Release of endogenous vasopressors during and after cardiopulmonary resuscitation

Karl H Lindner, Thomas Haak, Andreas Keller, Ulrich Bothner, Keith G Lurie

Abstract

Objective—To assess whether plasma endothelin, adrenaline, noradrenaline, arginine vasopressin, adrenocorticotropin, and cortisol concentrations were higher during cardiopulmonary resuscitation in patients in whom resuscitation was successful than in those in whom it failed, and to measure the concentrations of these hormones in the immediate post-resuscitation phase.

Design—Prospective, descriptive study.

Setting—Emergency medical service at a university hospital.

Patients—60 patients with cardiac arrest out of hospital.

Interventions—Blood samples were drawn and blood pressure and heart rate were measured during cardiopulmonary resuscitation, before and after the first dose of adrenaline was given and at 5, 15, 30, and 60 minutes after the restoration of spontaneous circulation. Plasma hormone concentrations were measured by radioimmunoassays.

Results—24 of the 60 patients were successfully resuscitated and admitted to hospital; 36 were not. During cardiopulmonary resuscitation before adrenaline was given, the plasma concentration of endothelin (mean (SEM)) in resuscitated and in not resuscitated patients was 4.3 (0.9) pg/ml and 5.5 (0.4) pg/ml respectively (NS), adrenaline was 14.1 (2.0) ng/ml and 25.3 (3.6) ng/ml ($P < 0.01$), noradrenaline was 5.0 (0.9) ng/ml and 8.4 (1.1) ng/ml ($P < 0.05$), arginine vasopressin was 193 (28) pg/ml and 70 (9) pg/ml ($P < 0.001$), adrenocorticotropin was 128 (34) pg/ml and 57 (6) pg/ml ($P < 0.05$), and cortisol was 18 (3) μ g/dl and 15 (2) μ g/dl (NS). During cardiopulmonary resuscitation after adrenaline was given endothelin in resuscitated and in not resuscitated patients was 4.0 (1.0) pg/ml and 5.3 (0.5) pg/ml (NS), adrenaline was 145 (16) ng/ml and 201 (21) ng/ml ($P < 0.05$), noradrenaline was 3.9 (0.9) ng/ml and 8.3 (1.1) ng/ml ($P < 0.01$), arginine vasopressin was 177 (27) pg/ml and 58 (9) pg/ml ($P < 0.001$), adrenocorticotropin was 234 (92) pg/ml and 85 (9) pg/ml ($P < 0.001$), and cortisol was 17 (2) μ g/dl and 13 (2) μ g/dl (NS).

Conclusions—Despite a tremendous adenosympathetic response, the lower arginine vasopressin and adrenocorticotropin concentrations during car-

diopulmonary resuscitation in patients in whom resuscitation failed may influence vital organ perfusion and hence the success of resuscitation. Plasma concentrations of arginine vasopressin and adrenocorticotropin may have a more important effect on outcome than previously thought.

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Keywords: endothelin; catecholamines; arginine vasopressin (antidiuretic hormone); cardiopulmonary resuscitation

Severe stress such as that occurring with cardiac arrest and cardiopulmonary resuscitation activates the sympathetic nervous system, causing a rise in plasma catecholamine concentrations.^{1,2} When arterial hypotension stimulates the baroreceptor reflex, other vasopressor pathways such as release of arginine vasopressin and the renin-angiotensin system, are also activated.^{3,4} In stress states, including ischaemia, circulating concentrations of endothelin, a long-lasting arterial and venous vasoconstrictor derived from endothelial cells, are increased.⁵ As yet, there are no reports of endothelin concentrations during and after cardiopulmonary resuscitation. The purpose of this study was to: (a) measure plasma concentrations of endothelin, adrenaline, noradrenaline, arginine vasopressin, adrenocorticotropin, and cortisol in patients in cardiac arrest and during the resuscitation effort and (b) to measure the concentrations of these hormones in the immediate post-resuscitation phase.

Patients and methods

After approval by our institutional committee on human experimentation, 60 consecutive adults with out-of-hospital arrest were included in the study. Cardiopulmonary resuscitation was performed in each case in accordance with the 1993 recommendations of the European Resuscitation Council⁶ and was supervised by a physician from the emergency care department of Ulm University Hospital. All patients were given 1 mg of adrenaline intravenously during cardiopulmonary resuscitation. When resuscitation was not successful, adrenaline was administered every three minutes at increasing doses of 1 mg, 3 mg, and 5 mg. Sodium bicarbonate (1 mmol/kg) was given if the second dose of adrenaline failed to restore spontaneous circulation. No further drugs were used during cardiopulmonary resuscitation. A study proto-

Department of Anaesthesiology and Critical Care Medicine, University of Ulm, Ulm, Germany
K H Lindner
A Keller
U Bothner

Centre of Internal Medicine, Johann Wolfgang Goethe-University, Frankfurt, Germany
T Haak

Cardiac Arrhythmia Centre, Cardiovascular Division, Department of Medicine, University of Minnesota, USA
K G Lurie

Correspondence to: Dr K H Lindner, Universitäts-klinik für Anästhesiologie, Klinikum der Universität Ulm, Steinhövelstrasse 9, 89075 Ulm (Donau), Germany.

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col check by means of an on-site tape recording of resuscitation-related events was performed by a supplementary member of the rescue team. We excluded injured patients, patients in whom adrenaline was administered endobronchially, children under 14, and patients in whom spontaneous circulation was restored by three rapid, consecutive direct current shocks without further cardiopulmonary resuscitation measures. Restoration of spontaneous circulation was defined as the return of a spontaneous palpable carotid pulse—that is, a systolic blood pressure of approximately 60 mm Hg for an undefined time.⁷ Blood samples were taken from an external jugular vein 60 to 120 seconds before and after the first adrenaline dose during cardiopulmonary resuscitation, and 5, 15, 30, and 60 min after spontaneous circulation was restored. Adrenaline was administered into the other external jugular vein. Each of the 10 ml blood samples was collected in a pre-chilled polystyrene tube containing ethylenediamine tetra acetic acid (EDTA, 1 mg/ml) and placed on ice until centrifugation. Centrifugation was done at 3000 rpm for 10 min at 4°C. Blood samples for plasma catecholamine measurements were collected in lithium heparinate syringes filled with 100 µl of an antioxidative solution (61 mg glutathione and 76 mg/ml EDTA). The plasma was then separated, immediately frozen, and stored at -80°C until analysis. At the same time that blood samples were taken, blood pressure (by sphygmomanometry with auscultation) and heart rate (by electrocardiogram monitor) were recorded.

Endothelin was measured in duplicate by an endothelin-1,2,3 sensitive radioimmunoassay (Biomedica, Vienna), as described by Haak *et al.*⁸ Endothelin was extracted from plasma by absorption on prewashed SepPak C₁₈ cartridges (Waters/Millipore, Watford, Hertfordshire) by slow passage of 5 ml plasma samples in 50 l/ml acetonitrile with a vacuum manifold (Henning, Berlin). After the cartridge was washed with 4 ml of methanol/water in a volume ratio of 10:90, the absorbed peptides were eluted by 4 ml of the same solution in a volume ratio of 85:15 and dried at 37°C under a stream of nitrogen. Standards (human/porcine endothelin-1, Peninsula Laboratories, Belmont, California), ¹²⁵I-labelled anti-endothelin antibodies, and plasma extracts were dissolved in a radioimmunoassay buffer. The antibody used in these studies does not cross-react with pro endothelin-1 ("big endothelin") or endothelin-3 to a substantial degree. Furthermore, the antibody does cross-react significantly with endothelin-2, but endothelin-2 has not been found to circulate in humans. Endothelin-3 does not bind to high-affinity endothelin_A type receptor, which mediates vasoconstriction.⁹ In 50 historic controls of normal resting subjects, endothelin (mean (SEM)) was 0.9 (0.1) pg/ml.⁸

The analysis of plasma catecholamine concentrations was based on their selective isolation by adsorption onto surface-activated aluminium oxide at a pH of 8.6 (2M Tris buffer), followed by elution with a solution

containing 250 mg EDTA, 500 mg of sodium disulphide, and 12.5 ml/l of 0.2M acetic acid and measurement by high performance liquid chromatography with electrochemical detection (Waters Associates, Milford, Massachusetts).² The method is sensitive to less than 10 pg/ml of adrenaline or noradrenaline. The coefficient of variation for adrenaline, calculated at an adrenaline concentration of 600 pg/ml, was 6.0. The coefficient of variation for noradrenaline, calculated at a noradrenaline concentration of 998 pg/ml, was 6.4. In normal humans, the ranges of resting plasma adrenaline and noradrenaline concentrations with this assay are between 50 pg/ml and 200 pg/ml and between 250 pg/ml and 500 pg/ml, respectively.

We measured arginine vasopressin 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.¹⁰ The cross-reactions of the arginine vasopressin antiserum determined at 50% binding have been found to be 100% for arginine vasopressin, 0.25% for lysine arginine vasopressin, 0.001% for oxytocin, and 0.001% for vasotocin. Intra and inter assay coefficients of variation were below 7%. The method is sensitive to less than 0.8 pg/ml. The normal range of plasma arginine vasopressin concentration is between 1 pg/ml and 3 pg/ml.

Adrenocorticotropin was measured in duplicate by radioimmunoassay (adrenocorticotropin-125J IRMA Paesel, Eurodiagnostics, Frankfurt) with a sensitivity of 2 pg/ml. Intra-assay coefficients of variation were less than 2% in the range between 60 pg/ml and 1600 pg/ml, and inter-assay coefficients of variation were less than 6%. The normal range in our laboratory is 20–50 pg/ml.

Cortisol was measured in duplicate by solid-phase radioimmunoassay (Coat-A-Count Cortisol-RIA, Diagnostic Products Corporation, Los Angeles) with a sensitivity of 0.2 µg/dl. Intra-assay coefficients of variation were below 2% in the range between 5 and 50 mg/dl, and inter-assay coefficients of variation were below 6%. The normal range lay between 5 µg/dl and 25 µg/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.

STATISTICAL ANALYSIS

Fisher's exact test was used for categorical data and Student's *t* test (two tailed) for unpaired and paired observations was used for continuous data. In patients admitted to hospital, one-way analysis of variance for repeated measures was used to analyse the data obtained during resuscitation and at the four points (5, 15, 30, and 60 min) of observation during the post-resuscitation phase. The strength of correlations between single variables was investigated with the squared Pearson product-moment correlation coefficient. All data are expressed as mean (SEM). A *P* value less than 0.05 was regarded as significant.

Table 1 Demographic data and intervals for all patients

Characteristic	Resuscitated (n = 24)	Failed resuscitation (n=36)	P
Male sex	16 (67%)	25 (69%)	1.000
Age (yr) (mean (SEM))	64 (3)	68 (3)	0.228
Witnessed arrests	18 (75%)	24 (67%)	0.345
Collapse-resuscitation interval in witnessed arrest (min)	7.0 (1.2)	8.2 (2.0)	0.445
CPR instituted by bystander	7 (29%)	9 (25%)	1.000
Initial ECG rhythm			
VF	16 (65%)	16 (44%)	0.194
Asystole, EMD	8 (35%)	20 (56%)	—
Response time (min)	7.8 (1.2)	7.5 (1.1)	0.685
Interval from starting CPR to first adrenaline dose (min)	8.2 (1.4)	7.8 (1.6)	0.899
Interval from starting CPR to ROSC (min)	14.2 (2.5)	—	—
Hours of survival	110 (56)	—	—
Discharged from hospital	12 (50%)	—	—

Values are mean (SEM). CPR, cardiopulmonary resuscitation; EMD, electromechanical dissociation; ROSC, restoration of spontaneous circulation.

Results

Table 1 shows the demographic data and key time intervals during cardiopulmonary resuscitation. Resuscitation was possible in 24 patients and was not possible despite continuation of resuscitation efforts for at least 30 min in 36. There were no significant differences between these two groups with respect to sex, age, whether the arrest was witnessed or not, whether or not a bystander instituted cardiopulmonary resuscitation, initial electrocardiogram rhythm, or response time. In witnessed arrests there was no significant difference in the collapse-resuscitation interval between those patients who could be resuscitated and admitted to hospital and those in whom spontaneous

circulation could not be restored. The time between the start of cardiopulmonary resuscitation and administration of the first adrenaline dose was similar in both groups, and the interval from starting cardiopulmonary resuscitation to restoration of spontaneous circulation was 14.2 (2.5) min. All patients successfully resuscitated were haemodynamically stable for at least 60 min without catecholamine treatment. Twelve of the 24 patients who were admitted to hospital survived for an average of 110 (56) hours after the restoration of spontaneous circulation. Twelve patients were discharged from the hospital without major neurological deficits. The demographic data and key intervals during resuscitation efforts for these 12 patients were not significantly different from those for the 12 patients who died in hospital.

During cardiopulmonary resuscitation (both before and after adrenaline was given), mean plasma endothelin concentrations in hospitalised patients were not significantly different from those in patients whose circulation could not be restored (table 2). After successful resuscitation, mean endothelin concentrations ranged from 4.6 (0.9) pg/ml at 5 min and 2.8 (0.3) pg/ml at 60 min (table 3). Values in both groups of patients were significantly higher than in controls.⁸

Mean plasma adrenaline and noradrenaline concentrations during cardiopulmonary resuscitation were considerably higher in all patients than in normal resting subjects. Before adrenaline, the concentrations in resuscitated patients

Table 2 Plasma hormone concentrations during cardiopulmonary resuscitation in resuscitated and non-resuscitated patients before and after adrenaline administration

Hormone†	Before adrenaline		After adrenaline	
	Resuscitation (n = 12)	Failed resuscitation (n = 14)	Resuscitation (n = 24)	Failed resuscitation (n = 36)
Endothelin (pg/ml) (0.6–1.2)	4.3 (0.9)	5.5 (0.4)	4.0 (1.0)	5.3 (0.5)
Adrenaline (ng/ml) (0.05–0.2)	14.1 (2.0)	25.3 (3.6)**	145 (16)‡	201 (21)*‡
Noradrenaline (ng/ml) (0.25–0.5)	5.0 (0.9)	8.4 (1.1)*	3.9 (0.9)	8.3 (1.1)**
Arginine vasopressin (pg/ml) (1–3)	193 (28)	70 (9)***	177 (27)	58 (9)***
Adrenocorticotropin (pg/ml) (25–50)	128 (34)	57 (6)*	234 (92)†	85 (9)***
Cortisol (µg/dl) (5–25)	18 (3)	15 (2)	17 (2)	13 (2)

*P < 0.05, **P < 0.01, ***P < 0.001 for comparisons between resuscitated and non-resuscitated patients; †P < 0.01, ‡P < 0.001 before and after adrenaline. Values are mean (SEM). †Normal ranges of hormone values are given in parentheses. To convert values for endothelin to pmol/l multiply by 0.402, to convert adrenaline to nmol/l multiply by 5.458, to convert values for noradrenaline to nmol/l multiply by 5.911, to convert arginine vasopressin to pmol/l multiply by 0.922, and to convert values for adrenocorticotropin to pmol/l multiply by 0.220, and to convert values for cortisol to nmol/l multiply by 27.59.

Table 3 Plasma hormone concentrations (mean (SEM)) during cardiopulmonary resuscitation and in the post-resuscitation phase in all patients

Hormone*	After ROSC					P
	During CPR	5 min	15 min	30 min	60 min	
Endothelin (pg/ml) (0.6–1.2)	3.7 (0.5)	4.6 (0.9)	4.2 (0.7)	4.0 (0.7)	2.8 (0.3)	NS
Adrenaline (ng/ml) (0.05–0.2)	123 (11)	23 (2)	19 (1)	13 (1)	10 (1)	< 0.001
Noradrenalin (ng/ml) (0.25–0.5)	6.1 (0.7)	2.7 (0.4)	2.1 (0.3)	2.0 (0.4)	1.8 (0.3)	< 0.001
Arginine vasopressin (pg/ml) (1–3)	172 (17)	117 (13)	72 (7)	44 (4)	24 (2)	< 0.001
Adrenocorticotropin (pg/ml) (25–50)	228 (46)	204 (33)	145 (16)	128 (14)	109 (11)	< 0.001
Cortisol (µg/dl) (5–25)	23 (2)	20 (2)	25 (1)	26 (1)	25 (1)	< 0.05

*Normal ranges are given in parentheses. P value refers to analysis of repeated measures over time. ROSC restoration of spontaneous circulation; CPR, cardiopulmonary resuscitation. See table 2 for conversion factors.

Table 4 Demographic data and time intervals of all patients with witnessed ventricular fibrillation

Characteristic	Resuscitated (n = 13)	Failed resuscitation (n = 11)	P
Male sex	8 (62%)	7 (64%)	1.000
Age (yr) (mean (SEM))	58 (4)	62 (3)	0.228
Collapse-resuscitation interval (min)	6.2 (1.4)	6.0 (1.8)	0.930
CPR instituted by bystander	4 (31%)	3 (27%)	1.000
Response time (min)	6.0 (1.1)	5.8 (1.2)	0.685
Interval from starting CPR to first adrenaline dose (min)	7.6 (1.0)	7.3 (0.9)	0.899
Interval from starting CPR to ROSC (min)	12.8 (2.6)	—	—
Hours of survival	146 (42)	—	—
Discharged from hospital	7 (54%)	—	—

Values are mean (SEM). CPR, cardiopulmonary resuscitation; EMD, electromechanical dissociation; ROSC, restoration of spontaneous circulation.

were 14.1 (2.0) ng/ml and 5.0 (0.9) ng/ml, respectively, during cardiopulmonary resuscitation, and in patients in whom resuscitation failed concentrations were 25.3 (3.6) ng/ml and 8.4 (1.1) ng/ml (intergroup comparisons $P < 0.01$ for adrenaline and $P < 0.05$ for noradrenaline) (table 2). After adrenaline administration, plasma adrenaline and noradrenaline concentrations were still significantly higher in patients in whom resuscitation failed. After successful resuscitation, mean adrenaline and noradrenaline concentrations decreased to 10 (1) ng/ml and 1.8 (0.3) ng/ml, respectively, at 60 min (table 3).

Mean plasma arginine vasopressin concentrations during cardiopulmonary resuscitation before adrenaline were 193 (28) pg/ml in resuscitated patients and 70 (9) pg/ml in those patients in whom resuscitation failed ($P < 0.001$) (table 2). After adrenaline, concentrations were also significantly higher in resuscitated patients. Compared with the concentrations measured in normal subjects, concentrations were markedly increased during the first hour after successful resuscitation (table 3). The mean concentration of arginine vasopressin gradually decreased. There were significant differences between the arginine vasopressin concentration during cardiopulmonary resuscitation and at 15, 30, and 60 min after resuscitation.

Mean plasma adrenocorticotropin concentrations during cardiopulmonary resuscitation both before and after adrenaline were significantly higher in patients admitted to hospital than in those in whom spontaneous circulation

could not be restored (table 2). In resuscitated patients values were significantly higher after adrenaline. In the first hour after spontaneous circulation was restored, mean adrenocorticotropin concentration gradually decreased to 109 (11) pg/ml at 60 min (table 3). In patients admitted to hospital, there was a significant difference between the adrenocorticotropin concentration during cardiopulmonary resuscitation and at 60 min after spontaneous circulation was restored (table 3). In all cardiac arrest patients, adrenocorticotropin concentrations were higher than those measured in normal controls.

Mean plasma cortisol concentrations before and after adrenaline were not significantly higher in patients admitted to hospital than in those in whom resuscitation failed (table 2). Despite high adrenocorticotropin concentrations during and after cardiopulmonary resuscitation, plasma cortisol concentrations were within the normal range or only a little above (table 3).

Endothelin, adrenaline, noradrenaline, arginine vasopressin, adrenocorticotropin, and cortisol concentrations were not significantly different in the subgroup of 12 patients who were discharged from hospital and those in the patients who were successfully resuscitated but did not survive.

There was positive correlation between endothelin and arginine vasopressin during cardiopulmonary resuscitation in resuscitated patients before ($n = 12$, $r^2 = 0.632$, $P < 0.001$) and after administration of adrenaline ($n = 24$, $r^2 = 0.602$, $P < 0.001$). The correlation between adrenaline and noradrenaline concentrations and also between catecholamines and the other hormones was poor both during and after cardiopulmonary resuscitation. At no point after successful resuscitation could a significant correlation be found between any of the hormones and arterial blood pressure or heart rate.

Despite the fact that there were no significant differences between the successful resuscitation and failed resuscitation groups, there was a trend towards a higher percentage of unfavourable characteristics (such as age, unwitnessed arrests, asystole, and electromechanical dissociation) in the failed resuscitation group. We therefore focused on the

Table 5 Plasma hormone concentrations during cardiopulmonary resuscitation in all patients with witnessed ventricular fibrillation

Hormone	Before adrenaline		After adrenaline	
	Resuscitated (n = 8)	Failed resuscitation (n = 6)	Resuscitated (n = 13)	Failed resuscitation (n = 11)
Endothelin (pg/ml) (0.6–1.2)	4.0 (0.8)	4.2 (0.6)	3.9 (0.6)	4.5 (0.6)
Adrenaline (ng/ml) (0.05–0.02)	12.2 (1.4)	20.6 (3.2)**	124 (18)‡	186 (24)‡*
Noradrenaline (ng/ml) (0.25–0.5)	4.2 (0.8)	7.8 (1.4)*	4.0 (0.8)	9.4 (1.2)**
Arginine vasopressin (pg/ml) (1–3)	180 (32)	82 (12)***	156 (24)	52 (8)***
Adrenocorticotropin (pg/ml) (25–50)	116 (30)	52 (8)*	208 (86)†	112 (18)***
Cortisol (µg/dl) (5–25)	22 (4)	18 (3)	19 (3)	16 (4)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between resuscitated and failed resuscitated patients; † $P < 0.01$, ‡ $P < 0.001$ before and after adrenaline. Values are mean (SEM). Normal range of hormone values are given in parentheses. See table 2 for conversion factors.

subgroup of patients with witnessed ventricular fibrillation, and found that the demographic data of these patients were almost identical in both groups (table 4). A further analysis of hormonal data of these patients confirmed that these patients showed the same differences in hormonal profile as in the total patient population (table 5).

Discussion

Our results showed that during cardiopulmonary resuscitation, plasma arginine vasopressin and adrenocorticotropin concentrations were significantly higher in patients in whom spontaneous circulation was restored than in those who could not be resuscitated. In contrast, though plasma endothelin concentrations in the jugular vein were approximately twofold to threefold higher in resuscitated patients than in controls, there was no difference in endothelin concentrations between resuscitated and failed resuscitated patients. However, parallel increases in plasma arginine vasopressin and endothelin during cardiopulmonary resuscitation were found only in resuscitated patients. Both before and after administration of adrenaline plasma adrenaline and noradrenaline concentrations were significantly higher in patients in whom resuscitation failed than in resuscitated patients, as reported by others.¹¹ Because there was a trend to more adverse demographic characteristics in the failed resuscitation group, we looked at patients with witnessed ventricular fibrillation and found the same hormonal pattern as in the total population.

Endothelin-1, the biologically active form of endothelin, was measured in our study because of its potentially important role in the regulation of vascular tone in several stress states.^{5 12 13} Plasma endothelin concentrations are increased in patients with a number of potentially life-threatening disorders, including congestive heart failure, myocardial infarction, ischaemic heart disease, subarachnoid haemorrhage, pre-eclampsia, sepsis, and vasovagal syncope. During cardiopulmonary resuscitation, we also observed a rapid release of endothelin in both resuscitated and failed resuscitated patients. This increase may play a part in peripheral vasoconstriction and in shifting blood to vital organs.¹⁴ Like arginine vasopressin, endothelin is synthesised in neurons of the paraventricular nuclei of the hypothalamus and is stored in the posterior pituitary.¹³ Kaufmann *et al* described a coincident increase in plasma endothelin and arginine vasopressin during vasovagal syncope and concluded that when syncope is associated with acute block of vasoconstrictor sympathetic outflow, the baroreceptor reflex causes release of arginine vasopressin and endothelin from the neurohypophysis.¹⁵ Both baroreceptor activation and hypoxia may account for the endothelin release during cardiopulmonary resuscitation, suggesting that release of the neurohypophyseal content is an important part of the physiological response to cardiac arrest. Once increased, plasma endothelin concentrations remained increased during the post-resuscitation phase, unlike other stress hormones such as adrena-

line, noradrenaline, and arginine vasopressin. Although this is probably a result of continuous release of endothelin from endothelial cells and from the posterior pituitary, it may represent impaired clearance. It is noteworthy that in our study a positive correlation was found between endothelin and arginine vasopressin concentrations in resuscitated patients, whereas no correlation was observed between these two hormones in patients in whom resuscitation failed.

The significantly lower arginine vasopressin and adrenocorticotropin concentrations in the failed resuscitation group may be caused by an insufficient release from the posterior and anterior pituitary, the reason for this is unknown. Impaired release of endothelin from the posterior pituitary could be compensated for by release from the endothelial cells. Schultz *et al* reported that despite higher adrenocorticotropin concentrations in cardiac arrest cortisol concentrations were lower than reported in other stress states.¹⁶

A massive adrenosympathetic discharge was observed in patients during out-of-hospital cardiac arrest. After administration of 1 mg adrenaline there was a further massive increase in plasma adrenaline concentration. These results accord with those of others who have reported similar findings in animal models and in humans.^{17 18} We observed significantly higher adrenaline and noradrenaline concentrations in failed resuscitation than in successful resuscitation, both before and after adrenaline administration. Thus some release of catecholamines is critical for vital organ perfusion and restoration of spontaneous circulation, but too much is associated with a poor prognosis. It is unclear at this time whether this balance is secondary to the complex alpha and beta activities of different doses of catecholamines or to other factors critical for maintaining adequate organ perfusion.

Significant differences in hormone concentrations between the resuscitated and failed resuscitated patients demonstrate that a special hormonal constellation is associated with and may be closely linked to restoration of spontaneous circulation. An increased understanding of the complex endogenous release of stress hormones may help in the development of better ways to administer stress hormone "cocktails" to improve the outcome of patients in cardiac arrest, which at present is still poor.¹⁹

In the present study the standard drug treatment that accompanied mechanical cardiopulmonary resuscitation may have influenced plasma hormone concentrations. The interval between the start of cardiopulmonary resuscitation and administration of adrenaline was the same in all patients. Only adrenocorticotropin in resuscitated patients was significantly higher after exogenous adrenaline: this effect may have been mediated by β adrenoceptors.²⁰ Our study does have limitations. We were able to obtain hormonal data before adrenaline in only about 50% of cases, because our study protocol was designed to prevent any delay in adrenaline administration as a result of blood sampling. A further analysis of demographic data confirmed

that this subgroup was representative of the entire patient population. Hormone concentrations may also be influenced by the patient's condition in the minutes and hours before cardiac arrest. But in all patients the history indicated a sudden cardiac event. We cannot exclude the possibility that the difference in plasma adrenaline concentration may reflect better mixing and/or metabolism of the exogenous adrenaline related to greater cardiac output and splanchnic flow in those who were successfully resuscitated. A lower cardiac output during cardiopulmonary resuscitation might also impair the release of pituitary arginine vasopressin and adrenocorticotropin. On the other hand, the significantly higher adrenaline and noradrenaline concentrations before adrenaline administration in patients in whom resuscitation failed demonstrate that the observed differences in hormone concentrations are not caused by differences in organ perfusion.

This study showed that plasma concentrations of endothelin, catecholamines, arginine vasopressin, and adrenocorticotropin rise rapidly during cardiopulmonary resuscitation. The pattern of endothelin and arginine vasopressin release suggest that both are released from the neurohypophysis. Despite the considerable sympathochromaffin response, the lower arginine vasopressin and adrenocorticotropin concentrations during cardiopulmonary resuscitation in patients in whom resuscitation failed may influence coronary and cerebral perfusion pressure as well as cell membrane and organ stability, and hence the success of resuscitation. Administration of arginine vasopressin seems to improve the perfusion of vital organs during cardiac arrest and it may give better results than adrenaline.^{21,22} A more comprehensive evaluation of fundamental hormonal responses to the stress of cardiac arrest may improve outcome in patients with only a marginal chance of survival.

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