blood gases were observed for 1 h, and organ blood flow was measured at 5 and 30 min after return of spontaneous circulation.

Values were expressed as mean ± SEM. Comparisons of hemodynamic variables and blood flow values within groups after exsanguination were performed with Student's paired *t*-test and Wilcoxon's signed rank test, respectively. To compare hemodynamic and blood gas variables between groups, two sample Student's *t*-tests were used with equal variances, or unequal variances as called for by *f*-test and different group sizes. Because blood flow data were distributed unevenly, they are expressed as medians with minimum and maximum. The Mann-Whitney *U*-test was used to determine differences between groups. Survival was compared by using a Kaplan-Meier survival table and Mantel-Cox log rank test. Statistical significance was considered to be at the $P < 0.05$ after Bonferroni correction for multiple comparisons.

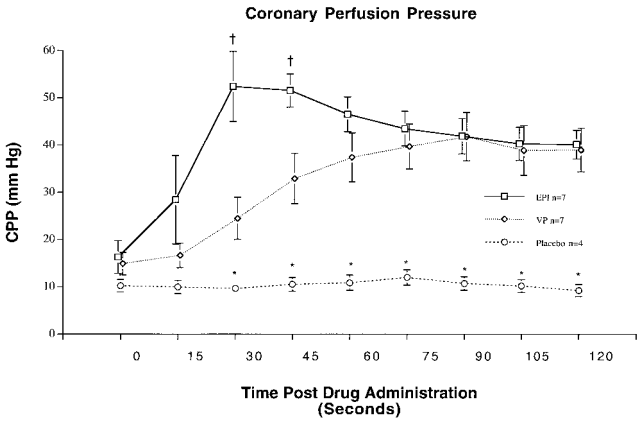

Figure 1. Mean ± SEM coronary perfusion pressure during resuscitation after the administration of 200 μg/kg epinephrine (□) versus 0.8 unit/kg vasopressin (◇) versus saline placebo (○). CPP = coronary perfusion pressure; EPI = epinephrine, VP = vasopressin. †$P < 0.05$ for epinephrine versus vasopressin; *$P < 0.05$ for saline placebo versus epinephrine and vasopressin. Time is given in seconds after drug administration.

Results

Before the induction of hypovolemic shock, there were no differences in weight, temperature, hemodynamic variables, organ blood flows, and blood gases between groups. After withdrawal of 35% blood volume, mean arterial blood pressure and abdominal organ blood flow values were significantly decreased compared with baseline values; however, they were comparable between groups (Tables 2–4).

Coronary perfusion pressure during CPR increased more rapidly in epinephrine versus vasopressin pigs, but reached comparable levels 90 s after drug administration; placebo pigs had a coronary perfusion pressure of approximately 10 mm Hg throughout the study (Figure 1). Three epinephrine, and two vasopressin animals required a repeated dose of the same

Table 2. Hemodynamic Variables During Normovolemia, After Exsanguination During Hypovolemia, During Cardiopulmonary Resuscitation, and During the Postresuscitation Phase in Pigs

	Prearrest		Postresuscitation phase (min)				
	Normovolemia	Hypovolemia	5	15[a]	30[a]	45[b]	60
HR (bpm)							
Epinephrine	117 ± 3	153 ± 15*	266 ± 13†	243 ± 18	222 ± 19	230 ± 23	NA
Vasopressin	119 ± 3	153 ± 10*	221 ± 13	194 ± 9	189 ± 7	195 ± 9	203 ± 9
Saline placebo	135 ± 5	165 ± 15*	NA	NA	NA	NA	NA
MAP (mm Hg)							
Epinephrine	74 ± 5	30 ± 2*	132 ± 21	42 ± 4	24 ± 3	22 ± 2	NA
Vasopressin	72 ± 9	28 ± 3*	79 ± 13	37 ± 3	34 ± 3	33 ± 5	40 ± 6
Saline placebo	75 ± 6	20 ± 2*	NA	NA	NA	NA	NA
dp/dt (mm Hg/s)							
Epinephrine	969 ± 85	832 ± 128	4153 ± 736‡	1761 ± 240‡	696 ± 212	348 ± 96	NA
Vasopressin	1089 ± 74	745 ± 185	1606 ± 404	863 ± 128	788 ± 85	829 ± 129	1170 ± 145
Saline placebo	1308 ± 86	946 ± 144	NA	NA	NA	NA	NA

All variables are given as mean ± SEM.
[a] n = 5.
[b] n = 2 for epinephrine.
Prearrest indicates measurements before induction of cardiac arrest. CPR = cardiopulmonary resuscitation. Hypovolemia = after loss of 35% blood volume; DA = drug administration, HR = heart rate, MAP = mean arterial pressure, dp/dt = myocardial contractility, NA = not applicable.
* $P < .05$ hypovolemia vs. normovolemia.
† $P = .03$ epinephrine versus vasopressin.
‡ $P < .0125$ epinephrine versus vasopressin.
No statistical analysis was performed beyond 45 min after return of spontaneous circulation due to low sample size.

Table 3. Blood Gas Variables During Normovolemia, After Exsanguination During Hypovolemia, During Cardiopulmonary Resuscitation, and During the Postresuscitation Phase in Pigs

	Prearrest		CPR		Postresuscitation Phase (min)				
	Normovolemia	Hypovolemia	Before DA	2 min After DA	5	15[a]	30[a]	45[b]	60
pH (arterial)									
Epinephrine	7.46 ± .01	7.50 ± .01	7.51 ± .02	7.48 ± .04	7.29 ± .03	7.11 ± .01‡	7.17 ± .03	7.22 ± .04	NA
Vasopressin	7.44 ± .01	7.46 ± .02	7.45 ± .02	7.47 ± .05	7.31 ± .03	7.26 ± .04	7.27 ± .03	7.29 ± .04	7.34 ± .02
Saline placebo	7.48 ± .04	7.57 ± .02	7.49 ± .08	7.41 ± .03	NA	NA	NA	NA	NA
pH (mixed venous)									
Epinephrine	7.43 ± .01	7.40 ± .01	7.27 ± .03	7.26 ± .02	7.25 ± .02	7.04 ± .02§	7.04 ± .03	7.03 ± .04	NA
Vasopressin	7.42 ± .01	7.37 ± .01	7.20 ± .02	7.26 ± .05	7.21 ± .03	7.17 ± .04	7.15 ± .03	7.16 ± .03	7.26 ± .04
Saline placebo	7.46 ± .05	7.38 ± .05	7.25 ± .04	7.18 ± .02	NA	NA	NA	NA	NA
Pco_2 (arterial)									
Epinephrine	35.5 ± 1.7	32.1 ± 1.6	25.1 ± 1.7	18.9 ± 2.2	29.9 ± 2.4	39.1 ± 5.7	34.3 ± 3.0	22.6 ± 5.1‖	NA
Vasopressin	36.6 ± 0.8	32.2 ± 2.6	27.4 ± 2.0	19.2 ± 2.3	32.0 ± 1.4	35.9 ± 2.6	36.6 ± 2.4	36.9 ± 3.2	33.0 ± 4.3
Saline placebo	33.9 ± 1.1	28.8 ± 3.1	25.7 ± 4.7	27.2 ± 4.6	NA	NA	NA	NA	NA
Pco_2 (mixed venous)									
Epinephrine	39.7 ± 1.6	45.8 ± 2.3*	60.8 ± 5.0	46.8 ± 3.5	40.7 ± 3.7	69.6 ± 2.3	68.7 ± 3.2§	62.2 ± 7.0	NA
Vasopressin	36.6 ± 2.4	46.9 ± 2.2*	68.5 ± 6.2	45.5 ± 8.2	47.1 ± 4.4	56.2 ± 4.9	57.5 ± 3.6	57.1 ± 3.3	51.8 ± 5.5
Saline placebo	36.3 ± 3.3	40.1 ± 5.6	56.6 ± 2.6	60.8 ± 3.9†	NA	NA	NA	NA	NA

All variables are given as mean ± SEM.
[a] n = 5.
[b] n = 2 for epinephrine.
Prearrest indicates measurements before induction of cardiac arrest. CPR = cardiopulmonary resuscitation, Hypovolemia = after loss of 35% blood volume; DA = drug administration; NA, not applicable.
* $P < .05$ hypovolemia versus normovolemia.
† $P < .05$ saline placebo versus epinephrine or vasopressin.
‡ $P = .015$ epinephrine versus vasopressin.
§ $P = .045$ epinephrine versus vasopressin.
‖ $P < 0.05$ epinephrine versus vasopressin.
No statistical analysis was performed beyond 45 min after return of spontaneous circulation due to low sample size.

vasopressor to restore spontaneous circulation. Six of seven epinephrine animals, seven of seven vasopressin swine, but none of four placebo pigs had return of spontaneous circulation.

At 5 min after return of spontaneous circulation, mean arterial blood pressure and blood flow to the heart, the cerebrum, and the adrenal glands were significantly increased ($P < 0.01$) in the epinephrine

Table 4. Myocardial, Cerebral, Kidney, Adrenal, Liver, Pancreas, and Small Intestine Blood Flow During Normovolemia, After Exsanguination During Hypovolemia, and During the Postresuscitation Phase in Pigs

	Prearrest		Postresuscitation phase (min)	
	Normovolemia	Hypovolemia	5	30[a]
Left ventricular blood flow				
Epinephrine	58 (43–266)	56 (32–91)	888 (383–2,875)*	61 (28–93)
Vasopressin	69 (49–107)	46 (33–96)	137 (40–409)	71 (62–114)
Saline placebo	66 (21–89)	20 (8–29)	—	—
Global cerebral blood flow				
Epinephrine	24 (22–26)	24 (18–28)	93 (53–112)*	15 (11–23)
Vasopressin	26 (19–33)	26 (13–34)	38 (9–78)	19 (16–28)
Saline placebo	20 (11–25)	10 (5–15)	—	—
Right kidney blood flow				
Epinephrine	400 (285–720)	88 (2–190)†	2 (1–29)*	2 (0–44)*
Vasopressin	480 (220–550)	40 (3–93)†	96 (12–161)	44 (16–98)
Saline placebo	390 (220–435)	50 (0–100)†	—	—
Left kidney blood flow				
Epinephrine	390 (275–755)	97 (4–190)†	2 (0–31)*	0 (0–48)*
Vasopressin	490 (245–560)	41 (7–92)†	102 (13–151)	46 (17–105)
Saline placebo	400 (225–450)	55 (5–95)†	—	—
Right adrenal blood flow				
Epinephrine	80 (75–145)	90 (25–120)	630 (310–1015)*	27 (15–55)*
Vasopressin	95 (55–125)	50 (20–70)	190 (35–385)	71 (38–108)
Saline placebo	90 (85–95)	25 (10–45)	—	—
Left adrenal blood flow				
Epinephrine	95 (75–155)	100 (25–130)	790 (470–1205)*	37 (28–70)*
Vasopressin	95 (50–160)	55 (30–70)	230 (45–385)	78 (57–127)
Saline placebo	90 (85–95)	30 (15–50)	—	—
Pancreas blood flow				
Epinephrine	43 (17–74)	14 (9–19)†	2 (0–5)	7 (2–16)*
Vasopressin	43 (15–73)	10 (3–26)†	3 (0–8)	15 (10–29)
Saline placebo	—	—	—	—
Small intestine blood flow				
Epinephrine	49 (14–86)	28 (11–49)†	14 (4–35)	14 (2–18)
Vasopressin	49 (26–71)	23 (9–51)†	17 (7–65)	36 (13–50)
Saline placebo	—	—	—	—

All variables are given as median (minimum–maximum). Blood flow is given as $mL \cdot min^{-1} \cdot 100g^{-1}$.
Prearrest = measurements before the induction of cardiac arrest, — = not applicable.
[a] $n = 5$ for epinephrine.
* $P < 0.05$ epinephrine versus vasopressin.
† $P < 0.05$ hypovolemia versus baseline.

group compared with the vasopressin group; however, renal blood flow was significantly decreased. The calculated mean ± SEM double product (systolic arterial pressure · heart rate) was 34,500 ± 8,500 in the epinephrine, and 19,900 ± 3,500 in the vasopressin group ($P < 0.05$). Mean arterial pressure and renal, adrenal, and pancreas blood flow further decreased in the epinephrine group during the postresuscitation phase, and were significantly decreased at 30 min compared with the vasopressin pigs (Tables 2–4). There were no differences in Po_2 values during the entire experiment between groups. Epinephrine animals developed a profound metabolic acidosis by 15 min of return of spontaneous circulation, and by 60 min, all epinephrine animals had died. The vasopressin swine had less acidosis, and all survived ≥55 min (Tables 2–4, Figure 2). Calculated mean ± SEM base excess values at 15 and 30 min after return of spontaneous circulation were −13.8 ± 0.5 and −15.3 ± 0.6 in the epinephrine group, and −10.5 ± 0.7 and −8.9 ± 0.6 in the vasopressin group, respectively ($P = 0.001$ at 30 min).

Discussion

Results from this study demonstrate that in this model of hemorrhagic shock and cardiac arrest, immediate CPR rates were similar with both vasopressin and epinephrine. However, in contrast to epinephrine, vasopressin maintained perfusion to the kidneys, minimized acidosis, and sustained life for 1 h after resuscitation. Moreover, epinephrine, but not vasopressin, resulted in severe rebound hypertension during the postresuscitation phase, which may be fatal, especially in the setting of continuing hemorrhage.

Resuscitation from hemorrhagic shock and subsequent cardiac arrest is a major clinical challenge in the

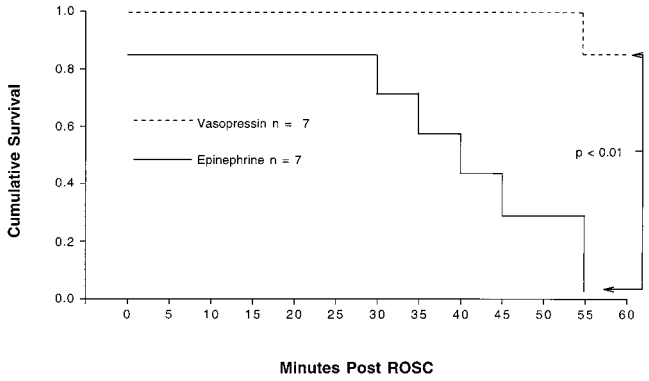

Figure 2. Kaplan-Meier cumulative survival plot for time to death after resuscitation with either 0.8 unit/kg vasopressin (- -) or 200 μg/kg epinephrine (—). No saline placebo pig had return of spontaneous circulation. Percentage of survival is indicated on the *y* axis. Time is given in minutes after return of spontaneous circulation. ROSC = return of spontaneous circulation, defined as an unassisted pulse with a mean arterial pressure ≥ baseline values. The *P* value refers to the statistical significance of the difference of survival between groups over the entire 60-min period.

care of patients after motor vehicle accidents, gunshot or stab wounds, and combat. Furthermore, prehospital treatment of combat casualties differs from civilian trauma for greater difficulties with vascular access, logistic requirements, and longer transport times. Nevertheless, 20% of combat casualties who experienced exsanguination in the battlefield, had wounds in which first aid could have controlled the bleeding (16). In these patients, resuscitation efforts may be worthwhile, and eventually life-saving, even if on-scene treatment is limited. Although we are aware that patients who develop cardiac arrest after hemorrhage usually develop pulseless electrical activity or asystole, there is evidence that severe trauma or penetrating injuries may also cause ventricular fibrillation caused by myocardial contusion or coronary air embolism (17,18). Therefore, our volume-controlled hemorrhagic shock model may reflect a combat scenario, when adequate fluid replacement may be impossible during transport. Accordingly, this study was designed to focus on the first 60 minutes after successful resuscitation with a maximum of two bolus doses of either epinephrine or vasopressin given during cardiac arrest in controlled hemorrhagic shock.

The hemodynamic effects of closed chest external cardiac massage in profound hemorrhagic shock is considered unlikely to provide adequate organ perfusion for trauma victims (18,19). However, when initiating external chest compressions after four minutes of cardiac arrest in our model, coronary perfusion pressure was surprisingly high at approximately 15 mm Hg. In this regard, we speculate that the remaining blood volume in our shock model was just above the threshold which renders resuscitation possible at all. Nevertheless, because it is impossible to estimate the amount of blood loss in the prehospital setting, initiation of external cardiac massage may be worthwhile in hemorrhagic cardiac arrest.

The vasopressin and epinephrine doses we used have been previously shown to provide a similar pressor response (20) and maximal vital organ perfusion during normovolemic cardiac arrest (7). Furthermore, epinephrine doses as large as 200 μg/kg improved resuscitation of asystole and electromechanical dissociation in patients (21), although survival to hospital discharge was not influenced by the epinephrine dose (22). Accordingly, both epinephrine and vasopressin significantly improved coronary perfusion pressure in this model of hemorrhagic shock and ventricular fibrillation, although blood pressure during CPR increased more slowly after vasopressin than after epinephrine (23). However, the increase in coronary perfusion pressure after the administration of both drugs is more acute in the hypovolemic animal, reflecting the smaller distribution volume during hypovolemia.

We observed that large-dose epinephrine resulted in a hyperadrenergic state that included severe hypertension, tachycardia, and subsequently excessive cardiac contractility during the early postresuscitation phase. Berg et al. (24) reported that when 200 μg/kg epinephrine was administered during CPR, there was a resultant hyperadrenergic state with increased arterial blood pressures at five minutes after return of spontaneous circulation; furthermore, large-dose epinephrine was associated with a greater early mortality rate. The marked overshoot in blood pressure, secondary to epinephrine we also observed may exceed the cerebral autoregulation threshold and could be deleterious for trauma patients because of the development of cerebral edema or even enhanced bleeding. Moreover, the epinephrine-treated animals had decreased pH values in both arterial and mixed venous blood, which may be considered indicative of tissue hypoperfusion and anaerobic metabolism (25). The underlying mechanism may be, in part, an excessive epinephrine-mediated β-stimulation, which results in an excessive metabolism that the heart is unable to maintain, especially during low blood flow states, such as during shock and CPR (26). The significantly lower renal perfusion in the epinephrine-treated animals also contributed to the metabolic acidosis. Low pH values depress cardiac function (27) and extraordinarily high myocardial metabolic demands of the immediate postresuscitation phase, as observed in the epinephrine group, further contribute to myocardial lactate accumulation. Accordingly, we speculate that large-dose epinephrine may cause cardiocirculatory failure by critically increasing the myocardial oxygen demand, thus resulting in increased mortality rates in

the postresuscitation phase. Interestingly, large or repeated doses of epinephrine were reported to contribute to circulatory failure as early as 1919 (28).

Our results demonstrate that the administration of vasopressin during CPR resulted in improved hemodynamic stability after return of spontaneous circulation and improved intestinal, adrenal, and renal blood flow during the entire postresuscitation phase, although mean arterial blood pressure was still critically low, ranging between 30 and 40 mm Hg. This is remarkable because such a low blood pressure would normally be insufficient to maintain cardiocirculatory stability and homeostasis. In this regard, vasopressin appears to augment central blood volume by the preferential vasoconstriction of vessels in the skin, limb musculature, and carcass, thus acutely increasing systemic vascular resistance and central venous blood pressure via the V1 receptor (29). The absence of renal blood flow in the postresuscitation phase after large-dose epinephrine was striking and has not been previously reported (7). In contrast, renal and intestinal perfusion after vasopressin were stable for 60 minutes, and more animals in the vasopressin group survived. It is generally thought that renal artery blood flow is the least affected by vasopressin (30), whereas the mesenteric vascular bed is considered to be highly vasopressin sensitive (29,30). It has thus been speculated that the pressor action of endogenous vasopressin may be exerted mainly in the mesenteric vascular territory, and that mesenteric vasoconstriction is the most important factor in the development of irreversible shock (31). Our current findings in hypovolemic shock are supported by recent data demonstrating that although vasopressin decreased gut perfusion in the postresuscitation phase, this effect lasts <30 minutes, and does not impair renal function (32).

Some limitations of the current study should be noted. Although the amount of blood volume removed caused hypovolemic shock and is comparable to results from other investigations (10), we are unable to report whether different exsanguination times or volumes would have yielded different results. Furthermore, the effects of the vasopressors may vary depending on the dosage of vasopressors used. We did not replace intravascular volume during and after resuscitation, and are not able to determine whether adequate infusion therapy would have rendered one-hour survival more likely. Finally, we elected to use a ventricular fibrillation model of cardiac arrest. It is the most straightforward arrhythmia model to control experimentally, because the time between onset of hypovolemic shock and cardiac arrest is important for consistency in the model. Consequently, we do not yet know if our results are applicable in cardiac arrest secondary to asystole and pulseless electrical activity.

In conclusion, treatment of hypovolemic cardiac arrest with vasopressin, but not epinephrine or saline placebo, resulted in sustained vital organ perfusion, less metabolic acidosis in the postresuscitation phase, and subsequently improved survival. Based on these findings, clinical evaluation of vasopressin during hypovolemic cardiac arrest may be warranted.

References

1. Trunkey DD. Trauma. Sci Am 1983;249:28–35.
2. Rosemurgy AS, Norris PA, Olson SM. Prehospital traumatic cardiac arrest: the cost of futility. J Trauma 1993;35:468.
3. Shimazu S, Shatney CH. Outcomes of trauma patients with no vital signs on hospital admission. J Trauma 1983;23:213–6.
4. Suominen P, Räsänen J, Kivioja A. Efficacy of cardiopulmonary resuscitation in pulseless pediatric trauma patients. Resuscitation 1997;36:9–13.
5. Robertson C, Steen P, Adgey J, et al. European Resuscitation Council guidelines for adult advanced life support: a statement from the working group on advanced life support, and approved by the executive committee of the European Resuscitation Council. Resuscitation 1998;37:81–90.
6. Guidelines for cardiopulmonary resuscitation and emergency cardiac care Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part III. Adult advanced cardiac life support. JAMA 1992;268:2199–241.
7. Lindner KH, Prengel AW, Pfenninger EG, et al. Vasopressin improves vital organ blood flow during closed-chest CPR in pigs. Circulation 1995;91:215–21.
8. Lindner KH, Dirks B, Strohmenger HU, et al. A randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1996;349:535–7.
9. Landry DW, Levin HR, Gallant EM, Seo S, et al. Vasopressin pressor hypersensivity in vasodilatory shock. Crit Care Med 1997;25:1279–82.
10. Ericsson BF. Hemodynamic effect of vasopressin: an experimental study in normovolemic and hypovolemic anesthetized dogs. Acta Chir Scand Suppl 1971;414:1–29.
11. Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation 1999;100:226–9.
12. Idris AH, Becker LB, Ornato JP, et al. Utstein-style guidelines for uniform reporting of laboratory CPR research. Resuscitation 1996;33:69–84.
13. Heymann MA, Payne BD, Hoffmann JI, Rudolph AM. Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
14. Hannon JP, Bossone CA, Wade CE. Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci 1990;40:293–8.
15. Lurie KG, Coffeen P, Shultz J, et al. Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. Circulation 1995;91:1629–32.
16. Shoemaker WC, Peitzman AB, Bellamy R, et al. Resuscitation from severe hemorrhage. Crit Care Med 1996;24:S12–23.
17. Cotter G, Moshkovitz Y, Barash P, et al. Ventricular fibrillation in the patient with blunt trauma: not always exsanguination. J Trauma 1996;41:345–7.
18. Mattox KL, Feliciano DV. Role of external cardiac compressions in truncal trauma. J Trauma 1982;2:934–6.
19. Luna GK, Pavlin EG, Kirkman T, et al. Hemodynamic effects of external cardiac massage in trauma shock. J Trauma 1989;29:1430–3.
20. Lindner KH, Ahnefeld AW, Bowdler IM. Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model. Am J Emerg Med 1991;9:27–31.

21. Lindner KH, Ahnefeld FW, Pregel AW. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. Acta Anaesthesiol Scand 1991; 35:253–6.
22. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med 1992;327:1051–5.
23. Mulligan KA, McKnite SH, Lindner KH, et al. Synergistic effects of vasopressin plus epinephrine during cardiopulmonary resuscitation. Resuscitation 1997;35:265–71.
24. Berg RA, Otto CW, Kern KB, et al. High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study. Crit Care Med 1994;22:282–90.
25. Bergman KS, Harris BH. Arterious pH difference: a new index of perfusion. J Pediatr Surg 1988;23:1190–2.
26. Ditchey RV, Rubio-Perez A, Slinker BK. Beta-adrenergic blockade reduces myocardial injury during experimental cardiopulmonary resuscitation. J Am Coll Cardiol 1994;24:804–12.
27. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG. The nature of irreversible shock: experimental and clinical observations. Ann Surg 1964;160:682–710.
28. Erlanger J, Gasser HS. Circulatory failure due to adrenalin. Am J Physiol 1919;49:345–75.
29. Ericsson BF. Effect of vasopressin on the distribution of cardiac output and organ blood flow in the anesthetized dog. Acta Chir Scand 1971;137:729–38.
30. Reid IA, Schwartz J. Role of vasopressin in the control of blood pressure. Front Neuroendocrinol 1984;8:177–97.
31. Errington ML, Rocha E Silva M. Vasopressin clearance and secretion during hemorrhage in normal dogs and in dogs with experimental diabetes insipidus. J Physiol 1972;227:395–418.
32. Voelckel WG, Lindner KH, Wenzel V, et al. Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. Crit Care Med 2000;28:1083–8.