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ANDRZEJ MYSIAK[1], BERND W. BÖTTIGER[2], MAŁGORZATA KOBUSIAK-PROKOPOWICZ[1], STEPHAN A. PADOSCH[2]

Serum β-endorphin and Catecholamine Concentrations After Successful Resuscitation

Stężenie β-endorfiny i katecholamin w surowicy u chorych po skutecznej resuscytacji krążeniowo-oddechowej

[1] Department and Clinic of Cardiology, Silesian Piasts University of Medicine in Wrocław, Poland
[2] Department of Anesthesiology, University of Heidelberg, Germany

Abstract

Objectives. The aim of this prospective study was to assess the relation between hemodynamic changes and β-endorphin and catecholamine levels in cardiac arrest survivors in the early postresucitation period.
Material and Methods. Thirty-two patients in whom spontaneous circulation (ROSC) was restored successfully after cardiac arrest due to non-traumatic reasons were enrolled. Hemodynamic measurements were carried out within the first 24 hours. Serum β-endorphin and catecholamine levels were assessed by the radioimmunometric method.
Results. All the patients in whom ROSC was obtained (groups I and II) revealed significantly increased β-endorphin levels compared with the control group (III). The highest mean serum β-endorphin level was observed in patients who died in hospital (279.3 ± 223.25 pg/ml, group II) compared with patients who survived until discharge (148.5 ± 70.4 pg/ml, group I) ($p < 0.05$). The differences in catecholamine levels in patients from groups I and II compared with group III were statistically significant ($p < 0.05$). Survivors demonstrated higher systemic vascular resistance (2830.4 ± 227.3 dyn/s/cm^5) and lower cardiac index (2.1 ± 0.5 l/min/m^2) than non-survivors (2425.6 ± 1118.9 dyn/s/cm^5 and 2.5 ± 0.4 l/min/m^2) ($p < 0.05$). Patients who died in hospital after ROSC had significantly higher HR, lower MAP, higher CVP, lower PVRI, lower MPAP, and lower PCWP than patients who survived until discharge.
Conclusions. The observed changes in the hemodynamic profile in patients after ROSC in connection with changes in β-endorphin level can depict the role of β-endorphin in the distortion of the regulation of vascular peripheral resistance after cardiac arrest (**Adv Clin Exp Med 2007, 16, 5, 635–642**).

Key words: beta-endorphin, catecholamines, hemodynamics, post-resuscitation period, systemic vascular resistance.

Streszczenie

Cel pracy. Ocena zależności między dynamiką zmian parametrów hemodynamicznych a stężeniami β-endorfiny i katecholamin w surowicy we wczesnym okresie poresuscytacyjnym u chorych po przebytym zatrzymaniu krążenia z przyczyn nieurazowych.
Materiał i metody. Do badania zakwalifikowano 32 chorych, u których udało się skutecznie przywrócić krążenie spontaniczne (ROSC) po zatrzymaniu krążenia spowodowanym przyczynami nieurazowymi. Grupę kontrolną stanowiło 31 pacjentów diagnozowanych kardiologicznie, którzy nie znajdowali się w stanie zagrożenia życia i nie przebyli zatrzymania krążenia. Próbki krwi do badań biochemicznych pobierano z żyły szyjnej wewnętrznej bezpośrednio po przyjęciu na oddział intensywnej terapii kardiologicznej. Stężenie β-endorfiny i katecholamin w surowicy oznaczano metodami radioimmunologicznymi. Parametry hemodynamiczne oceniano po założeniu cewnika Swana-Ganza do tętnicy płucnej w pierwszej dobie po przyjęciu.
Wyniki. Po przywróceniu krążenia spontanicznego u wszystkich badanych chorych (grupa I – chorzy, którzy przeżyli do wypisu ze szpitala i grupa II – chorzy, którzy zmarli podczas dalszej hospitalizacji) wykazano istotne zwiększenie stężenia β-endorfiny w surowicy w porównaniu z grupą kontrolną (grupa III). Większe stężenie β-endorfiny w surowicy obserwowano u chorych, którzy zmarli podczas hospitalizacji (279,3 ± 223,25 pg/ml, grupa II); w porównaniu z chorymi, którzy przeżyli do wypisu ze szpitala (148,5 ± 70,4 pg/ml, grupa I) ($p < 0,05$). Obserwowano również istotne statystycznie różnice w odniesieniu do stężenia katecholamin w surowicy u chorych

z grup I i II w porównaniu z osobami z grupy kontrolnej (grupa III; $p < 0,05$). Chorzy, którzy przeżyli wykazywali istotnie większy systemowy opór naczyniowy (SVRI: 2830,4 ± 227,3 dyn/sek/cm^{-5}) i mniejszy wskaźnik sercowy (CI: 2,1 ± 0,5 l/min/m^2) niż chorzy, którzy zmarli podczas hospitalizacji (SVRI: 2425,6 ± 1118,9 dyn/sek/cm^{-5} i CI: 2,5 ± 0,4 l/min/m^2) ($p < 0,05$). Chorzy, którzy zmarli podczas hospitalizacji charakteryzowali się także istotnie większą częstotliwością serca, mniejszym średnim ciśnieniem tętniczym, większym ośrodkowym ciśnieniem żylnym, mniejszym naczyniowym oporem płucnym, mniejszym średnim cisnieniem w tętnicy płucnej i mniejszym ciśnieniem zaklinowania w porównaniu z chorymi, którzy przeżyli do wypisu ze szpitala.
Wnioski. Obserwowane zmiany w profilu hemodynamicznym u chorych po ROSC w powiązaniu ze zmianami stężenia β-endorfiny w surowicy mogą wskazywać na związek zwiększonego uwalniania β-endorfiny z zaburzeniami systemowego oporu naczyniowego i adaptacji układu krążenia w tej grupie pacjentów (**Adv Clin Exp Med 2007, 16, 5, 635–642**).

Słowa kluczowe: β-endorfina, katecholaminy, parametry hemodynamiczne, ROSC, obwodowy opór naczyniowy.

As seen in experimental studies so far, cardiac arrest and cardiopulmonary resuscitation (CPR) lead to maximum stimulation of the adrenergic system and the highest endogenously released plasma catecholamine levels [1, 2]. However, large therapeutic doses of epinephrine during CPR are often necessary to improve perfusion pressure in order to achieve success in resuscitation efforts in animal experiments [3] and in patients as well as in the post-resuscitation period [4]. After untreated myocardial infarction, high endogenous catecholamine levels have been shown not to correlate with such clinical parameters as blood pressure (BP) and heart rate (HR) [5]; moreover, clinical studies on patients in the post-resuscitation period revealed that high plasma endogenous levels of catecholamines increased neither BP nor HR [6]. In fact, abnormalities in endocrine function, for example regarding the hypothalamo-pituitary axis, are frequently observed in critically ill patients [7], summarily with a potential imbalance of endogenous vasoactive substances. Moreover, the role of β-endorphin, a stress hormone which is rapidly released as part of the neuroendocrine response to various stimuli in post cardiac arrest and the restoration of spontaneous circulation, has not been studied [8].

The aim of this study was to assess the serum levels of released β-endorphin and catecholamines during the early post-resuscitation period to investigate if they were different in survivors and non-survivors and also to assess a possible correlation between the serum levels of these substances and hemodynamic variables in the post-resuscitation period. The present authors hypothesize that the increased release of vasodilatation substances is connected with worse balance of the circulatory system in the early period of ROSC.

Material and Methods

The study protocol was approved by Institutional Review Board of the Wrocław Medical University. Data was collected prospectively from patients admitted consecutively to the intensive care unit (ICU) after cardiopulmonary resuscitation due to non-traumatic cardiac arrest in whom spontaneous circulation (ROSC) had been successfully restored. Overall, 32 adult patients, including 11 women and 21 men, were enrolled (mean age: 63.9 ± 13.1 years) (Table 1). The study included patients in whom a cardiac etiology was presumed to be the immediate cause of sudden cardiac arrest. Patients with underlying non-cardiac cause of arrest, such as trauma, hypoxia, or hemorrhagic shock, were not enrolled. The control group included 31 persons (13 women and 18 men mean age: 55.5 ± 18.9 years) who were patients hospitalized for assessment of the cardiovascular system, were not in a life-threatening condition, and had not suffered from cardiac arrest. The diagnosis in 16 of them confirmed ischemic heart disease, in 8 of them hypertension, in 5 of them mitral valve prolapse, and 2 were diagnosed as healthy.

The study patients were assessed in the following groups: patients who survived until discharge (group I, n = 10), patients who died during their hospital stay (group II, n = 22), and the controls (group III, n = 31) (Table 1). None of the patients studied had received cyclooxygenase inhibitor therapy prior to hospitalization. Cardiopulmonary resuscitation and defibrillation were performed by emergency physicians of the Emergency Care Unit in Wrocław in strict accordance with the European Resuscitation Council Guidelines [9, 10]. According to the Utstein guidelines, ROSC was defined as the return of a spontaneous palpable carotid pulse with a systolic blood pressure 60 mm Hg [11]. The patients were subsequently submitted to further routine diagnostic procedures and conventional therapy appropriate for their individual conditions, with the aim of stabilizing circulation and respiration as well as normalization of central nervous system (CNS) function. Immediately after admission to the ICU the patients were equipped with a pulmonary artery

Table 1. Epidemiological data

Tabela 1. Dane epidemiologiczne

	Survivors (Przeżyli) n = 10	Non-survivors (Zmarli) n = 22	Non-survivors (Zmarli) < 48 hrs n = 5	Non-survivors (Zmarli) > 48 hrs n = 17
Age – years (Wiek – lata)	57.2 ± 11.8	64.7 ± 12.1	67.8 ± 5.9	66.3 ± 9.7
Cause of cardiac arrest (Przyczyna zatrzymania krążenia)				
Myocardial infarction (Zawał mięśnia sercowego)	4	7	2	5
Cardiogenic shock (Wstrząs kardiogenny)	1	6	2	4
Unstable angina pectoris (Niestabilna dławica piersiowa)	4	3	–	3
Pulmonary embolism (Zatorowość płucna)	1	2	1	1
Electrolyte disturbances (Zaburzenia elektrolitowe)	–	2	–	2
Unknown (Nieznana)	–	2	–	2
Initial cardiac rhythm (Początkowy rytm serca)				
Asystolia (Asystolia)	2	7	2	5
VF	8	12	2	10
PEA	–	3	1	2
Bystander witnessed cardiac arrest (Zatrzymanie krążenia w obecności świadka)	8	18	3	15
Time from alarm to arrival of emergency team – min (Czas od zatrzymania krążenia do przybycia zespołu pogotowia ratunkowego – min)	4.3 ± 3.2	7.2 ± 4.1	7.8 ± 5.4	5.9 ± 2.7
Duration of CPR – min (Czas trwania CPR – min)	5.86 ± 4.84	17.1 ± 8.9	37.5 ± 8.5	13.3 ± 2.3
Duration of cardiac arrest without CPR – min (Czas trwania zatrzymania krążenia do momentu podjęcia CPR – min)	1.26 ± 0.9	3.01 ± 2.1	6.9 ± 3.8	2.9 ± 2.0
Electrical defibrillation (Defibrylacja)	8	12	2	10

catheter (PAC) placed in the internal jugular vein; at the same time, blood samples were taken. Only blood samples taken on admission were included in the study.

Multiple organ failure was assessed during the first 24 hrs after ROSC on the basis of average parameters required for calculations according to APACHE II score (Acute Physiology And Chronic Health Evaluation) [12].

Blood samples for the determination of β-endorphin levels were drawn into pre-chilled syringes containing EDTA (0.3 ml, 77 mol/l) and tromethamol (1 mg/ml blood). The samples were centrifuged at 1600 rpm for 15 min at 0°C, blood plasma was separated and stored at –70°C before analysis. Plasma immunoreactive β-endorphin levels were directly assayed by the immunoradiometric assay method with reagents supplied by Peninsula Laboratories, Inc., Bachem California, USA (RIK 8616). The intra- and inter-assay coefficients of variation (CVs) were 2.6% and 8%, respectively.

Blood samples for total plasma catecholamine determination were collected in lithium heparinate monovettes containing 100 µl of an antioxidative solution containing 61 g/l glutathione and 76 g/l EDTA. The samples were centrifuged at 2000 rpm for 20 min and plasma was separated and stored at –20°C before analysis. Plasma levels of total catecholamines were determined by immuno-

Table 2. Hemodynamic profile of the examined patients

Tabela 2. Profil hemodynamiczny chorych

Parameters (Wskaźniki)	Survivors until discharge (I) (Przeżyli do wypisu (I)) n = 10	Non-survivors (II) (Zmarli (II)) n = 22	I vs. II
HR l/min (AS uderzenia/min)	82.3 ± –4.2	104.1 ± 10.1	*
MAP mm Hg	83.4 ± 3.3	78.1 ± 22.7	*
CVP mm Hg	9.1 ± 1.3	10.2 ± 2.2	ns.
PVRI dyn/s/cm^5 (PVRI dyn/sec/cm^{-5})	407.6 ± 75.4	381.4 ± 136.7	*
MPAP mm Hg	27.1 ± 5.6	26.6 ± 10.6	ns.
PCWP mm Hg	16.3 ± 2.6	15.9 ± 3.4	*
SVRI dyn/s/cm^5 (SVRI dyn/sec/cm^{-5})	2830.4 ± 227.3	2425.6 ± 118.9	*
CI l/min/m^2	2.1 ± 0.5	2.5 ± 0.4	*

* Statistically significant difference ($p < 0.05$).

* Istotność różnic; p < 0,05.

assay supplied by Catechola, Immunotech, Prague, Czech Republic (REA kit). The intra- and inter-assay coefficients of variation were 4.1% and 7.4–13.4%, respectively.

Hemodynamic measurements were carried out prior to the outset of catecholamine therapy. Hemodynamic data were obtained via a femoral artery catheter into (Viggo-Spectramed, Helsinborg, Sweden) and a pulmonary artery catheter via the internal jugular vein (Braun, Melsungen, Germany). Measurements of the heart rate, arterial blood pressure, and cardiac output were obtained within 60 min after restoration of spontaneous circulation. Cardiac stroke volume was determined as the mean value from three successive measurements.

The following hemodynamic parameters and calculated derivatives were included: heart rate (HR), central venous pressure (CVP), average arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), average pulmonary pressure (MPAP), pulmonary vascular resistance index (PVRI), cardiac index (CI), and systemic vascular resistance index (SVRI). Heart rate and arterial pressure were recorded continuously. Cardiac output was measured by the thermodilution technique using 10-ml aliquots of cold (< 8°C) water (Simonsen & Well, Denmark).

Statistical Analysis

After checking by means of the χ^2 compatibility test and the λ-Kolmogorow-Smirnow test, the normal distribution of the investigated values was calculated. Statistical analysis was carried out on the basis of measurements of value variability (arithmetic means, standard deviation, mode, and median) and the frequency of occurrence of certain values (Student's *t*-test). Straight correlation coefficients (Pearson's *r*) were investigated. For investigation of correlations between single parameters, the free-rank correlation coefficient of Spearman and the test for the correlation of not normally distributed data were applied. Moreover, the significance of differences between mean values of the indices of the levels of the investigated hormonal parameters in the patients in the individual groups was assessed by comparison with the theoretical value according to a normal distribution and Student's *t*-test.

Results

With regard to hemodynamic profile, patients in group II revealed increased HR, lower MAP, higher CVP, lower PVRI, lower MPAP, lower PCWP, lower SVRI and higher CI than group I patients ($p < 0.05$) (Table 2). Group II demonstrated higher serum β-endorphin levels than group I and controls (279.3 ± 223.25 vs. 148.5 ± 50.1 and 110.5 ± 10.9 pg/ml, respectively, $p < 0.05$). The differences also reached the level of statistical significance between the control group and the two study groups ($p < 0.05$) (Table 3). Patients in groups I and II revealed increased levels of catecholamines in comparison with controls (2.17 ± 1.1 and 2.26 ± 0.97 vs. 1.2 ± 0.46 nmol/l, respectively, $p < 0.05$). The difference in catecholamine

Table 3. Biochemical profile of the examined patients

Tabela 3. Profil biochemiczny chorych

Parameters (Wskaźniki)	Survivors until discharge (I) (Przeżyli do wypisu (I)) n =10	Non-survivors (II) (Zmarli (II)) n = 22	Controls (III) (Grupa kontrolna (III)) n = 31	I vs. II	I vs. III	II vs. III
β-endorphin serum level – pg/ml (β-endorfina – stężenie w surowicy – pg/ml)	148.5± 50.1	279.3 ± 223.25	110.5 ± 10.9	*	*	*
Serum catecholamine level – nmol/l (Katecholaminy – stężenie w surowicy – nmol/l)	2.17 ± 1.1	2.26 ± 0.97	1.2 ± 0.46	ns.	*	*

* Statistically significant difference ($p < 0.05$).

* Istotność różnic; $p < 0,05$.

level in patients from groups I and II was not statistically significant (Table 3). Patients in group I presented lower APACHE II score than the non-survivors of group II (13.21 ± 2.8 vs. 27.24 ± 1.03, $p < 0.05$).

Group I revealed a positive correlation between serum total catecholamine levels and SVRI ($r = +0.77$, $p < 0.05$). In group II, a statistically significant negative correlation was found between β-endorphin serum levels and SVRI ($r = –0.7$, $p < 0.05$).

Discussion

Systemic resistance during cardiac arrest and subsequent CPR decreases to zero. The values remain low also after ROSC. Thus the restoration of adequate systemic resistance, whether spontaneous or resulting from therapeutic interventions, is one of the main elements determining the function of the peripheral circulation and, ultimately, prognosis. Experimental studies have demonstrated that during ischemia and reperfusion the contractility of the blood vessels decreases as a result of "stunning" [13]. The increase in plasma β-endorphin level during ischemia and early reperfusion was attenuated after selective kappa-opioid receptor antagonist nor-binaltorphimine (nor-BNI). Compared with the control experiment, nor-BNI left global hemodynamics, regional myocardial blood flow, and catecholamine levels unchanged. In conclusion, nor-BNI improves recovery from myocardial stunning after regional myocardial ischemia in chronically instrumented dogs [14].

The analysis of numerous reports on the role of opioids in the regulation of homeostasis in patients in critical conditions has confirmed a potentially beneficial effect of β-endorphine as an endogenous vasodilator decreasing cardiac afterload [15]. β-endorphin's effect is produced by both depressing specific central cardiovascular and respiratory control units and facilitating central vagal projections [16]. As demonstrated in human and animal investigations, unfavorable effects of opiate receptor antagonists may occur in patients and healthy subjects with increased vascular systemic resistance or may appear in situations where the systemic resistance is determined to a higher degree by factors other than neurohumoral balance [17, 18].

In the present study, all patients in whom ROSC was achieved revealed significantly increased serum β-endorphin levels compared with non-ROSC control patients. The highest serum β-endorphin levels were found in patients who died during their hospital stay. High serum levels of endogenous vasodilators may significantly impair adaptation of the circulatory system. As mentioned before, undesirable hemodynamic effects caused by exogenous vasodilators may be expected only in the case of initially increased systemic resistance.

The extent of increased serum catecholamine level was found to be a prognostic factor after cardiac arrest and during CPR [19]. During cardiac arrest and CPR the decrease in the amount and sensitivity of α- and β-adrenergic receptors may result in decreased metabolic and hemodynamic response to a high level of catecholamines in the early post-resuscitation phase [6, 20].

The hemodynamic effects of increased or decreased β-endorphin level may be due to a lack of balance between the effects of vasoconstrictive and vasodilating compounds as well as between the vascular reactivity and adaptation capability and susceptibility of the myocardium.

The present investigation revealed higher CI

values in patients who died in relation to the other subjects, pointing towards the development of an existing adaptation capability of the heart muscle (increased stroke volume and heart rate), which, however, was not able to normalize low arterial blood pressure due to very low systemic resistance. At the same time it should be stressed that normalization of arterial pressure does not directly determine normal tissue flow [21].

The patients who died in the post-resuscitation period were characterized by lower vascular resistance and higher cardiac index than those who survived. In earlier studies it was observed that systemic vascular resistance was also lower and cardiac index was higher in patients with septic shock who died [22–24]. This kind of hemodynamic profile, as in septic shock, was revealed in the patients of the present study after ROSC. An interesting observation is that the kinetics of neurohormones and inflammatory factors are the same in patients after ROSC and in septic shock [25–28].

These facts suggest that modulation of hemodynamic parameters might contribute to stabilization of the cardiovascular system in the post-resuscitation period. Administration of conventional pharmacological agents potentially affecting the hemodynamics through changes in the preload and afterload does not bring the expected effects in many patients. The results of the therapy are determined by the proportions between the doses of exogenous vasodilating or vasoconstrictive agents and antagonized endogenous substances. The administration of naloxone or epinephrine alone may increase the resuscitation rate, and both drugs are equally effective for CPR in a rat asphyxia model. However, the mechanism by which naloxone produces its efficacy during CPR remains unclear and further experimentation will be necessary [29].

On the basis of the obtained results, antagonization of β-endorphin may be justified in some patients who have high serum β-endorphin levels and low vascular systemic resistance, while in others with increased systemic vascular resistance it may lead to potentially unfavorable consequences. Possible indications for the use of equivalents of endogenous β-endorphin antagonists (ACTH, melanocortin) as well as opiate receptor antagonists should be based on earlier assessment of the levels of hormones in the blood. Perhaps the wrong proportions between the levels of both kinds of substances produce imbalance, the eradication of which might contribute to improvement in hemodynamics after ROSC.

Study Limitations

The number of investigated patients was small, although comparable to those of similar studies carried out by other authors. However, taking into account the need for multi-aspect pathophysiological analysis, larger material would be required. The coordination and unification of prospective, multicenter studies on this group of patients is difficult due to the requirements of life-saving procedures as well as technical and economical reasons.

It cannot be excluded that the mean levels of the investigated parameters in a group of patients with similar degrees of multi-organ failure were "washed out" by levels obtained from patients who died as a result of intrahospital "unexpected death". These incidents, especially when the investigated population is scarce, may obviously affect the formulation of a neurohumoral model in patients after ROSC. As can be seen, the taxonomical problem largely determines the results of investigations carried out on the non-homogenous population of patients in critical conditions.

The authors conclude that the patients who died during hospitalization following ROSC showed multiorgan failure, more substantial release of β-endorphin, and a more serious balance defect of the circulatory system. The observed changes in the hemodynamic profile in patients following ROSC in connection with changes in β-endorphin level can depict the role of β-endorphin in the distortion of the regulation of vascular peripheral resistance after cardiac arrest.

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Address for correspondence:

Małgorzata Kobusiak-Prokopowicz
Department and Clinic of Cardiology
Silesian Piasts University of Medicine
Pasteura 4
50-368 Wrocław
Poland
Tel.: +48 71 784 22 35
E-mail: kobusiak@poczta.fm

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