

Stress Hormone Response during and after Cardiopulmonary Resuscitation

Karl H. Lindner, M.D.,* Hans U. Strohmenger, M.D.,* Hermann Ensinger, M.D.,* Wulf D. Hetzel, M.D.,†
Friedrich W. Ahnefeld, M.D.,‡ Michael Georgieff, M.D.‡

The purpose of this study was to assess whether plasma adrenocorticotropic, cortisol, vasopressin, and renin concentrations are higher in resuscitated than in nonresuscitated patients during cardiopulmonary resuscitation, and whether there are possible correlations between these hormones and blood pressure or heart rate in the immediate postresuscitation phase. Of 34 consecutive patients (36-85 yr of age) with out-of-hospital cardiac arrest, 20 could be successfully resuscitated and admitted to hospital, whereas in the remaining 14 patients restoration of spontaneous circulation could not be achieved. During cardiopulmonary resuscitation, median adrenocorticotropic, cortisol, vasopressin, and renin concentrations in the external jugular vein were 237 pg/ml, 32.6 µg/dl, 122 pg/ml, and 46.5 ng/l, respectively, in resuscitated patients, and 45 pg/ml ($P = 0.018$), 18.4 µg/dl ($P = 0.481$), 88 pg/ml ($P = 0.049$), and 11 ng/l ($P = 0.017$), respectively, in nonresuscitated patients. Median adrenocorticotropic, cortisol, vasopressin, and renin concentrations were 101 pg/ml, 34.6 µg/dl, 22 pg/ml, and 25 ng/l, respectively, 60 min after successful resuscitation. No significant correlations were found between hormone levels and blood pressure or heart rate, but there was a significant negative correlation between the interval from collapse to the start of cardiopulmonary resuscitation and plasma cortisol concentrations during cardiopulmonary resuscitation (Spearman rank correlation coefficient = -0.967 , $P < 0.001$), indicating an impaired cortisol release from the adrenal cortex. The lower hormone concentrations of the nonresuscitated patients measured during cardiopulmonary resuscitation might indicate an impairment in neuroendocrine response. (Key words: Heart: cardiopulmonary resuscitation. Hormones: adrenocorticotropic, cortisol; vasopressin (antidiuretic hormone).)

IN RECENT YEARS it has been postulated that cardiac arrest and cardiopulmonary resuscitation (CPR) are the most severe forms of stress to which the organism can be subjected.¹ Cardiac arrest and the subsequent activation of the sympathetic nervous system trigger the release of epinephrine and norepinephrine from the adrenal medulla; in addition, there is spill-over of the norepinephrine released from sympathetic nerve terminals.^{2,3} These responses lead to the highest epinephrine and norepinephrine concentrations recorded in either humans or animals.⁴⁻⁶ During CPR, extremely high plasma cate-

cholamine concentrations are necessary to cause peripheral vasoconstriction and a redistribution of blood flow to the myocardium and cerebrum.⁷

Acute stress also stimulates the secretion of anterior and posterior pituitary hormones such as adrenocorticotropic (ACTH) and arginine vasopressin (antidiuretic hormone), a polypeptide synthesized by the nerve cells of the supraoptic and paraventricular nuclei of the hypothalamus.⁸ ACTH in turn stimulates the production of cortisol, which is an important factor in protecting the organism from stress in that it acts synergistically with catecholamines.⁹

The role of other vasopressor systems such as arginine vasopressin and renin-angiotensin have not, as yet, been evaluated during and after CPR in humans or in animals. A potential interaction between the sympathoadrenal system, arginine vasopressin, and the renin-angiotensin system might play an important part in the maintenance of perfusion pressures during CPR and therefore could influence resuscitation success. The plasma concentrations of ACTH, cortisol, arginine vasopressin, and renin during and after CPR have not been studied in humans with out-of-hospital cardiac arrest, nor have possible correlations between these hormone concentrations and blood pressure and heart rate been investigated in the immediate postresuscitation period. In addition to addressing these questions, we investigated whether the plasma concentrations of these substances are higher in patients who are successfully resuscitated than in those who are not. To do this, we measured the concentrations of the aforementioned hormones in patients being treated for out-of-hospital cardiac arrest and correlated these results with hemodynamic and clinical variables.

Materials and Methods

The study group consisted of 34 consecutively treated adults who had suffered an out-of-hospital cardiac arrest. CPR was performed in accordance to the 1986 recommendations of the American Heart Association and was supervised by a physician of the Emergency Care Department of Ulm University Hospital. All patients received 1 mg epinephrine intravenously every 5 min during CPR. The mean total dose of epinephrine administered to the 20 patients was 2.00 ± 0.18 mg (range 1-4 mg). During this period, spontaneous circulation was not restored in any patient, and CPR measures had to be continued. So-

* Staff Anesthesiologist.

† Professor of Internal Medicine.

‡ Professor of Anesthesiology.

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Address reprint requests to Dr. Lindner: Universitätsklinik für Anästhesiologie, Klinikum der Universität Ulm, Steinhövelstraße 9, 7900 Ulm (Donau), Germany.

dium bicarbonate was administered in a dose of 1 mmol/kg if spontaneous circulation was not restored after the second epinephrine dose. No additional drugs were used during CPR. A study protocol check by means of an on-site tape-recording of events was carried out by a member of the rescue team. Trauma patients, patients in whom epinephrine was administered endobronchially, children less than 14 yr of age, and patients in whom spontaneous circulation could be restored with three rapid, consecutive direct-current shocks without further CPR measures were excluded from the investigation. This prospective study was approved by our institutional committee on human experimentation.

In all patients, blood samples were taken from the external jugular vein between 60 and 120 s after the first epinephrine dose during CPR and at 5, 15, 30, and 60 min after restoration of spontaneous circulation. According to the guidelines for uniform reporting of data from out-of-hospital cardiac arrest (Utstein style), restoration of spontaneous circulation was defined as the return of a spontaneous palpable carotid pulse, which is a systolic blood pressure of approximately 60 mmHg for an undefined period of time.¹⁰ Each of these 10-ml blood samples was collected in a prechilled plastic syringe and placed on ice until centrifugation at 3,000 rpm for 10 min. The plasma was then separated and stored at -76°C until analysis. At the same points in time, blood pressure (sphygmomanometry with auscultation) and heart rate (ECG monitor) were recorded.

ACTH was measured in duplicate by radioimmunoassay (ACTH-125J IRMA Paesel, Eurodiagnostics, Frankfurt, Germany) with a sensitivity of 2 pg/ml. Intraassay coefficients of variation were less than 2% in the range between 60 and 1,600 pg/ml, and interassay coefficients of variation were less than 6%. The normal range in our laboratory is 20–50 pg/ml. Plasma cortisol was measured in duplicate by solid-phase radioimmunoassay (Coat-A-Count Cortisol-RIA, Diagnostic Products Corporation, Los Angeles, CA), with a sensitivity of 0.2 $\mu\text{g}/\text{dl}$. Intraassay coefficients of variation were less than 2% in the range between 5 and 50 $\mu\text{g}/\text{dl}$, and interassay coefficients of variation were less than 6%. The normal range lay between 5 and 25 $\mu\text{g}/\text{dl}$. The cross-reactions of the cortisol antiserum have been determined as 100% for cortisol, 1.5% for 11-deoxycorticosterone, 0.53% for dexamethasone, and 0.15% for progesterone. Because the cross-reaction with prednisolone was 46%, one patient with a history of prednisolone treatment for polyarthritis was excluded from the study.

Plasma arginine vasopressin was measured in duplicate by a radioimmunoassay double antibody procedure without prior extraction of the sample, using a modification of the method described by Glick and Kagan.¹¹ The cross-reactions of the vasopressin antiserum have been deter-

mined at 50% binding and found to be 100% for arginine vasopressin, 0.25% for lysine vasopressin, 0.001% for oxytocin, and 0.001% for vasotocin. Intra- and interassay coefficients of variation were less than 7%. The method is sensitive to less than 0.8 pg/ml. The normal range of the plasma arginine vasopressin concentration is 1–3 pg/ml. Plasma renin concentrations were measured in duplicate with a radioimmunoassay kit (Renin IRMA, Institut Pasteur, Lyon, France) using two monoclonal antibodies that recognize only active renin in human plasma.¹² Intra- and interassay coefficients of variation were less than 5%. This method is sensitive to less than 6 ng/l, and the normal range lies between 10 and 30 ng/l.

STATISTICAL ANALYSIS

Differences in the demographic characteristics of patients who were admitted to the hospital and those who were not were assessed using Fisher's exact test and Student's *t* test. Because the assumption of approximately normal distribution was not satisfied, the Mann-Whitney U test (two-tailed) was used to determine differences in the plasma measurements of the two groups. In patients admitted to the hospital, the Friedman test was used to analyze the data obtained during resuscitation and at the four following points of observation during the postresuscitation phase. This was followed by further analyses using the Wilcoxon signed rank test and Bonferroni correction for multiple comparisons. The normally distributed data of blood pressure and heart rate are reported as mean \pm SEM. For investigation of correlations between single parameters, the distribution-free rank correlation coefficient of Spearman (r_s) and the test for the correlation of not normally distributed data were used. Statistical significance was considered to be at the $P < 0.05$ level.

Results

Of the 34 patients included in the study, 20 (59%) could be successfully resuscitated, whereas in 14 (41%) restoration of spontaneous circulation was not possible, despite continuation of resuscitation efforts over a period of at least 30 min (table 1). There were no significant differences between these two groups with respect to sex, age, presence or absence of a witness to the arrest, incidence of CPR instituted by a bystander, initial ECG rhythm, or response time. In witnessed arrests, there was no significant difference between the two groups in the interval between collapse and the start of CPR. The interval between starting CPR and obtaining the first blood sample was similar in both groups. The interval from starting CPR to restoring spontaneous circulation was 12.6 ± 0.8 min. Each of the 20 patients survived for at least 2 h after the restoration of spontaneous circulation and had systolic blood pressures greater than 100 mmHg without further

TABLE 1. Demographic Data of Patients and Time Intervals

Characteristic	Resuscitated Patients (n = 20)	Nonresuscitated Patients (n = 14)	P
Male sex	15 (75)	10 (71)	1.000
Age (yr)	63.4 ± 3.6	64.5 ± 3.3	.831
Witnessed arrests	13 (65)	6 (43)	.296
Collapse-to-start of CPR interval (min)	7.2 ± 1.0	10.5 ± 2.2	.132
CPR instituted by bystander	2 (10)	1 (7)	1.000
Initial ECG rhythm			
Ventricular fibrillation	10 (50)	4 (29)	.409
Asystole	6 (30)	7 (50)	—
Electromechanical dissociation	4 (20)	3 (21)	—
Response time (min)	6.1 ± 0.5	8.1 ± 1.2	.315
Interval from starting CPR to first blood sample (min)	5.7 ± 0.6	5.4 ± 0.8	.788
Interval from starting CPR to ROSC (min)	12.6 ± 0.8	—	—
Hours of survival	26.7 ± 6.1	—	—
Discharged from hospital	5 (25)	—	—

Data are shown as mean ± SEM.

CPR = cardiopulmonary resuscitation; ROSC = restoration of spontaneous circulation.

Data in parentheses are percent of patient population.

drug therapy. The average survival time was 26.7 ± 6.1 h. Five patients were discharged from the hospital without major neurologic deficits. The demographic data and time intervals of these five patients were not significantly different from those of the 15 patients who died during their hospitalization.

The median plasma ACTH concentration was markedly increased during CPR at 237 pg/ml (range 29–572 pg/ml) in patients admitted to the hospital, compared with only 45 pg/ml (range 1–794 pg/ml) in those in whom restoration of spontaneous circulation could never be achieved ($P = 0.018$) (table 2). During the first hour after restoration of spontaneous circulation, the plasma ACTH concentration of resuscitated patients decreased gradually to 101 pg/ml (11–469 pg/ml) at 60 min (table 3). In these patients, a significant difference was measured between the ACTH concentration during CPR and the concentration at 60 min after restoration of spontaneous circulation (table 3).

Median plasma cortisol concentration was not significantly different between resuscitated patients (32.6 µg/dl, range 5.9–74.7 µg/dl) and those who were not resuscitated (18.4 µg/dl, range 9.6–70.1 µg/dl) (table 2). At the four points of observation after successful resuscitation, median plasma cortisol concentrations were between 32.7 and 36.2 µg/dl (table 3). Despite the high plasma ACTH concentrations during and after CPR, plasma cortisol concentrations during that period were only moderately increased above the normal range.

During CPR, median arginine vasopressin concentration was 122 pg/ml (range 20–469 pg/ml) in resuscitated

patients and 88 pg/ml (range 5–156 pg/ml) in nonresuscitated patients ($P = 0.049$) (table 2). Compared to the concentrations measured in normal subjects, plasma vasopressin concentrations were still markedly increased during the 1st h after successful resuscitation (table 3). The median arginine vasopressin concentration at 5 min after resumption of spontaneous circulation was 105 pg/ml (range 24–410 pg/ml). This value gradually decreased to 22 pg/ml (range 11–110 pg/ml) at 60 min after successful resuscitation. A significant difference was measured between the vasopressin concentration during CPR and the concentration at the 15-, 30-, and 60-min points of observation.

Median plasma renin concentrations were significantly higher in patients admitted to the hospital (46.5 ng/l, range 22–88 ng/l) than in those not resuscitated (11.0 ng/l, range 9–40 ng/l) (table 2). In patients admitted to the hospital, plasma renin concentrations during and at the following four points in time after CPR were not significantly different (table 3).

Heart rate and blood pressure values are shown in table 4. At no point after successful resuscitation could a significant correlation be found between concentration of any of the hormones and arterial blood pressure or heart rate. In all witnessed cardiac arrests a strong negative correlation was found between the interval from collapse to the start of CPR and plasma cortisol concentrations during CPR ($n = 19$, $r_s = -0.967$, $P < 0.001$) (fig. 1). No significant correlation was measured between the interval from collapse to the start of CPR and ACTH, arginine vasopressin, and renin concentrations either during or after CPR. During CPR, plasma ACTH concentrations correlated with plasma arginine vasopressin concentrations in all 34 patients ($n = 34$, $r_s = 0.770$, $P < 0.001$) (fig. 2). A weaker but still significant correlation between these two hormones was found at 5 min ($n = 20$, $r_s = 0.569$, $P = 0.013$) and at 15 min ($n = 20$, $r_s = 0.489$, $P = 0.033$) after restoration of spontaneous circulation, whereas at 30 and 60 min the correlation was not significant. In the subgroup of 5 patients who were discharged

TABLE 2. Plasma Hormone Concentrations during Cardiopulmonary Resuscitation in Resuscitated and Nonresuscitated Patients

Hormone	Resuscitated Patients (n = 20)	Nonresuscitated Patients (n = 14)	P
Adrenocorticotropin (pg/ml) (25–50)	237 (29–572)	45 (1–794)	.018
Cortisol (µg/dl) (5.0–25.0)	32.6 (5.9–74.7)	18.4 (9.6–70.1)	.481
Arginine vasopressin (pg/ml) (1–3)	122 (20–469)	88 (5–156)	.049
Renin (ng/l) (10–30)	46.5 (22–88)	11 (9–40)	.017

Data are shown as median and range.

The normal range of values is displayed after the name of the hormone in the left column.

TABLE 3. Plasma Adrenocorticotropin, Cortisol, Arginine Vasopressin, and Renin Concentration during Cardiopulmonary Resuscitation (CPR) and in the Postresuscitation Phase

	CPR	Time (min) after ROSC				P
		5	15	30	60	
Adrenocorticotropin (pg/ml) (25-50)	237 (29-572)	211 (29-385)	143 (32-282)	131 (9-222)	101 (11-469)*	.003
Cortisol (μg/dl) (5.0-25.0)	32.6 (5.9-74.7)	36.2 (5.0-77.0)	32.7 (4.8-80.5)	34.0 (6.5-79.2)	34.6 (5.3-83.8)	.704
Arginine vasopressin (pg/ml) (1-3)	122 (20-469)	105 (24-410)	67.5 (14-191)†	40 (14-83)†	22 (11-110)†	.001
Renin (ng/l) (10-30)	46.5 (22-88)	40.5 (14-134)	34 (10-123)	40.5 (10-136)	25 (9-140)	.060

Data are shown as median and range.
The normal range of values is displayed after the name of the hormone in the left column.
P value refers to analysis at different points in time.

ROSC = restoration of spontaneous circulation.
* P < .05 versus values during CPR.
† P < .01 versus values during CPR.

from the hospital, ACTH, cortisol, arginine vasopressin, and renin concentrations were not significantly different from those patients who were successfully resuscitated but did not survive.

Discussion

The major findings of our investigation are that during CPR the endogenously released concentrations of both ACTH and arginine vasopressin are significantly greater in patients in whom spontaneous circulation can be restored than in those in whom it cannot. Despite high plasma concentrations of ACTH during CPR and during the 1st h after successful resuscitation, cortisol concentrations were only moderately increased. Mechanical CPR measures were accompanied by standardized drug therapy, which could have influenced hormone concentrations both during and after CPR. However, since the time interval from starting CPR to taking the first blood sample and administering epinephrine was the same in all patients, epinephrine-induced changes in hormone concentrations should be similar in both groups. We deliberately measured hormone concentrations after administration of epinephrine during CPR, because epinephrine is the standard drug treatment for cardiac arrest and is almost always required for restoration of spontaneous circulation. We did not take additional blood samples for measurement of plasma catecholamines, because this aspect has already been described in previous investigations.^{4,6}

ACTH release, which plays a major role in protecting the organism from stress, is a nonspecific reaction to noxious stimuli such as exhaustive exercise, hemorrhage, surgery, hypoxia, and hypercapnia.¹³ Not only corticotrophin-releasing factor but also catecholamines and vasopressin may cause an increase in plasma ACTH concentration.¹³ ACTH secretion is stimulated by the arginine vasopressin reaching the adenohipophysis through the peripheral circulation, and to an even greater extent by the arginine vasopressin transported by pituitary portal circulation.¹⁴ As in acute hemorrhage,¹⁵ we found a high correlation coefficient between ACTH and arginine vasopressin during cardiac arrest and CPR, whereas after restoration of spontaneous circulation this correlation was less close. It therefore could be that the exogenously administered epinephrine caused an increase in ACTH during CPR. During and after surgery, plasma ACTH concentrations have been found to correlate well with the degree of surgical stress¹⁶; however, the increase in ACTH secretion was often far greater than that required to produce a maximal adrenocortical response.¹⁷ The physiologic effects of elevated concentrations in stressed subjects include the release of cortisol,⁸ adrenal epinephrine, and

TABLE 4. Blood Pressure and Heart Rate during the First Hour after Restoration of Spontaneous Circulation (ROSC)

Time after ROSC (min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (min ⁻¹)
5	100 ± 6	66 ± 5	108 ± 6
15	111 ± 6	72 ± 4	104 ± 4
30	113 ± 5	71 ± 4	101 ± 4
60	106 ± 4	68 ± 4	96 ± 3

Data are shown as mean ± SEM.

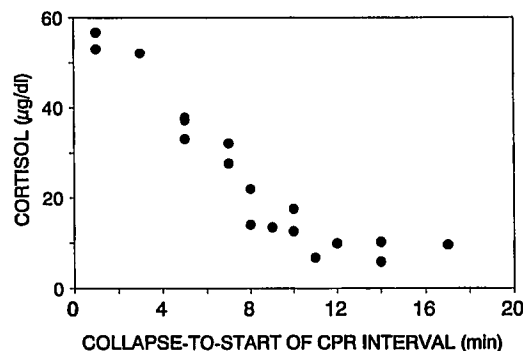


FIG. 1. Correlation between collapse-to-start of cardiopulmonary resuscitation (CPR) interval and plasma cortisol concentrations during CPR in all witnessed cardiac arrests (n = 19, Spearman rank correlation coefficient = -.967, P < .001).

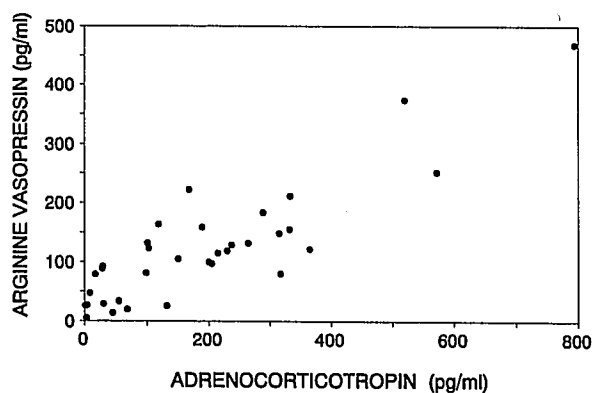


FIG. 2. Correlation between plasma adrenocorticotropin and arginine vasopressin concentrations during cardiopulmonary resuscitation in all patients ($n = 34$, Spearman rank correlation coefficient = .770, $P < .001$).

norepinephrine¹⁸ and the antagonism of the hypotensive effects of endogenous opioids on the circulation.¹⁹ Hypoxia and acidosis during cardiac arrest and CPR may lead to changes in hypothalamic activity, which in turn provoke a pituitary response.

In our investigation, the highest ACTH concentrations measured during CPR were found in patients in whom restoration of spontaneous circulation was possible. During the 1st h after CPR, the values gradually declined. In witnessed arrests we found no correlation between the interval from collapse to the start of CPR and plasma ACTH concentrations. Intensive care patients who develop cardiac arrest and are resuscitated (interval between collapse and the start of CPR presumably less than 1 min) have been found to have an increase in plasma ACTH only slightly above the upper limit of the normal range.²⁰ It should be taken into consideration, however, that intensive care patients who develop cardiac arrest for a nontechnical reason may have a different hormonal reaction to patients with out-of-hospital cardiac arrest. During CPR, plasma ACTH concentrations were significantly less in nonresuscitated patients than in resuscitated patients, a difference that may have been caused by an impaired neuroendocrine response. It is open to discussion whether these lower concentrations influenced the perfusion pressures achieved during cardiac compression.

Cortisol is released in stress situations of varied etiology.⁸ Moderately injured patients have been found to have plasma cortisol increases in proportion to the severity of their trauma.²¹ In those with more extensive injuries, plasma cortisol concentrations decreased in relation to ACTH as well as in absolute terms, and this was associated with a worse survival rate.²¹ Similarly, severe hemorrhagic shock in rats led to an inverse relationship between plasma corticosterone and shock severity.²² Cortisol has been reported to act synergistically with epinephrine. The mechanisms postulated include a cortisol-induced inhibition of

catechol-O-methyl transferase and blockade of catecholamine reuptake.^{9,23} Despite the high ACTH concentrations in our resuscitated patients, plasma cortisol concentrations during and after CPR were less than in resuscitated intensive care patients. Based on the observation that a strong negative correlation exists between the interval from collapse to the start of CPR and cortisol concentrations, it can be postulated that cardiac arrest leads to an impairment of cortisol release from the adrenal cortex, the severity of which appears to depend on the duration of global hypoxia. The lack of a significant correlation between the interval from collapse to the start of CPR and the other hormone concentrations indicates that there is no general decrease in stress response with longer intervals between collapse and the start of CPR. Currently, it is unclear whether a low cortisol concentration during CPR decreases the vasoconstricting properties of catecholamines and whether cortisol administration might improve on this.

Arginine vasopressin can be regarded as a classical stress hormone: it is released by various stimuli such as pain, emotion, vasovagal syncope, anesthetics, surgery, and cardiac and circulatory shock.²⁴ During acute hemorrhage in dogs, arginine vasopressin plays an important role in causing peripheral vasoconstriction and in maintaining perfusion pressures.²⁵ In cardiac emergencies such as acute myocardial infarction, arginine vasopressin concentrations were found to be highest—approximately 15 pg/ml—at hospital admission.²⁶ When cardiac failure and hypotension develop after acute myocardial infarction, a marked release of arginine vasopressin has been reported.²⁷ In patients with congestive heart failure, however, infusion of arginine vasopressin up to concentrations of an average of 15 pg/ml caused a decrease in cardiac output.²⁸

There are as yet no reports about the extent and time course of vasopressin release during cardiac arrest and the immediate postresuscitation phase. In comparison to reported arginine vasopressin concentrations in patients with acute myocardial infarction^{26,27} or with severe burn injury,²⁹ we measured excessively high concentrations both during and after CPR. In hemorrhagic and septic shock, the release of vasoconstrictors such as catecholamines and arginine vasopressin occurs within about 30 min after onset of the insult.^{30,31} During cardiac arrest and CPR we found that extremely high concentrations are reached within a few minutes. Administration of analgesic opioids, which are known to increase arginine vasopressin levels,²⁴ was not required during the brief period of observation in our study. Despite these high vasopressin concentrations we did not observe adverse cardiocirculatory effects, such as arterial hypertension or bradycardia, during the 1st h after restoration of spontaneous circulation. In patients who were successfully resuscitated, ar-

arginine vasopressin concentrations were significantly higher than in those patients who were not. Whether the moderate difference observed is in any way causal currently remains unclear.

In acute, uncomplicated myocardial infarction, plasma renin and angiotensin II concentrations were within normal limits on hospital admission but were increased on the third day.²⁶ Patients with left ventricular failure already had increased plasma renin and angiotensin II concentrations on admission, but further marked and persistent increases occurred on the following day.²⁶ The results of these studies together with our finding that increased plasma renin concentrations were only moderately increased during CPR and in the 1st h after successful resuscitation therefore indicate that renin release is not an immediate response.

During CPR, ACTH, cortisol, arginine vasopressin, renin, and the sympathoadrenal system may interact, leading to a combined effect in mediating peripheral vasoconstriction and thus increasing myocardial and cerebral perfusion pressures and hence resuscitation success. In a pig model, we were able to demonstrate that administration of arginine vasopressin during CPR does indeed increase myocardial blood flow.³² Administration of the standard epinephrine dose, as in our investigation (approximately 15 $\mu\text{g}/\text{kg}$), may in many cases not be able to increase perfusion pressures sufficiently, because of a down-regulation or an uncoupling of receptors under these conditions.³³ High-dose epinephrine (> 15 $\mu\text{g}/\text{kg}$) during CPR increases short-term survival in animals and in humans,³⁴⁻³⁶ but its effect on the plasma concentrations of the above-mentioned hormones is not currently known.

We conclude that cardiac arrest and CPR in out-of-hospital patients trigger the release of very high plasma ACTH and arginine vasopressin concentrations. Despite this increase in ACTH, no adequate increase in plasma cortisol concentrations was observed, possibly because of an impaired function of the adrenal cortex. Currently we do not know whether the lower ACTH, arginine vasopressin, and renin concentrations in nonresuscitated patients are solely the result of an impairment in neuroendocrine response, including exhaustion of the system, or whether these lower concentrations are an operative factor resulting in a lesser degree of peripheral vasoconstriction and hence an insufficiently high myocardial blood flow for the restoration of spontaneous circulation. In the latter case, one could speculate that administration of these substances might potentiate the vasoconstricting effects of catecholamines.

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