The role of the immuno-inflammatory response in patients after cardiac arrest

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Abstract

Introduction: The aim of the research was to assess whether concentrations of inflammatory markers in blood of patients after cardiac arrest (CA) are related to their clinical state and survival.

Material and methods: Forty-six patients, aged 63 ±12 years, 21 of them after out-of-hospital CA and 25 after in-hospital CA, were enrolled in the study. Twenty-five patients survived and were discharged from hospital (CA-S); 21 died during hospitalization (CA-D). The clinical state of the patients was evaluated by the Glasgow Coma Scale (GCS) and the Acute Physiology and Chronic Health Evaluation II (APACHE II). On the day immediately after CA (day 1) and on the following day (day 2) the plasma concentration of high specific C-reactive protein (hs-CRP), tumour necrosis factor (TNF)-α, interleukin-10 and interleukin-6 (Ile-6) were measured.

Results: In CA-D patients, compared with CA-S, a significantly higher concentration of hs-CRP (on day 1, 19 ±5 vs. 15 ±4; on day 2, 21 ±3 vs. 16 ±5 mg/l, $p < 0.001$) and Ile-6 (on day 1, 24.9 ±19.8 vs. 9.2 ±11.3; on day 2, 24.2 ±19.7 vs. 6.9 ±6.8 IU/ml, $p < 0.001$) was found. The level of TNF-α was greater in CA-D on day 1 (0.42 ±0.75 vs. 0.18 ±0.21 IU/ml, $p < 0.04$). Concentrations of hs-CRP and Ile-6 were correlated with the scores of GCS and APACHE II. Using logistic regression analysis and ROC curves the prognostic value of hs-CRP and Ile-6 for survival was proven.

Conclusions: Post-cardiac arrest immuno-inflammatory response, reflected mainly in elevated plasma concentration of hs-CRP and Ile-6, is not only correlated with patients' clinical state but also with prediction of survival.

Key words: cardiac arrest, post-cardiac arrest syndrome, survival, interleukin, C-reactive protein.

Introduction

Cardiac arrest (CA), the sudden cessation of effective cardiac pumping function [1], is still a major clinical problem with a high rate of early and long-term mortality [2, 3].

Since 1960, when Kouwenhoven described the technique of closed-chest cardiac massage and defibrillation in patients with CA [4], and 1966, when the first original consensus statement on cardiopulmonary resuscitation [5] was published by the National Academy of Sciences – National Research Council Ad Hoc Committee on Cardiopulmonary

Resuscitation, despite introducing novel resuscitation methods over recent decades, no significant progress in survival following successful cardiopulmonary resuscitation of in-hospital and out-of-hospital CA has been made [2, 6, 7]. It pinpoints that further enhancement of survival after CA may be achieved by focusing on the vitally important pathophysiological state after resumption of spontaneous circulation, which should be more thoroughly studied and treated [2].

It was Negovsky who, in the early 1970s, recognized the pathology caused by complete whole-body ischaemia [8], the so-called post-CA syndrome, a complex combination of possible brain injury, myocardial dysfunction and systemic ischaemia/reperfusion response, which implies activation of coagulation and immunologic pathways, increasing the risk of multiple organ failure and infection [2, 9, 10].

Very few studies have tried to determine the role for survival of systemic inflammatory response in the intermediate phase after CA, i.e. ranging from 6-12 until 72 h after CA [2, 11, 12]. Of these studies, the research of Adrie *et al.* on the role of interleukins in this period is particularly unique [11]. This is why the first aim of our research was to assess the possible relationship between concentration of markers of the immuno-inflammatory response and survival of patients in the intermediate phase after CA. The second aim was to evaluate the relationship between levels of the aforementioned markers and the patients' clinical state after CA.

Material and methods

The study was approved by the Bioethics Committee of the Medical University of Lodz with no requirement of informed patient consent due to their severe clinical state or unconsciousness after CA.

Patients

We enrolled 46 consecutive patients with a mean age of 63 ± 12 years, 31 men and 15 women, hospitalized directly after CA in the Department of Anaesthesiology and Intensive Care Therapy or in the Intensive Care Unit of the Department of Cardiology of the First Chair of Cardiology and Cardiac Surgery of the Medical University of Lodz in 2005. Fourty-five percentage of the patients suffered out-of-hospital and 55% in-hospital CA. The mechanism of CA was ventricular fibrillation or pulseless ventricular tachycardia in 78% of the patients and asystole or pulseless electrical activity in 22%. In 43 patients CA occurred during acute coronary syndrome, in 1 due to dilated cardiomyopathy, and in 2 it was caused by severe respiratory insufficiency. Detailed information on the patients is available in Table I. In the first 24 h

Table I. Selected clinical information on patients who survived hospitalization and were discharged from hospital and patients who died in hospital

Data	Patients after CA		CA-S vs. CA-D Value of *p*
	CA-S (*n* = 25)	CA-D (*n* = 21)	
Age [years]	62.6 ±10.6 (47-80)	64.2 ±13.3 (34-89)	NS
No. of men [*n* (%)]	17 (68%)	14 (67%)	NS
IHCA [*n* (%)]	16 (64%)	10 (48%)	NS
OHCA [*n* (%)]	9 (36%)	11 (52%)	NS
VF/VT [*n* (%)]	21 (84%)	10 (48%)	0.01
Asystole/PEA [*n* (%)]	4 (16%)	11 (52%)	0.01
Comorbidities:			
Diabetes [*n* (%)]	9 (36%)	2 (10%)	0.04
Hypertension [*n* (%)]	18 (72%)	11 (52%)	NS
Myocardial infarction [*n* (%)]	9 (36%)	7 (33%)	NS
Severe heart failure [*n* (%)]	1 (4%)	3 (14%)	NS
Stroke [*n* (%)]	2 (8%)	4 (19%)	NS
COPD [*n* (%)]	3 (12%)	5 (24%)	NS
GCS [score]	9 ±5 (3-15)	5 ±3 (3-13)	0.005
APACHE II [score]	21 ±10 (5-39)	28 ±2 (8-41)	0.02

CA – cardiac arrest, CA-S, CA-D – patients after CA who survived hospitalization and were discharged from hospital, ones who died in hospital, respectively, No. of men – number of men in the group, IHCA – patients who suffered in-hospital cardiac arrest, OHCA – patients who suffered out-of-hospital cardiac arrest, VT/VF, asystole/PEA – patients with CA due to ventricular fibrillation or ventricular tachycardia, or due to asystole or pulseless electrical activity, COPD – chronic obstructive pulmonary disease, GCS – Glasgow Coma Scale, APACHE II – Acute Physiology and Chronic Health Evaluation II, NS – non-significant

after CA, cardiogenic shock was observed in 5 patients. The appropriate treatment, including percutaneous coronaroplasty, intra-aortic balloon pumping, mechanical ventilation and suitable pharmacology, was used for all the patients. Hypothermia or coronary artery bypass grafting was not applied. Patients in whom CA occurred in the final stages of chronic wasting diseases or CA was related to mechanical trauma were not included in the study.

On the first day of hospitalization 2 patients died, on the second day 1 patient, and on the third day 2 patients. Finally, 2 groups were created: 21 patients who died during hospitalization (CA-D) and 25 patients who survived and after achieving optimally stable function of all vital organs and systems were discharged from the intensive care unit (CA-S). Most CA-S patients were discharged home; some of them were transferred to another facility due to individual need of additional treatment, all of them on spontaneous respiration, without circulatory support and in a good neurological state.

Methods of data collection

At 8.00 a.m. on the day following the CA (day 1) and the next day (day 2) the clinical state of the patients after CA was determined by means of the Glasgow Coma Scale (GCS), assessing the state of the central nervous system [13, 14], and Acute Physiology and Chronic Health Evaluation II (APACHE II), describing the general clinical state [13, 15, 16]. Values of the scales of the patients after CA are exhibited in Table II.

Blood venous samples were taken from the patients of both groups at 8.00 a.m. on day 1, i.e. 4-16 h after CA, and on day 2, i.e. after a further 24 h. From these samples, morphologic parameters of blood, including white blood count (WBC), were evaluated (for this purpose we employed ABX Micros 60 Haematology System, produced by Horiba ABX, France, and required reagents: ABX Lysebio, ABX Monoclair, ABX Eosinofix, ABX Basolyse II and ABX Diluent). Other typical biochemical parameters, not mentioned in the rest of this article, were also measured.

The blood samples were centrifuged at rotational speed of 4000 rpm for 1 min using a high-speed brushless centrifuge (MPW-350, produced by MPW Med. Instruments, Poland). The plasma samples recovered in this way were immediately frozen at –70°C. Using enzyme-linked immunosorbent assay (ELISA) and a microplate reader (Microplate Reader Model Σ 960, produced by Metertech Inc., Taiwan) we determined the plasma concentration of the following parameters related to the inflammatory state: high sensitivity C-reactive protein (hs-CRP), tumour necrosis factor α (TNF-α), interleukin-6 (Ile-6) and interleukin-10 (Ile-10). For assessing their levels we used a high-sensitivity enzyme immunoassay for the quantitative determination of C-reactive protein (CRP) concentration in human plasma (produced by DRG International, Inc., USA), and 3 kits for determining the concentrations of interleukins: Human IL-6 Immunoassay, Human IL-10 Immunoassay and Human TNF-α/TNFSF1A Immunoassay (manufactured by R&D Systems, Inc., USA).

Statistical analysis

Parameters composed of quantitative data collected from patients of CA-D and CA-S were analysed for being of normal distribution by the Shapiro-Wilk test. For comparison of the parameters of normal distribution in both groups, a *t*-test and relative to it the Cochran-Cox test were employed, depending on the results of the comparison of the variations assessed by Levene's test. The Mann-Whitney test was used for comparison of quantitative data of parameters with non-normal distribution in any of the two groups being compared. For comparison of parameters of qualitative value between the groups, placed in a two-by-two occurrence array, depending on the expected value and the total number of the sample being analysed, χ^2 test, χ^2 test with Yates

Table II. Clinical state of patients who survived hospitalization and patients who died in hospital on 2 consecutive days after cardiac arrest, evaluated by means of the Glasgow Coma Scale and Acute Physiology and Chronic Health Evaluation II

Scale	Day after CA	Patients after CA		CA-S vs. CA-D Value of *p*
		CA-S	CA-D	
GCS	Day 1	12 ±4 (3-15)	7 ±5 (3-15)	0.001
	Day 2	13 ±4 (3-15)	6 ±5 (3-15)	0.0001
APACHE II	Day 1	12 ±9 (2-27)	23 ±9 (3-37)	0.0004
	Day 2	12 ±10 (2-34)	15 ±11 (2-30)	NS

CA – cardiac arrest, GCS – Glasgow Coma Scale, APACHE II – Acute Physiology and Chronic Health Evaluation II, CA-S, CA-D – patients after CA who survived hospitalization and were discharged from hospital, ones who died in hospital, respectively, day 1 – the day following the day of CA, day 2 – the day after day 1, NS – non-significant

correction, V-squared test or Fisher exact test was employed.

A statistical hypothesis, H_0, assuming no difference in the value or occurrence of a parameter between the groups, and an alternative hypothesis, H_1, assuming a significant difference, were put forth. As the significant value of statistical significance (p) to reject H_0 and to accept H_1, a level below 0.05 was accepted.

The relationship of the quantitative parameters with scores of GCS and APACHE II in the 2 days after CA was determined by calculating Spearman's rank correlation coefficient.

To assess a possible correlation between the parameters mentioned above (independent variables) and demise or survival after CA (dependent dichotomic variable) we created univariate models by means of logistic regression analysis (LRA). For each independent variable, the regression coefficient with its statistical significance and odds ratio was calculated, assuming a 95% confidence interval.

The appraisal of possible association between the parameters of immuno-inflammatory state (independent variables) and the outcome of CA (dependent dichotomic variable) was also performed using receiver operating characteristic (ROC) curves, determining the area under the curve (AUC) and the cut-off point, the value of a parameter that reveals optimal sensitivity and specificity for predicting the outcome of CA with the highest accuracy. After assessing the shape of the ROC curve, an evident relationship between the variables was recognized arbitrarily when AUC was greater than 0.75 and the lower limit of the 95% confidence interval for AUC was above 0.5.

For computed mathematical calculations Statistica 8 Pl software was employed (produced by StatSoft Inc, USA).

Results

Due to a graver clinical state the patients who died after CA revealed lower scores of GCS and higher ones of APACHE II than patients who survived hospitalization (Table II).

In CA-D, compared with CA-S, significantly higher concentrations of hs-CRP and Ile-6 on day 1 and day 2 were noted (Table III). The concentration of TNF-α was significantly higher in CA-D only on day 1. There was no significant difference in concentration of Ile-10 and WBC between CA-D and CA-S.

Inflammatory response and clinical state

A significant correlation between the clinical state of the patients after CA and the parameters of inflammatory state was found (Table IV). Concentrations of hs-CRP and Ile-6, measured on day 1 and day 2, were negatively correlated with the score of GCS and positively with the values of APACHE II, assessed on both days. The level of TNF-α on day 1 was negatively correlated with scores of GCS and positively with values of APACHE II on day 1 and day 2. The concentration of TNF-α on day 2 was negatively correlated with scores of GCS and positively with values of APACHE II assessed on day 1. The level of Ile-10 on day 2 was positively correlated with the score of APACHE II on the same day.

Using GCS and APACHE II, no significant difference in WBC between CA-D and CA-S (Table III),

Table III. Values of the parameters involved in immune-inflammatory response after cardiac arrest in patients who survived hospitalization and patients who died in hospital

Parameter	Day after CA	Patients after CA		CA-D vs. CA-S Value of p
		CA-S	CA-D	
hs-CRP [mg/l]	Day-1	15±4 (6.6-22.4)	19 ±5 (7.0-24.4)	0.001
	Day-2	16±5 (3.4-22.7)	21 ±3 (13.1-24.8)	0.0007
Ile-6 [IU/ml]	Day-1	9.2±11.3 (0.4-47.4)	24.9 ±19.8 (2.14-54.8)	0.001
	Day-2	6.9 ±6.8 (0.21-24.7)	24.2 ±19.7 (2.53-54.1)	0.001
Ile-10 [IU/ml]	Day-1	0.50 ±1.21 (0.0-4.41)	0.48 ±0.91 (0.0-3.61)	NS
	Day-2	0.21 ±0.59 (0.0-2.73)	0.32 ±0.66 (0.0-2.53)	NS
TNF-α [IU/ml]	Day-1	0.18 ±0.21 (0.0-0.83)	0.42 ±0.75 (0.0-3.46)	0.04
	Day-2	0.18 ±0.18 (0.0-0.56)	0.47 ±0.99 (0.04-4.24)	NS
WBC [10^9/l]	Day-1	13.9 ±4.3 (9.0-21.7)	11.5 ±4.3 (4.3-21.3)	NS
	Day-2	11.9 ±4.0 (8.6-14.3)	12.4 ±4.8 (3.3-18.3)	NS

CA – cardiac arrest, CA-S, CA-D – patients after CA who survived hospitalization and were discharged from hospital, ones who died in hospital, respectively, day 1 – the day following the day of CA, day 2 – the day after day 1, NS – non-significant, hs-CRP – high-sensitivity C-reactive protein, TNF-α – tumour necrosis factor α, Ile-6 – interleukin-6, Ile-10 – interleukin-10, WBC – white blood count

Table IV. Correlations among clinical state of all patients after cardiac arrest, described by the Glasgow Coma Scale and Acute Physiology and Chronic Health Evaluation II, and values of the parameters associated with post-resuscitation inflammatory reaction, expressed by means of Spearman's rank correlation coefficients

Parameter		GCS		APACHE II	
		Day 1	Day 2	Day 1	Day 2
hs-CRP	Day 1	–0.38	–0.43	0.44	–
	Day 2	–0.39	–0.37	0.50	0.33
Ile-6	Day 1	–0.57	–0.53	0.65	–
	Day 2	–0.49	–0.51	0.55	0.44
Ile-10	Day 1	–	–	–	–
	Day 2	–	–	–	0.41
TNF-α	Day 1	–0.34	–0.37	0.38	–
	Day 2	–0.37	–	0.39	–
WBC	Day 1	–	–	–	–
	Day 2	–	–	–	–

GCS – score of Glasgow Coma Scale, APACHE II – score of Acute Physiology and Chronic Health Evaluation II, day 1 – the day following the day of CA, day 2 – the day after day 1, hs-CRP, TNF-α, Ile-6, Ile-10 – concentration of high-sensitivity C-reactive protein, tumour necrosis factor α, interleukin-6 and interleukin-10, respectively, WBC – white blood count

nor a significant correlation between WBC and the scores of the scales assessing clinical state after CA was observed (Table IV).

Inflammatory response and survival after cardiac arrest

In the univariate model created by means of logistic regression analysis, a significant correlation of concentrations of hs-CRP and Ile-6 as continuous variables with the outcome of CA was found (Table V). Prognostic value for survival of levels of these parameters of immuno-inflammatory state on both days was also proven after assessing the ROC curves (Figures 1-4), with AUC above 0.75 and calculated cut-off points revealing good sensitivity, specificity and accuracy.

Discussion

Not many previous studies have been devoted to the post-cardiac arrest inflammatory response [2, 11, 12]. Adrie *et al.* [11] in their exceptional study showed a marked increase in plasma cytokines of patients successfully resuscitated after CA, especially in non-survivors. But it is our research where the differences in the blood concentration of immuno-inflammatory markers in the intermediate

Table V. Relations among concentrations of the parameters associated with post-resuscitation inflammatory reaction and survival after cardiac arrest assessed with univariate model created by logistic regression analysis

Parameter		OR of the model	Value of *p* the model	Unit OR (95% CI)	Value of *p* of the parameter in the model
hs-CRP	On day 1	6.4	0.002	1.25 (1.06-1.48)	0.012
	On day 2	7.5	0.0006	1.4 (1.06-1.84)	0.017
Ile-6	On day 1	4.8	0.001	1.07 (1.02-1.12)	0.01
	On day 1	4.7	0.0004	1.11 (1.02-1.21)	0.02
Ile-10	On day 2	–	–	–	–
	On day 2	–	–	–	–
TNF-α	On day 1	–	–	–	–
	On day 2	–	–	–	–
WBC	On day 1	–	–	–	–
	On day 2	–	–	–	–

Day 1 – the day following the day of cardiac arrest, day 2 – the day after day 1, OR – odds ratio, CI – confidence interval, unit OR (95% CI) – odds ratio for a unit change in the explanatory variable with 95% confidence interval in brackets, p value of the model – value of the goodness of fit of χ^2 statistic of the univariate model, hs-CRP, TNF-α, Ile-6, Ile-10 – concentration of high-sensitivity C-reactive protein, tumour necrosis factor α, interleukin-6 and interleukin-10, respectively, WBC – white blood count

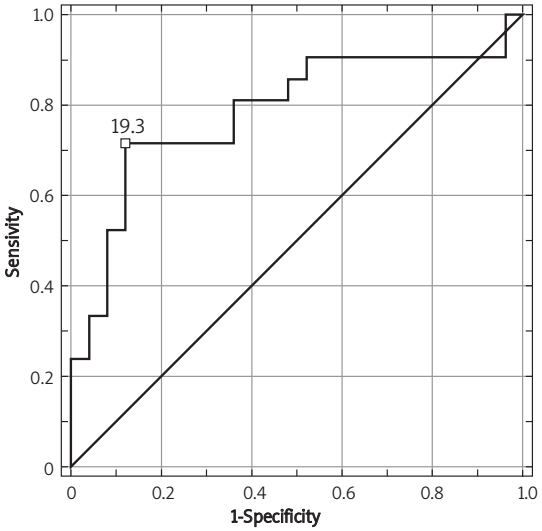

Figure 1. ROC curve of prediction of the outcome of cardiac arrest with the concentration of high specific C-reactive protein on day 1

AUC 0.785 (0.642-0.927) cut off point: 19.3 (sensivity 0.714, specificity 0.88, accuracy 0.804)

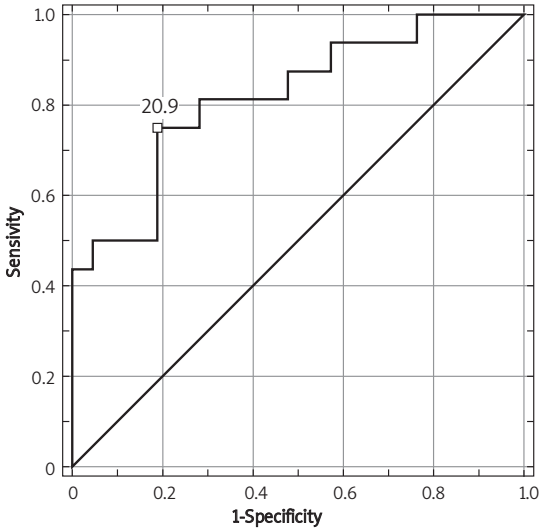

Figure 2. ROC curve of prediction of the outcome of cardiac arrest with the concentration of high specific C-reactive protein on day 2

AUC 0.818 (0.68-0.957) cut off point: 20.9 (sensivity 0.750, specificity 0.810, accuracy 0.784)

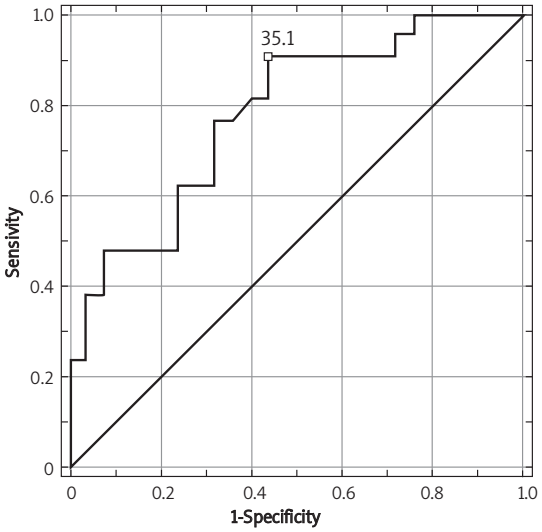

Figure 3. ROC curve of prediction of the outcome of cardiac arrest with the concentration of interleukin-6 on day 1

AUC 0.776 (0.642-0.91) cut off point: 35.1 (sensivity 0.905, specificity 0.560, accuracy 0.717)

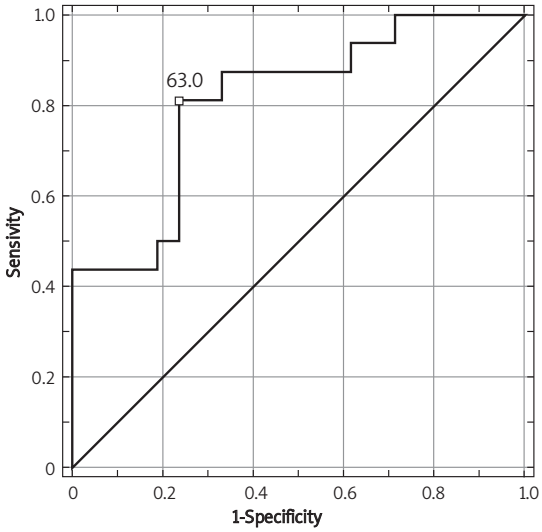

Figure 4. ROC curve of prediction of the outcome of cardiac arrest with the concentration of interleukin-6 on day 2

AUC 0.81 (0.668-0.951) cut off point: 63.0 (sensivity 0.813, specificity 0.762, accuracy 0.784)

phase after CA between patients who died and who survived after CA have not only been highlighted and correlated with the clinical state, but proved to possess prognostic value as well.

C-reactive protein turned out to be an important marker of inflammation after CA. Of the enrolled patients after CA, in the 93% who suffered acute coronary syndrome we observed a significant relationship of elevated concentration of hs-CRP with a poorer state of the central nervous system and worse clinical state, as well as with bad prognosis. In patients in the first 2 days of acute myocardial infarction a predictive value of concentration of CRP for survival was documented by Ziakas *et al.* [17]. Moreover, Zebrack *et al.* [18] ascertained that an increased level of CRP is related to a higher risk of death or non-death-ended myocardial infarction in patients with stable and unstable coronary artery disease.

In this research, the biological mechanism of the relationship between the level of CRP and survival after CA was not determined. However, patho-

mechanisms mentioned by other authors may be involved. Satoh *et al.* [19] found that poorer systolic function of the left ventricle correlated with increase in local production of interleukins in the myocardium, which was influenced by growth of levels of CRP in patients with dilated cardiomyopathy. A higher risk of coronary events and greater mortality associated with expression of adhesion molecules (ICAM-1) on the walls of coronary arteries due to an elevated level of CRP was described by Yeh [20].

Ile-6 is considered to be one of the most important cytokines of multidirectional activity [21, 22]. It is of little surprise that this interleukin is involved in the systemic response triggered by such severe stress as CA-induced whole-body hypoxia [11]. In our research, a greater concentration of Ile-6 was strongly correlated with a worse clinical state of patients after CA. We also demonstrated the predictive value of an elevated level of Ile-6 for death after CA. Adrie *et al.* [11] also described a higher concentration of Ile-6 in non-survivors than survivors on the first day after CA. In the available literature, a high level of Ile-6 is considered to be associated with an increased number of coronary events and elevated mortality in patients with acute coronary syndrome and with stable angina [23-25]. Geppert *et al.* [26] recognised the level of Ile-6 as an independent prognostic factor of 30-day survival in patients suffering acute myocardial infarction and shock. A poorer prognosis after CA, or in coronary artery disease, may be due to a correlation with the concentration of Ile-6 aggravation of multiorgan dysfunction in cardiogenic and septic shock, described by Geppert *et al.* [27].

To sum up, on the basis of the previous research mentioned above and the results of our study, we consider the level of CRP and Ile-6 to be prognostic factors of survival after CA.

It is believed that the main biological function of Ile-10 is inhibition of the inflammatory response [28]. Adrie *et al.* [11] described a higher level of Ile-10 on the first day in post-CA patients who subsequently died. On the second day after CA we observed a greater mean concentration of Ile-10 in the patients who died after CA than in the ones who survived. Moreover, there was a significant relationship on day 2: the worse the general clinical state, the higher the concentration of Ile-10. Thus, we assume that Ile-10 plays a role in the modulation of the inflammatory response in the later stage of the post-resuscitation period. We did not prove that the concentration of Ile-10 may be a prognostic factor of survival after CA.

Tumour necrosis factor-α, produced mainly by blood cells, is an interleukin of pleiotropic activity [29, 30]. In patients after CA we found the correlation between an elevated concentration of TNF-α and a worse state of the central nervous system, or poorer general state, to be more distinct on the first day after CA. On that day we also noted a significantly higher level of TNF-α in the patients who died than in those who survived. This is why we suspect that the concentration of TNF-α may be related to survival in the early post-resuscitation period despite a lack of proven correlation of TNF-α with the outcome of CA in logistic regression analysis. The available literature confirms our opinion on the vital importance of a TNF-α surge in critical care; signs of shock [31], impairment of internal organs [31] or acute respiratory insufficiency [30] were described as caused by a sudden secretion of TNF-α. In the early stage of the post-resuscitation period, a negative correlation between the concentration of TNF-α and ejection fraction of the left ventricle of the heart, known as an important predictive factor of survival [32], was described by Niemann [33] in a study on animals.

Leukocytes are involved in the damage of vascular endothelium and myocardium by means of an ischaemic-reperfusion mechanism [34], the phenomenon present in the post-resuscitation period [12]. An elevated number of leukocytes is considered to be important for the severely sick, which is reflected in a higher APACHE II score [15], describing the general clinical state [13, 15, 16]. Regardless of these facts, we found no correlation of WBC with either prognosis or clinical state after CA.

In conclusion, the post-cardiac arrest immuno-inflammatory response, reflected mainly in elevated plasma concentration of CRP and Ile-6, is not only correlated with patients' clinical state but also with prediction of survival. This suggests that anti-inflammatory treatment of patients after CA might become a novel therapeutic approach that has an impact on the outcome after CA.

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