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CELLULAR & MOLECULAR BIOLOGY LETTERS
Volume 12 (2007) pp 162 - 175
http://www.cmbl.org.pl

DOI: 10.2478/s11658-006-0062-y

Received: 11 May 2006
Revised form accepted: 06 September 2006
Published online: 06 December 2006

Short communication

N-TERMINAL BRAIN NATRIURETIC PROPEPTIDE LEVELS CORRELATE WITH PROCALCITONIN AND C-REACTIVE PROTEIN LEVELS IN SEPTIC PATIENTS

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Abstract: The aim of this study was to find the relationship between N-terminal brain natriuretic propeptide (NT-proBNP), procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations in septic patients. This was a prospective study, performed at Medical University Hospital No. 5 in Łódź. Twenty patients with sepsis and severe sepsis were included in the study. N-terminal brain natriuretic propeptide, procalcitonin and C-reactive protein concentrations, and survival were evaluated. In the whole studied group (128 measurements), the mean NT-proBNP, procalcitonin and C-reactive protein concentrations were,

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Abbreviations used: ACCP/SCCM – American College of Chest Physicians/Society of Critical Care Medicine; APACHE II score – acute physiological and chronic health evaluation ii score; BNP – brain natriuretic peptide; CRP – C-reactive protein; NT-proBNP – N-terminal brain natriuretic propeptide; PCT – procalcitonin; SIRS – systemic inflammatory response syndrome; SOFA score – sepsis-related organ failure assessment score

respectively: 140.80±84.65 pg/ml, 22.32±97.41 ng/ml, 128.51±79.05 mg/l. The correlations for the NT-proBNP level and procalcitonin and C-reactive protein levels were 0.3273 ($p<0.001$) and 0.4134 ($p<0.001$), respectively. NT-proBNP levels correlate with PCT and CRP levels in septic patients. In the survivor subgroup, the mean NT-proBNP plasma concentrations were significantly lower than in the non-survivor subgroup.

Key words: N-terminal brain natriuretic propeptide, Procalcitonin, C-reactive protein, Sepsis, Severe sepsis

INTRODUCTION

In 1992, the American College of Chest Physicians (ACCP) and the American Society of Critical Care Medicine (SCCM) published their official definitions of sepsis, severe sepsis and septic shock. These septic states are associated with poor prognoses and increased mortality [1]. For many years, studies have been conducted to find and introduce into clinical practice more sensitive and specific markers of the severity of the inflammatory response and organ dysfunction [2-5]. Procalcitonin (PCT) and C-reactive protein (CRP) blood concentrations are accepted sepsis markers. Cardiac dysfunction frequently accompanies severe sepsis and septic shock. N-terminal brain natriuretic propeptide (NT-proBNP) is a useful laboratory marker to indicate cardiac dysfunction [6-8]. Procalcitonin is a protein formed from 116 amino acids. In physiological conditions in thyroid C cells, PTC is a precursor of calcitonin, among others. Procalcitonin is generated as the result of the proteolysis of the pre-procalcitonin precursor protein, formed of 141 amino acids. In acute inflammatory reactions, an increase in PCT release to the blood is observed. Most probably, in those conditions, it does not originate from thyroid C cells. PCT is assumed to be synthesized in liver macrophages and monocytes, and also in pulmonary and intestinal neuroendocrine cells. The latest studies have also suggested that various types of blood leucocytes may be sites of PCT production [9-11]. PCT is a sensitive and specific marker of generalized bacterial, fungal or parasitic infection. The PCT level determined via the immunoluminometric method in subjects without generalized infection is <0.5 ng/ml. The level is not elevated or only insignificantly increased in the case of viral infection, while it demonstrates high dynamics of increase in septic patients, even reaching values exceeding 1000 ng/ml. The PCT level is generally not affected by injury, surgery, chronic inflammatory processes, autoimmune diseases or applied drugs with few exceptions. Serum PCT concentration correlates with the severity of sepsis, and is a reliable factor in determining the prognosis and response to the treatment. Initial studies estimating the correlation between PCT concentration and the severity of sepsis were carried out by Zeni *et al.* and published in 1994 [12]. They demonstrated that in cases of severe clinical course, the serum PCT concentration is higher. These observations were confirmed by later studies. PCT was also found to be the only serum marker other than neopterin enabling differentiation between sepsis and severe sepsis [13, 14].

The serum levels of CRP, an acute-phase protein synthesized by the liver following stimulus by various cytokines, markedly increase within hours of infection or inflammation. Numerous studies have demonstrated increased CRP levels in patients with sepsis [15-17].

N-terminal brain natriuretic propeptide is a newly described cardiac hormone. NT-proBNP consists of 76 amino acids and is formed from a propeptide pro-BNP, which is produced first of all in ventricular myocytes, and then splits in the blood serum into physiologically active brain natriuretic peptide and physiologically non-active NT-proBNP. Few studies demonstrated increased NT-proBNP levels in septic patients, but their relationship to PCT and CRP levels has not been evaluated [18, 19].

Considering that cardiac dysfunction is often present in patients with septic shock, and that PCT and CRP are markers of sepsis, we assumed that NT-proBNP levels correlate with PCT and CRP levels in septic patients. The aim of this study was to investigate the relationships between NT-proBNP and PCT and CRP plasma concentrations in septic patients.

MATERIALS AND METHODS

The approval of the Bioethics Committee of the Medical University in Łódź was obtained (No. RNN/26/03/KB), and 20 consecutive patients were qualified for the study: 15 men and 5 women. The basic data about the investigated group is given in Tab. 1.

The criteria of sepsis according to the definition accepted at the ACCP/SCCM conference (modified by the Polish Working Group on Sepsis [20]) were the basis for enrollment in the study [1, 2]. The investigations were carried out on each patient until the patient stopped meeting those criteria or died. All the patients were given verbal and written information about the potential risks and benefits of participation in the study. They gave written consent prior to the study.

Subjects were recruited consecutively from patients received by the ICU from 1st July 2003 to 31st July 2004. All the patients were treated by the same team of physicians, and care of the patients was conducted according to the same existing protocols. The standard treatment included administration of adequate antibiotics, control of the source of infection and supportive therapy (intravenous fluids, medication aiding the circulatory system, vasopressors, aiding failing organs). Two patients were given Recombinant Human Activated Protein C.

Blood serum NT-proBNP, PCT and CRP concentrations were determined for each patient at given time intervals. The first measurement was performed within 12 h of the patient's inclusion into the study, the second 12 h after the first, the third 24 h after the first, the fourth 48 h after the first, and the fifth and each subsequent measurement 48 h after the previous one. The quantitative determination of the NT-proBNP level (in pg/ml) (half life: 60-120 minutes) was based on the immunoenzymatic method: a test based on the competitive EIA

Tab. 1. Basic data for the studied group of patients.

Patient number	Sex	Age (yrs)	Length in ICU stay/ Length in hospital stay (days)	Basis for inclusion in the study *	Infection site	Microbial etiology	Initial number of scores in APACHE II	The highest number of organ failures	Death in the course of the study (Cause of death)
1	Male	49	4/59	S	Abdominal cavity	-	7	0	No
2	Male	39	44/44	S	Abdominal cavity	*P. aeruginosa*	14	3	No
3	Female	90	7/31	Ss	Abdominal cavity	-	17	1	No
4	Female	29	14/14	S	Abdominal cavity	*E. aerogenes*	9	5	Yes (MODS, DIC)
5	Male	33	13/88	Ss	Abdominal cavity	-	10	2	No
6	Male	49	55/55	Ss	Lungs/ Abdominal cavity	MRSA, *S.maltophilia*	19	4	No
7	Female	53	5/11	S	Abdominal cavity	-	3	1	No
8	Male	22	14/14	S	Lungs	MRSA	12	1	No
9	Male	70	11/11	Ss	Lungs	*P. aeruginosa*	14	1	No
10	Female	50	16/18	Ss	Abdominal cavity	MRSA, *E. cloacae*	17	4	Yes (MODS)
11	Male	47	7/16	Ss	CNS	-	11	2	No
12	Male	51	3/11	Ss	Abdominal cavity	-	8	1	No
13	Male	71	4/18	Ss	Abdominal cavity	*P. aeruginosa*	12	3	Yes (RCF)
14	Female	88	5/6	Ss	Abdominal cavity	-	10	1	No
15	Male	67	8/14	Ss	Abdominal cavity	MRSA	13	3	Yes (RCF)
16	Male	51	3/3	Ss	Lungs	-	24	4	Yes (RCF)
17	Male	59	6/31	Ss	Abdominal cavity	MRSA	7	2	No
18	Male	41	19/54	Ss	Abdominal cavity	MRSA	4	2	No
19	Male	30	14/15	Ss	Abdominal cavity	*E. coli*, *E. faecium*	11	2	No
20	Male	55	5/5	Ss	Lungs	-	17	4	Yes (RCF)

* Sepsis criteria according to the ACCP/SCCM definitions, modified by the Polish Working Group on Sepsis. DIC – disseminated intravascular coagulation; *E. aerogenes – Enterobacter aerogenes*; *E. cloacae – Enterobacter cloacae*; *E. faecium – Enterococcus faecium*; *E. coli – Escherichia coli*; MODS – multiple organ dysfunction syndrome; MRSA – methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa – Pseudomonas aeruginosa*; RCF – respiratory - circulatory failure; S – sepsis; *S. maltophilia – Stenotrophomonas maltophilia*; Ss – severe sepsis; *S. maltophilia – Stenotrophomonas maltophilia*

method. The reading was performed on an ETI Max 3000 analyzer (Dia Sorin) using Biomedica reagents. This competitive EIA test kit is designed to measure the immunoreactive N-terminal proBNP in diluted human serum, plasma or urine samples. In order to achieve high specificity, the kit incorporates an immunoaffinity purified sheep antibody specific for NT-proBNP (8-29), immobilized to the surface of a microtititer plate well. The assay is based on the competitive reaction of the unlabelled peptide in the standards or samples, and the horseradish peroxidase-labeled peptide (tracer) for the limiting binding sites of the NT-proBNP (8-29)-specific antibody. The concentration of the tracer and the concentration of the capture antibody are constant in all wells. Consequently, the only variable parameters of the system are the concentrations of the unlabelled peptides in the standards and samples. Hence, with increasing concentration of the peptide in the standard, the binding of the competing tracer is proportionally reduced. After removal of unbound tracer through washing, substrate (TMB) is added to the wells. The amount of HRP-labeled tracer bound to the microplate well proBNP (8-29) is quantitated by an enzyme-catalyzed color change detectable on a standard ELISA reader. The amount of color developed is inversely proportional to the amount of NT-proBNP immunoreactivity present in the standard or samples. A standard curve is plotted from the values measured, and the concentrations of NT-proBNP in the samples are calculated from this curve. In the Biomedica method, reference values for NT-proBNP are below 600 pg/ml (250 fmol/ml) in healthy persons.

The quantitative measurement of procalcitonin concentration (in ng/ml, half life: 22-23 hours) was performed with the immunoluminometric method using two monoclonal antigen-specific antibodies binding PCT. The luminescence was read in a BERLUX 250 luminator with a LUMI test PCT reagent (Brahms Diagnostica GmbH). In the Brahms Diagnostica GmbH method, the reference values for PCT are below 0.5 ng/ml in healthy persons.

To measure the CRP concentration (in mg/l, half life: 6-8 hours), the immuno-precipitation method was applied with the use of specific immunoglobulins. The measurements were performed with KonePro (Konelab) with Biomerieux reagents. In the Biomerieux method, the reference values for CRP are below 5 mg/l in healthy persons.

Assay characteristics and precise NT-proBNP, PCT and CRP determinations are presented in Tab. 2. The statistical analysis was performed with Statistica 5.1 PL (StatSoft, Poland) and Office 97 programs (Microsoft, Poland). To compare the tested parameters, adequate statistical tests were used, dependent on the quantity, sample matching, and the type of the investigated sample. To choose an appropriate test, it was checked whether the samples were the subject of normal distribution (Shapiro-Wilk test). When both samples had a normal distribution, T-Student's test was used for independent samples. When at least one sample had a distribution different from normal, Mann-Whitney's test was applied. The results of the testing were given in the form of $p<max$ (e.g. $p<0.05$). This means that a significant difference was observed at the distinguished level of

significance. The correlations between NT-proBNP and PCT and CRP concentrations were calculated. To determine the correlations, Spearman's correlation coefficient was calculated. The result was given in the form of $p<max$ (e.g. $p<0.05$).

Tab. 2. Assay characteristics and precision of NT-proBNP, PCT, CRP determinations.

Marker	Parameter				
NT-proBNP	Standard range:	0 to 1000 fmol/ml			
	Detection Limit:	5 fmol/ml			
	Intra-Assay	n=16	n=16		
	Mean (fmol/ml)	320	666		
	CV%	6.5%	4.0 %		
	Inter-Assay	n=3	n=3		
	Mean (fmol/ml)	320	666		
	CV%	4.4 %	3.8 %		
PCT	Standard range:	0.1-500 ng/ml			
	Detection Limit:	0.04 ng/ml			
	Intra-Assay	n=40	n=40	n=40	n=40
	Mean (ng/ml)	0.9	2.0	13.9	141.7
	CV%	3.8%	2	3.1	3.0
	Inter-Assay	n=122	n=69	n=120	n=116
	Mean (ng/ml)	0.4	2	15	98
	CV%	9.5%	5.6%	3.2%	3.2%
CRP	Standard range:	0 to 1000 mg/l			
	Detection Limit:	<2mg/l			
	Intra-Assay	n=20	n=20	n=20	
	Mean (mg/l)	10	48	108	
	CV%	2.49%	2.93%	3.19%	
	Inter-Assay	n=20	n=20	n=20	
	Mean (mg/l)	10	48	112	
	CV%	3.99%	2.45%	2.33%	

RESULTS

In total, 128 measurements (mean 6.4 for each patient) were performed in the investigated group. Six patients died (30%) from their underlying disease during the observation period of 28 days.

Some differences in the initial clinical parameters of the investigated groups where noticed. In the survivor subgroup, there were 3 patients (21.4%) with hypertension, 2 (14.3%) with ischemic heart disease, 2 (14.3%) with heart

failure, and 3 (21.4%) with diabetes. In the non-survivor subgroup, there were 3 patients (50.0%) with hypertension, 3 (50.0%) with ischemic heart disease, and one (16.7%) with chronic obstructive pulmonary disease.

In the whole studied group (128 measurements), the mean NT-proBNP, procalcitonin and C-reactive protein concentrations were respectively: 140.80±84.65 pg/ml, 22.32±97.41 ng/ml, 128.51±79.05 mg/l. Detailed data (mean, median, minimum, maximum and standard deviation) is presented in Tab. 3. The correlation of the NT-proBNP level and procalcitonin and C-reactive protein levels was 0.3273 ($p<0.001$) and 0.4134 ($p<0.001$), respectively.

Tab. 3. NT-proBNP, PCT and CRP levels in the studied group. Mean, median, minimum, maximum and standard deviation (SD).

	Number of measurements	Mean	Median	Min.	Max.	SD
NT-proBNP (pg/ml) in the whole studied group	128	140.80	115.35	19.70	399.00	84.65
PCT (ng/ml) in the whole studied group	128	22.32	1.25	0.00	666.69	97.41
CRP (mg/l) in the whole studied group	128	128.51	125.10	2.40	342.00	79.05
NT-proBNP (pg/ml) in survivor subgroup	93	124.45	101.20	19.70	308.70	77.75
PCT (ng/ml) in survivor subgroup	93	5.08	0.68	0.00	98.50	13.76
CRP (mg/l) in survivor subgroup	93	122.05	122.10	2.40	301.70	68.67
NT-proBNP (pg/ml) in non-survivor subgroup	35	184.27	177.60	59.60	399.00	87.93
PCT (ng/ml) in non-survivor subgroup	35	68.13	12.72	0.16	666.69	178.76
CRP (mg/l) in non-survivor subgroup	35	145.70	153.90	7.20	342.00	100.82

In the survivor subgroup (93 measurements), the mean NT-proBNP, procalcitonin and C-reactive protein concentrations were respectively: 124.45±77.75 pg/ml, 5.08±13.76 ng/ml, 122.05±68.67 mg/l. Detailed data (mean, median, minimum, maximum and standard deviation) is presented in Tab. 4. The correlation of the NT-proBNP level and procalcitonin and C-reactive protein levels was 0.485 ($p<0.001$) and 0.2506 ($p=0.015$), respectively.

In the non-survivor subgroup (35 measurements), the mean NT-proBNP, procalcitonin and C-reactive protein concentrations were respectively: 184.27±87.93 pg/ml, 68.13±178.76 ng/ml, 145.70±100.82 mg/l. Detailed data (mean, median, minimum, maximum and standard deviation) is presented in Tab. 4. The correlation

of the NT-proBNP level and procalcitonin and C-reactive protein levels was 0.3724 ($p=0.028$) and 0.6378 ($p<0.001$), respectively. The correlations of the NT-proBNP and PCT, CRP in the studied group are given in Tab. 4. In the survivor subgroup, the mean NT-proBNP and PCT plasma concentrations (124.45 pg/ml and 5.08 ng/ml, respectively) were significantly lower than in the non-survivor subgroup (184.27 pg/ml and 68.13 ng/ml, respectively) ($p<0.05$).

Tab. 4. The correlations of NT-proBNP with PCT and CRP in the studied group.

	NT-proBNP (in the whole studied group)	NT-proBNP (in survivor subgroup)	NT-proBNP (in non-survivor subgroup)
PCT (in the whole studied group)	y=0.3766x-30.701 R=0.3273 p<0.001	-	-
CRP (in the whole studied group)	y=0.386x+74.156 R=0.4134 p<0.001	-	-
PCT (in survivor subgroup)	-	y=0.0858x-5.5985 R=0.485 p<0.001	-
CRP (in survivor subgroup)	-	y=2213x+94.504 R=0.2506 p=0.015	-
PCT (in non-survivor subgroup)	-	-	y=0.7571x-71.392 R=0.3724 p=0.028
CRP (in non-survivor subgroup)	-	-	y=0.7313x+10.941 R=0.6378 p<0.001

R – correlation coefficient, correlation coefficients given in the table are statistically significant $p<0.05$.

DISCUSSION

For a patient to be diagnosed with severe sepsis or septic shock, they must have dysfunction of at least one organ. It may but need not be cardiac dysfunction. In the case of patients in septic shock, cardiac dysfunction is frequent. NT-proBNP is a recognized marker of cardiac dysfunction. Taking the above into account, an assumption was put forward that in septic patients, together with the intensification of the severity of sepsis, there comes an intensification of cardiac dysfunction (increase in NT-proBNP levels). PCT and CRP were used as markers of the intensification of sepsis severity. It is true, however, that CRP is a less specific marker of sepsis than PCT, but some studies have suggested that CRP may be an indicator of organ dysfunction [21-23]. NT-proBNP was used as the marker of cardiac dysfunction.

In the studies carried out by Castelli *et al.*, the mean serum concentration of PCT was 0.38 ng/ml in patients with SIRS (Systemic Inflammatory Response Syndrome), while in those with sepsis (patients with sepsis, severe sepsis or septic shock), it was 1.58 ng/ml [24]. In the studies of Tugrul *et al.*, in patients with severe sepsis and septic shock, the mean PCT concentrations were 19.25 ng/ml and 37.15 ng/ml, respectively, while in SIRS patients, it was 0.73 ng/ml [25]. According to the majority of researchers, a PCT concentration exceeding 10 ng/ml is associated with the development of severe infection and poor prognosis [26, 27]. The mean PCT concentration obtained in our study (22.32 ng/ml) is in agreement with the results reported by other authors. Pereira-Barretto *et al.* suggested that serum NT-proBNP concentrations exceeding 100 pmol/l allow for the identification of patients with heart failure, while concentrations over 270 pmol/l are observed in patients with severe heart failure [28]. Chua *et al.* described a significantly elevated level of NT-proBNP in patients in septic shock [21].

Comparing our results to those obtained by other authors, attention should be paid to the method used for NT-proBNP determination. A minor difference in the method may make this comparison impossible [29, 30]. Furthermore, according to Prontera *et al.*, healthy women (64.3±41.6 pg/ml, 7.59±4.91 pmol/l) showed significantly higher values of NT-proBNP than men (46.9±30.9 pg/ml, 5.53±3.64 pmol/l) [31]. In our study, the mean NT-proBNP concentration was below 200 pg/ml. It suggests that cardiac failure was not very significant in our septic patients. NT-proBNP levels correlated with the PCT and CRP levels in septic patients. To our knowledge, our study is the first to describe the correlation between NT-proBNP and PCT and CRP levels in septic patients.

In this study, we estimated the correlation not only in the investigated group of patients (128 measurements), but also in two subgroups: survivors (93 measurements) and non-survivors (35 measurements). In each subgroup, a significant positive correlation was observed between NT-proBNP concentrations and the concentrations of PCT and CRP. Attention should be paid to the markedly stronger correlation of NT-proBNP with PCT in the survivor subgroup (0.485, $p<0.001$) and of NT-proBNP with CRP in the non-survivor subgroup (0.6378 $p<0.001$). The explanation for this requires further study on a larger group of patients.

In our investigations, in the survivor subgroup, the mean NT-proBNP plasma concentrations were significantly lower than in the non-survivor subgroup. This is in agreement with the studies of Hoffman *et al.* [4]. The obtained results suggest that cardiac dysfunction played a more significant role in patients in the non-survivor subgroup.

In the studies of Brun-Buisson *et al.*, concerning patients with severe sepsis in intensive care units in France, mortality analyzed within a period of 30 days was 35%. In our study, mortality analyzed within a period of 28 days was 30%. Here the relatively low levels of NT pro-BNP that were reported for each patient make the presence of severe underlying cardiac dysfunction very unlikely.

However, two hypotheses should therefore be considered to partly explain this phenomenon and the relationship between NT pro-BNP and inflammatory markers.

Many patients with heart failure have stiff hearts with an increased wall thickness and small volumes, leading to diastolic dysfunction. Natriuretic peptides (BNP or NT-proBNP) might be used to detect patients with diastolic dysfunction, especially those patients with a restrictive filling pattern or pseudo-normalized mitral flow pattern and those who are symptomatic. However, patients with relaxation abnormalities and mild symptoms or who are asymptomatic may have normal levels of the natriuretic peptides, indicating no or only a slight elevation of the left ventricular filling pressures. Thus, low levels cannot be used as a rule-out diagnosis of diastolic dysfunction [32, 33]. However, it should be understood that BNP and NT-proBNP levels might be raised to different degrees, not only in heart failure but also in critical illness and various pulmonary diseases; in these situations, BNP and NT-proBNP may also serve as markers of severity and prognosis [34]. On the other hand, low levels of NT-proBNP in septic patients may result from minor myocardial cell damage and wall stress, due to supportive and fluid reanimation, which are both related to the severity of sepsis and critical illness (as expressed by inflammatory biomarkers levels).

The second hypothesis is connected with the potential up-regulation and release of natriuretic peptides by pro-inflammatory cytokines. The available data shows that an increase in circulating BNP is observed coincident with cardiac allograft rejection, and this is reversed upon treatment with anti-lymphocyte therapy, suggesting that pro-inflammatory cytokines may uniquely modulate BNP gene expression and secretion. Ma *et al.* investigated pro-inflammatory cytokines or conditioned medium (CM) derived from mixed-lymphocyte reaction (MLR) cultures in their ability to modulate ANF or BNP mRNA expression and secretion, as well as BNP promoter activity in cultured neonatal rat cardiomyocytes. On the basis of their results, they showed that the exposure of cultured rat cardiomyocytes to specific pro-inflammatory cytokines and MLR-CM results in the only known instance of upregulation of cardiac BNP at the transcriptional and translational levels without a corresponding increase in ANF gene expression. Furthermore, these effects were dependent on signaling by p38 MAP kinase. These findings reveal a unique discoordinated expression of BNP and ANF to inflammatory cytokines, and offer an opportunity to better understand the differential regulation of these two cardiac-derived endocrine hormones, which share receptors as well as biological properties. These relationships may also help to partly understand the cause of low levels of NT-proBNP in patients with severe sepsis [35-37].

Our study should be considered as a preliminary examination due to the small number of samples. There is considerable evidence that NT-proBNP levels primarily reflect underlying chronic myocardial dysfunction and active myocardial cell damage, and, in the available literature, several variables are

well known to potentially influence natriuretic peptide concentrations, including: age, gender, body mass index and renal function. These factors were not evaluated in our study.

In conclusion, NT-proBNP levels correlate with PCT and CRP levels in septic patients. In the whole investigated group, the correlation between NT-proBNP and CRP concentrations was more significant then the correlation between NT-proBNP and procalcitonin. In the survivor subgroup, the mean NT-proBNP plasma concentrations were significantly lower than in the non-survivor subgroup.

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