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## A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation

Volker Wenzel, M.D., Anette C. Krismer, M.D., H. Richard Arntz, M.D.,  
Helmut Sitter, Ph.D., Karl H. Stadlbauer, M.D., and Karl H. Lindner, M.D.,  
for the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group\*

### ABSTRACT

#### BACKGROUND

Vasopressin is an alternative to epinephrine for vasopressor therapy during cardiopulmonary resuscitation, but clinical experience with this treatment has been limited.

#### METHODS

We randomly assigned adults who had had an out-of-hospital cardiac arrest to receive two injections of either 40 IU of vasopressin or 1 mg of epinephrine, followed by additional treatment with epinephrine if needed. The primary end point was survival to hospital admission, and the secondary end point was survival to hospital discharge.

#### RESULTS

A total of 1219 patients underwent randomization; 33 were excluded because of missing study-drug codes. Among the remaining 1186 patients, 589 were assigned to receive vasopressin and 597 to receive epinephrine. The two treatment groups had similar clinical profiles. There were no significant differences in the rates of hospital admission between the vasopressin group and the epinephrine group either among patients with ventricular fibrillation (46.2 percent vs. 43.0 percent,  $P=0.48$ ) or among those with pulseless electrical activity (33.7 percent vs. 30.5 percent,  $P=0.65$ ). Among patients with asystole, however, vasopressin use was associated with significantly higher rates of hospital admission (29.0 percent vs. 20.3 percent in the epinephrine group;  $P=0.02$ ) and hospital discharge (4.7 percent vs. 1.5 percent,  $P=0.04$ ). Among 732 patients in whom spontaneous circulation was not restored with the two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group, but not in the epinephrine group (hospital admission rate, 25.7 percent vs. 16.4 percent;  $P=0.002$ ; hospital discharge rate, 6.2 percent vs. 1.7 percent;  $P=0.002$ ). Cerebral performance was similar in the two groups.

#### CONCLUSIONS

The effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.

From the Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens University, Innsbruck, Austria (V.W., A.C.K., K.H.S., K.H.L.); the Department of Medicine, Division of Cardiology-Pulmonology, Benjamin Franklin Medical Center, Free University, Berlin, Germany (H.R.A.); and the Institute for Theoretical Surgery, Philipps University, Marburg, Germany (H.S.). Address reprint requests to Dr. Lindner at the Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens University, Anichstr. 35, 6020 Innsbruck, Austria, or at volker.wenzel@uibk.ac.at.

\*The investigators who participated in the study group are listed in the Appendix.

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**T**HERE ARE MORE THAN 600,000 SUDDEN deaths in North America and Europe each year. More than half of these deaths occur before 65 years of age, which underscores the need for optimal cardiopulmonary resuscitation (CPR) strategies in order to improve patients' chances of survival.

Epinephrine has been used during CPR for more than 100 years<sup>1</sup> but has become controversial because it is associated with increased myocardial oxygen consumption, ventricular arrhythmias, and myocardial dysfunction during the period after resuscitation.<sup>2</sup> Since it was found that endogenous vasopressin levels in successfully resuscitated patients were significantly higher than levels in patients who died, it was postulated that it might be beneficial to administer vasopressin during CPR.<sup>3</sup> Laboratory studies of CPR revealed that vasopressin was associated with better blood flow to vital organs,<sup>4</sup> delivery of cerebral oxygen,<sup>5</sup> chances of resuscitation,<sup>6,7</sup> and neurologic outcome<sup>8</sup> than epinephrine. In a small clinical study, the use of vasopressin resulted in a significantly higher rate of short-term survival than epinephrine,<sup>9</sup> indicating that vasopressin may be a reasonable alternative to epinephrine for vasopressor therapy during CPR.

The current international guidelines for CPR recommend the use of epinephrine during cardiac resuscitation, with vasopressin considered only as a secondary alternative, because clinical data on vasopressin therapy have been limited.<sup>10,11</sup> We therefore conducted a clinical trial to assess the effects of vasopressin and epinephrine on survival among adults who have an out-of-hospital cardiac arrest and present with ventricular fibrillation, pulseless electrical activity, or asystole. The null hypothesis was that there would be no differences between the treatment groups in the rates of survival to hospital admission and survival to hospital discharge.

## METHODS

### STUDY PATIENTS

This study was conducted in 33 communities and involved 44 physician-staffed emergency medical service units in Austria, Germany, and Switzerland. Adult patients who had an out-of-hospital cardiac arrest and presented with ventricular fibrillation, pulseless electrical activity, or asystole requiring CPR with vasopressor therapy were included; the criteria for exclusion were successful defibrillation without the administration of a vasopressor, documented

terminal illness, a lack of intravenous access, hemorrhagic shock, pregnancy, cardiac arrest after trauma, an age of less than 18 years, and the presence of a do-not-resuscitate order.

### STUDY DESIGN

The study was designed as a double-blind, prospective, multicenter, randomized, controlled clinical trial; the primary end point was survival to hospital admission, and the secondary end point was survival to hospital discharge. The protocol was approved by the institutional review board of each participating center. For all patients, the requirement of informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.<sup>12</sup> The patients' families and surviving patients were informed about the trial, and the protocol specified that if there were any objections, the patient would be withdrawn from the study; there were no objections. Treatment assignments to the study drugs were randomly generated in blocks of 10, with stratification according to center. If all criteria for inclusion were met and none of the criteria for exclusion were met, patients who presented with pulseless electrical activity or asystole underwent randomization immediately; patients with ventricular fibrillation underwent randomization after the first three attempts at defibrillation had failed.

When a given patient underwent randomization, a box containing the study drugs — either two ampules of 1 mg of epinephrine (Suprarenin) or two ampules of 40 IU of vasopressin (Pitressin) — was opened, and either 1 mg of epinephrine or 40 IU of vasopressin was injected. The authenticity of both drugs was confirmed with the use of high-pressure liquid chromatography. If spontaneous circulation was not restored within three minutes after the first injection of the study drug, the same drug at the same dose was injected again. If spontaneous circulation was still not restored, the patient was given an additional injection of epinephrine at the discretion of the emergency physician who was managing the CPR attempt. All drugs were injected exclusively intravenously, followed by 20 ml of normal saline.

Investigators and physicians were unaware of the study-drug assignment unless decoding became clinically necessary for management in the period after resuscitation; if this occurred, the data and

safety monitoring committee was to be informed. Additional interventions such as the administration of sodium bicarbonate, atropine, lidocaine, or amiodarone and fibrinolysis were used at the discretion of the physician managing the CPR attempt.

**DOCUMENTATION**

The CPR attempt was documented according to the Utstein style<sup>13</sup>; data were entered into a data base by one investigator and were subsequently independently cross-checked twice by two other investigators who were unaware of the treatment-group assignment. Original data were made available to the data and safety monitoring committee for independent scrutiny. Neurologic function in the surviving patients was categorized according to a cerebral performance score.<sup>14</sup>

**STATISTICAL ANALYSIS**

An estimation of the number of patients needed was derived during the analysis of another study of out-of-hospital cardiac arrest.<sup>15</sup> The calculation was based on a possible drug-related improvement in the outcome of 25 percent, a significance level of 0.05, two-tailed analysis, and a power of 80 percent. According to this calculation, 571 patients per group might be necessary in order to show a clinically significant difference in the rates of hospital admission between the two treatment groups; the addition of a safety margin of 30 percent resulted in an estimate of 1500 patients for the entire trial. Analysis was performed according to the intention-to-treat principle; the chi-square test was used to determine differences between groups with respect to the primary and secondary end points. Odds ratios and their 95 percent confidence intervals were calculated. Comparisons of patient characteristics and survival outcomes were tested with the chi-square test, the chi-square test for trend, Fisher’s exact test, or Student’s t-test, as appropriate. Logistic-regression analysis was used to control for possible confounding effects of variables related to the different end points. All P values are two-sided; no corrections were made for multiple comparisons.

**RESULTS**

The study was conducted from June 1999 to March 2002; only one internal, blinded administrative interim analysis was performed in June 2000 after the randomization of 200 patients, and the results were revealed only to the data and safety monitoring com-

mittee. This analysis established that the study was safe, that randomization was working properly, and that no adverse events had been reported. Since funding had ended by December 2001, enrollment was stopped in March 2002. The treatment groups had similar clinical profiles (Tables 1 and 2); 88 of the patients who underwent randomization were later shown to meet criteria for exclusion, but they were included in the final analysis on an intention-to-treat basis. Thirty-three patients had to be excluded from the analysis because of a missing study-drug code (the characteristics of the patients who were included were similar to those of the patients who were excluded), and no significant differences were observed among different centers (Fig. 1).

The rate of survival to hospital admission was higher among patients with a witnessed cardiac arrest than among those with an unwitnessed cardiac arrest (352 of 920 patients [38.3 percent] vs. 41 of 255 patients [16.1 percent],  $P < 0.001$ ), and the rate was higher among patients who received basic life support within 10 minutes than among those who received such support more than 10 minutes after the cardiac arrest (291 of 665 patients [43.8 percent] vs. 107 of 517 patients [20.7 percent],  $P < 0.001$ ). The rates of hospital admission were similar between the two treatment groups both for patients with ventricular fibrillation and for those with pulseless electrical activity. Patients with asystole, however, were more likely to survive to hospital admission and to hospital discharge if they were treated with vasopressin than if they received epinephrine as initial therapy (Table 3). In an analysis including 732 patients in whom spontaneous circulation was not restored with the administration of the study

**Table 1. Cardiovascular History of the Patients.**

Variable	Vasopressin Group (N=589)	Epinephrine Group (N=597)	P Value
	<i>no./total no. (%)</i>		
Coronary heart disease	176/467 (37.7)	189/463 (40.8)	0.33
Hypertension	84/475 (17.7)	82/474 (17.3)	0.88
Diabetes	78/476 (16.4)	78/477 (16.4)	0.99
Left ventricular failure	59/467 (12.6)	59/468 (12.6)	0.99
Peripheral vascular disease	47/474 (9.9)	53/475 (11.2)	0.53
Cardiac arrhythmias	35/467 (7.5)	29/468 (6.2)	0.43
Pacemaker	20/474 (4.2)	18/474 (3.8)	0.74
Valvular heart disease	13/468 (2.8)	14/468 (3.0)	0.85
Cardiomyopathy	8/468 (1.7)	9/468 (1.9)	0.81

**Table 2. Base-Line Characteristics of the Patients.\***

Characteristic	Vasopressin Group (N=589)	Epinephrine Group (N=597)	P Value
Age — yr	66.5±14.4	65.9±14.2	0.45
Male sex — no./total no. (%)	402/580 (69.3)	421/591 (71.2)	0.47
Arrest witnessed — no./total no. (%)	448/583 (76.8)	472/592 (79.7)	0.53
CPR by bystander or family member — no./total no. (%)	111/589 (18.8)	107/597 (17.9)	0.68
Suspected cause of cardiac arrest — no./total no. (%)			
Myocardial infarction	262/454 (57.7)	249/449 (55.5)	0.49
Primary arrhythmia	99/455 (21.8)	109/452 (24.1)	0.40
Pulmonary embolism	64/456 (14.0)	53/455 (11.6)	0.28
Additional treatments given during CPR — no./total no. (%)			
Sodium bicarbonate	198/587 (33.7)	205/596 (34.4)	0.81
Atropine	139/587 (23.7)	151/597 (25.3)	0.51
Lidocaine	114/589 (19.4)	114/597 (19.1)	0.90
Amiodarone	75/589 (12.7)	88/597 (14.7)	0.32
Fibrinolysis	54/589 (9.2)	45/597 (7.5)	0.31
Initial cardiac rhythm — no./total no. (%)			
Ventricular fibrillation	223/589 (37.9)	249/597 (41.7)	0.18
Pulseless electrical activity	104/589 (17.7)	82/597 (13.7)	0.06
Asystole	262/589 (44.5)	266/597 (44.6)	0.98
Intervals — min†			
Duration of untreated cardiac arrest (before basic life support provided)	7.9±6.4	7.9±6.4	0.94
Time from basic life support			
To first defibrillation attempt	7.0±6.8	7.7±7.6	0.18
To endotracheal intubation	7.6±6.2	7.9±6.8	0.39
To intravenous cannulation	8.2±6.7	8.5±7.0	0.37
To first injection of study drug	9.6±6.6	10.2±7.4	0.15
To second defibrillation attempt	12.9±7.6	13.9±8.1	0.14
To second injection of study drug	13.3±6.8	13.9±7.9	0.16
To third defibrillation attempt	17.7±8.4	18.4±9.5	0.37
To standard protocol with epinephrine	17.5±7.9	17.6±8.3	0.91
To hospital admission	51.6±17.3	49.0±18.1	0.14

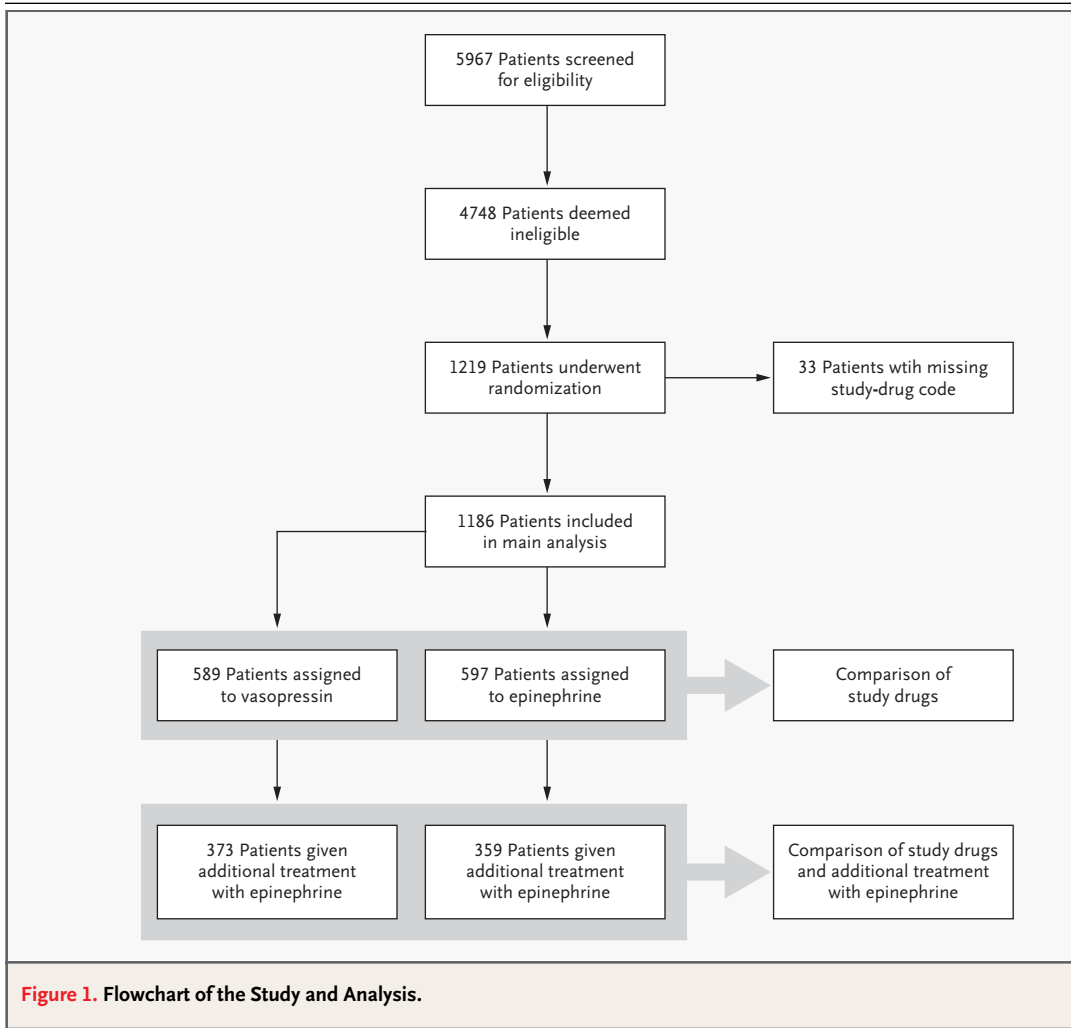
\* Plus–minus values are means ±SD. CPR denotes cardiopulmonary resuscitation.

† Intervals are given separately for the duration of untreated cardiac arrest and the periods from the provision of basic life support to each treatment procedure because bystanders may not have been able to judge the intervals accurately, owing to emotional stress.

drug, additional treatment with epinephrine (median dose, 5 mg; interquartile range, 2 to 10) resulted in a significant improvement in the survival rate in the vasopressin group ( $P=0.007$  by the chi-square test for trend) but not in the epinephrine group (Table 4). There was no significant difference between the two groups in cerebral performance (Tables 3 and 4).

With both study drugs, the rate of survival to

hospital admission was significantly improved by both amiodarone treatment (79 of 163 patients [48.5 percent] vs. 321 of 1023 patients [31.4 percent];  $P<0.001$ ; odds ratio, 2.1; 95 percent confidence interval, 1.5 to 2.9) and fibrinolysis (45 of 99 patients [45.5 percent] vs. 355 of 1087 patients [32.7 percent];  $P=0.01$ ; odds ratio, 1.7; 95 percent confidence interval, 1.1 to 2.6). After hospital admission, the code for the study drug was broken (the



treatment assignment was disclosed) for five patients in order to optimize post-resuscitation care.

## DISCUSSION

Our results did not confirm previous data that showed vasopressin to be more effective than epinephrine as adjunctive therapy in the treatment of patients with ventricular fibrillation and pulseless electrical activity.<sup>4-9</sup> This discrepancy raises the question of whether vasopressin improves perfusion pressures during CPR in patients with these conditions but does not improve the outcome.<sup>16</sup> Similarly, although some studies in animals have suggested that high-dose epinephrine during CPR has beneficial effects, this strategy caused a hyperadrenergic state and was associated with higher early mortality in other studies that used a preparation for pigs.<sup>17</sup>

Subsequent clinical studies with high-dose epinephrine did not show any benefit.<sup>2</sup> We were unable to determine whether problems in extrapolating from CPR performed in the laboratory to clinical experience were attributable to differences among species, the fact that our patients had underlying disease whereas the laboratory animals were otherwise healthy, or differences between out-of-hospital CPR and CPR performed under laboratory conditions.

In contrast to the findings regarding patients with ventricular fibrillation or pulseless electrical activity, we found that among patients with asystole, those who received vasopressin were about 40 percent more likely than those given epinephrine to reach the hospital alive. The extreme ischemia in patients with asystole may suggest a possible underlying mechanism. As has been shown in an *in vitro* study, vasopressin has vasoconstricting efficacy

**Table 3. Data on Outcomes in All 1186 Patients and on Cerebral Performance in 115 Patients at Hospital Discharge.\***

Variable	Vasopressin Group (N=589)	Epinephrine Group (N=597)	P Value	Odds Ratio (95% CI)
<i>no./total no. (%)</i>				
All patients				
Spontaneous circulation restored with study drugs	145/589 (24.6)	167/597 (28.0)	0.19	1.2 (0.9–1.5)
Hospital admission	214/589 (36.3)	186/597 (31.2)	0.06	0.8 (0.6–1.0)
Hospital discharge	57/578 (9.9)	58/588 (9.9)	0.99	1.0 (0.7–1.5)
Ventricular fibrillation				
Spontaneous circulation restored with study drugs	82/223 (36.8)	106/249 (42.6)	0.20	1.3 (0.9–1.8)
Hospital admission	103/223 (46.2)	107/249 (43.0)	0.48	0.9 (0.6–1.3)
Hospital discharge	39/219 (17.8)	47/245 (19.2)	0.70	1.1 (0.7–1.8)
Pulseless electrical activity				
Spontaneous circulation restored with study drugs	21/104 (20.2)	17/82 (20.7)	0.93	1.0 (0.5–2.1)
Hospital admission	35/104 (33.7)	25/82 (30.5)	0.65	0.8 (0.5–1.6)
Hospital discharge	6/102 (5.9)	7/81 (8.6)	0.47	1.4 (0.5–4.7)
Asystole				
Spontaneous circulation restored with study drugs	42/262 (16.0)	44/266 (16.5)	0.87	1.0 (0.7–1.6)
Hospital admission	76/262 (29.0)	54/266 (20.3)	0.02	0.6 (0.4–0.9)
Hospital discharge	12/257 (4.7)	4/262 (1.5)	0.04	0.3 (0.1–1.0)
Cerebral performance among all patients who survived to discharge				
Good cerebral performance	15/46 (32.6)	16/46 (34.8)	0.99	
Moderate cerebral disability	7/46 (15.2)	12/46 (26.1)	0.30	
Severe cerebral disability	9/46 (19.6)	7/46 (15.2)	0.78	
Coma or vegetative state	15/46 (32.6)	11/46 (23.9)	0.49	

\* Eleven patients in the vasopressin group (1.9 percent) and nine in the epinephrine group (1.5 percent) were lost to follow-up before hospital discharge. Eleven of the patients in the vasopressin group and 12 of the patients in the epinephrine group who survived to hospital discharge (19.3 percent and 20.7 percent, respectively) were lost to follow-up for cerebral performance. P values were not adjusted for multiple comparisons. An odds ratio of less than 1.0 represents an advantage for vasopressin. CI denotes confidence interval.

even in severe acidosis, when catecholamines are less potent.<sup>18</sup> Thus, vasopressin may be a more effective vasopressor than epinephrine in patients with asystole, resulting in better coronary perfusion pressure during cardiac resuscitation. Since improved coronary perfusion pressure during CPR improves survival,<sup>19</sup> vasopressin may be a better option than epinephrine for patients with asystole, who normally have the worst chance of survival of all patients with cardiac arrest. This post hoc observation could be tested in a trial restricted to such patients, for whom few treatment options are available.

In addition, improvement in the rate of survival to hospital discharge among patients who were treated with epinephrine after vasopressin may indicate that the interactions among vasopressin, epinephrine, and the underlying degree of ischemia during CPR may be more complex than was previ-

ously thought. When prolonged asphyxia has depleted endogenous epinephrine levels and caused fundamental ischemia in pigs, the administration of vasopressin combined with epinephrine results in coronary perfusion pressures triple those achieved with either epinephrine or vasopressin alone.<sup>20</sup> This finding suggests that the presence of one of these drugs may enhance the effects of the other, especially during prolonged ischemia. These data from experimental CPR are in agreement with the results of our current clinical trial, in which the combination of vasopressin and epinephrine was effective in patients about 25 minutes after cardiac arrest, at a time when a severe degree of ischemia must be assumed, but increasing doses of epinephrine alone were not effective.

In a recent study of in-hospital CPR in which vasopressin and epinephrine were reported to have

**Table 4. Data on Outcomes in 732 Patients Who Initially Received Vasopressin or Epinephrine and Subsequently Received Additional Treatment with Epinephrine and on Cerebral Performance in 29 Patients at Hospital Discharge.\***

Variable	Vasopressin Group (N=373)	Epinephrine Group (N=359)	P Value	Odds Ratio (95% CI)
All patients	<i>no./total no. (%)</i>			
Spontaneous circulation restored	137/373 (36.7)	93/359 (25.9)	0.002	0.6 (0.4–0.8)
Hospital admission	96/373 (25.7)	59/359 (16.4)	0.002	0.6 (0.4–0.8)
Hospital discharge	23/369 (6.2)	6/355 (1.7)	0.002	0.3 (0.1–0.6)
Ventricular fibrillation				
Spontaneous circulation restored	58/122 (47.5)	40/122 (32.8)	0.02	0.5 (0.3–0.9)
Hospital admission	37/122 (30.3)	25/122 (20.5)	0.08	0.6 (0.3–1.1)
Hospital discharge	13/121 (10.7)	6/121 (5.0)	0.09	0.4 (0.2–1.2)
Pulseless electrical activity				
Spontaneous circulation restored	18/64 (28.1)	14/56 (25.0)	0.70	0.8 (0.4–1.8)
Hospital admission	17/64 (26.6)	10/56 (17.9)	0.25	0.6 (0.2–1.4)
Hospital discharge	3/64 (4.7)	0/55	0.10	
Asystole				
Spontaneous circulation restored	61/187 (32.6)	39/181 (21.5)	0.02	0.6 (0.4–0.9)
Hospital admission	42/187 (22.5)	24/181 (13.3)	0.02	0.5 (0.3–0.9)
Hospital discharge	7/184 (3.8)	0/179	0.008	
Cerebral performance among all patients who survived to discharge				
Good cerebral performance	8/20 (40.0)	2/5 (40.0)	1.00	
Moderate cerebral disability	2/20 (10.0)	2/5 (40.0)	0.17	
Severe cerebral disability	2/20 (10.0)	1/5 (20.0)	0.50	
Coma or vegetative state	8/20 (40.0)	0/5	0.14	

\* Four patients in the vasopressin group (1.1 percent) and four in the epinephrine group (1.1 percent) were lost to follow-up before hospital discharge. Three of the patients in the vasopressin group and one patient in the epinephrine group who survived to hospital discharge (17.4 percent and 16.7 percent, respectively) were lost to follow-up for cerebral performance. P values are not adjusted for multiple comparisons. An odds ratio of less than 1.0 represents an advantage for vasopressin. CI denotes confidence interval.

similar effects, 87 percent of the patients in the vasopressin group also received epinephrine.<sup>21</sup> The usefulness of the deliberate administration of the combination of vasopressin and epinephrine during CPR is supported by clinical observations that the administration of epinephrine followed by vasopressin significantly improved coronary perfusion pressure,<sup>22</sup> the likelihood of restoration of spontaneous circulation,<sup>23</sup> and 24-hour survival rates.<sup>24</sup> The potential of this approach was demonstrated in our study by the improvement in the rates of survival to hospital discharge.

Among patients who needed additional treatment with epinephrine, many patients with a good neurologic outcome received the combination of vasopressin and epinephrine, but this strategy also resulted in an increase in the number of comatose

patients as compared with the use of epinephrine alone, although the difference was not statistically significant. This finding indicates that the combination of vasopressin and epinephrine effectively restored heart function but took effect too late to restore brain function in some patients. When one is starting a CPR attempt, it is difficult to predict what the level of brain function will be after resuscitation.<sup>25</sup> For example, of five patients with asystole in whom no bystander performed CPR (indicating that they had severe prolonged ischemia) who were resuscitated with the combination of vasopressin and epinephrine, four remained comatose, and only one had good cerebral performance at hospital discharge.

A multivariate analysis confirmed the results of previous investigations showing that patients whose

cardiac arrest was witnessed had a chance of survival more than twice that of patients who had an unwitnessed cardiac arrest, because CPR could be initiated earlier.<sup>26</sup> Correspondingly, the provision of basic life support within 10 minutes after the cardiac arrest resulted in a doubling of the rate of survival to hospital admission, validating the fundamental value of the early provision of basic life support.<sup>27</sup> In our trial, amiodarone and fibrinolysis were administered at the discretion of the physician who was managing the CPR attempt. Both of these interventions resulted in improved rates of survival to hospital admission, as has also been shown in other studies.<sup>28,29</sup>

Our study had some important limitations. Fewer patients underwent randomization than we intended, and the primary end point of survival to hospital admission is not optimal but is realistic for a trial of this type. The clinical care of successfully resuscitated patients in the emergency room, intensive care unit, ward, and rehabilitation facilities may vary among hospitals and could not be standardized by our study protocol, but it may have profoundly influenced outcomes. We did not collect dose-response data, and the cause of cardiac arrest could not be verified; both factors may have affected the success of CPR. Although the rate of survival to hospital discharge (9.7 percent) compares favorably with those cited in other reports, 2.2 per-

cent of our patients were comatose at hospital discharge before being transferred to a rehabilitation facility. Our data do not show whether hypothermia during the period after resuscitation could also have improved neurologic recovery, as has recently been described.<sup>25</sup>

In conclusion, the effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole. The use of vasopressin followed by epinephrine may be more effective than the use of epinephrine alone in patients with refractory cardiac arrest.

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#### APPENDIX

The following investigators participated in the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group (the number of patients enrolled at each center is given in parentheses): *Data monitoring committee* — D.A. Chamberlain (chair), University of Wales College of Medicine, Cardiff; W.F. Dick, Johannes-Gutenberg University, Mainz, Germany; L.L. Bossaert, P. Bruyneel, Antwerp University, Edegem, Belgium; *data analysis* — H. Sitter, H. Prünte, Institute for Theoretical Surgery, Philipps-University, Marburg, Germany; *central coordinating office* — V. Wenzel (chair); A.C. Krismer, K.H. Stadlbauer, V.D. Mayr, H.G. Lienhart, Leopold-Franzens University, Innsbruck, Austria, and Dispatchers of the Austrian Red Cross Emergency Medical Service, Innsbruck, Austria; *emergency medical service investigators* — H.R. Arntz, J. Breckwoldt, Benjamin Franklin Medical Center, Free University, Berlin, Germany (126); M.A. Baubin, W.G. Voelckel, Leopold-Franzens University, Innsbruck, Austria (115); M. Toursarkissian, German Red Cross Hospital Westend, Berlin, Germany (92); M.M. Menges, A. Jenner, Humboldt Hospital, Berlin, Germany (73); G. Prause, J. Kainz, Karl-Franzens University, Graz, Austria (65); M. Messelken, Hospital at Eichert, Göppingen, Germany (59); H.P. Milz, A. Röper, City Hospital, Center Campus, Bielefeld, Germany (54); F.L. Bertschat, Humboldt University, Virchow Campus, Berlin, Germany (49); G. Bürkle, F. Koberne, St. Josef's Hospital, Freiburg, Germany (48); G. Bandemer, A. Callies, Central Hospital Left of the Weser River, Bremen, Germany (47); B. Schmitz, J. Schüttler, Friedrich-Alexander University, Erlangen, Germany (45); T. Wilde, General Hospital Wandsbek, Hamburg, Germany (38); K. Ellinger, S. Burfeind, H.V. Genzwürker, Ruprecht-Karls University, Mannheim, Germany (34); J. Koppenberg, University Hospital, Regensburg, Germany (32); U. Ebmeyer, Otto-von-Guericke University, Magdeburg, Germany (31); B. Dirks, B. Lehle, University Hospital, Ulm, Germany (28); W. Ummenhofer, R. Albrecht, University Hospital, Basel, Switzerland (27); H. Trimmel, N. Gaberszig, County Hospital, Wiener Neustadt, Austria (27); J. Beneker, Trauma Hospital, Berlin, Germany (26); T. Schlechtriemen, K.-H. Altemeyer, City Hospital Winterberg, Saarbrücken, Germany (26); H. Wauer, T. Geyer, Humboldt University, Campus Charité, Berlin, Germany (25); S. Kleinschmidt, W. Wilhelm, Saarland University, Homburg, Germany (22); P. Lauber, R. Cartarius, St. Theresia Caritas Hospital, Saarbrücken, Germany (20); B.W. Böttiger, M. Bujard, Ruprecht-Karls University, Heidelberg, Germany (17); J. Switalski, G. Hemicker, City Hospital, Leverkusen, Germany (17); R. Lenz, County Hospital, St. Gallen, Switzerland (17); J. Koster, Cardiac Center, Bad Krozingen, Germany (14); F.U. Hahne, G. Edelhoff, County Hospital, Emmendingen, Germany (11); I. Besmer, County Hospital, Lucerne, Switzerland (11); P. Tietze-Schnur, Emergency Medical Service, Zeven, Germany (11); L. Fischer, Ernst-Moritz-Arndt University, Greifswald, Germany (8); D. Poppelbaum, Oskar-Ziethen Hospital, Berlin, Germany (4).

## REFERENCES

1. Gottlieb R. Ueber die Wirkung der Nennieren Extracte auf Herz und Blutdruck. *Arch Exp Path Pharmacol* 1896-97;38:99-112.
2. Paradis NA, Wenzel V, Southall J. Pressor drugs in the treatment of cardiac arrest. *Cardiol Clin* 2002;20:61-78.
3. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992;77:662-8.
4. Lindner KH, Prengel AW, Pfenninger EG, et al. Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. *Circulation* 1995;91:215-21.
5. Prengel AW, Lindner KH, Keller A. Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. *Stroke* 1996;27:1241-8.
6. Wenzel V, Lindner KH, Prengel AW, et al. Vasopressin improves vital organ blood flow after prolonged cardiac arrest with post-countershock pulseless activity in pigs. *Crit Care Med* 1999;27:486-92.
7. Wenzel V, Lindner KH, Krismer AC, Miller EA, Voelckel WG, Lingnau W. Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs. *Circulation* 1999;99:1379-84.
8. Wenzel V, Lindner KH, Krismer AC, et al. Survival with full neurologic recovery and no cerebral pathology after prolonged cardiopulmonary resuscitation with vasopressin in pigs. *J Am Coll Cardiol* 2000;35:527-33.
9. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997;349:535-7.
10. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. *Circulation* 2000;102:Suppl:I-1-I-384.
11. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: an international consensus on science. *Resuscitation* 2000;46:1-447.
12. Human Medicines Evaluation Unit. Note for guidance on good clinical practice (Clinical Practice Medicinal Products [CPMP]/International Conference on Harmonization [ICH]/135/95). In: Guidelines for good clinical practice. ICH topic E6. London: European Agency for the Evaluation of Medicinal Products, 1995:1-58.
13. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style: a statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991;84:960-75.
14. The Brain Resuscitation Clinical Trial II Study Group. A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest: design, methods, and patient characteristics. *Control Clin Trials* 1991;12:525-45.
15. Schneider T, Martens PR, Paschen H, et al. Multicenter, randomized, controlled trial of 150-J biphasic shocks compared with 200- to 360-J monophasic shocks in the resuscitation of out-of-hospital cardiac arrest victims. *Circulation* 2000;102:1780-7.
16. Babar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. *Resuscitation* 1999;41:185-92.
17. 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.
18. Fox AW, May RE, Mitch WE. Comparison of peptide and nonpeptide receptor-mediated responses in rat tail artery. *J Cardiovasc Pharmacol* 1992;20:282-9.
19. Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990;263:1106-13.
20. Mayr VD, Wenzel V, Voelckel WG, et al. Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. *Circulation* 2001;104:1651-6.
21. Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001;358:105-9.
22. Morris DC, Dereczyk BE, Grzybowski M, et al. Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. *Acad Emerg Med* 1997;4:878-83.
23. Lindner KH, Prengel AW, Brinkmann A, Strohmenger HU, Lindner IM, Lurie KG. Vasopressin administration in refractory cardiac arrest. *Ann Intern Med* 1996;124:1061-4.
24. Grmec Š, Kamenik B, Mally Š, et al. Vasopressin in refractory out-of-hospital ventricular fibrillation: preliminary results. *Crit Care* 2002;6:Suppl 1:P162. abstract.
25. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549-56. [Erratum, *N Engl J Med* 2002;346:1756.]
26. Eisenberg MS, Mengert TJ. Cardiac resuscitation. *N Engl J Med* 2001;344:1304-13.
27. Hallstrom A, Cobb L, Johnson E, Copass M. Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. *N Engl J Med* 2000;342:1546-53.
28. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341:871-8.
29. Böttiger BW, Bode C, Kern S, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. *Lancet* 2001;357:1583-5.

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