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NT-proBNP levels correlate with organ failure in septic patients: A preliminary report

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: The aim of the study was to evaluate the relationship between N-terminal brain natriuretic propeptide (NT-proBNP) plasma concentrations and the severity of organ dysfunction assessed by the Sepsis-related Organ Failure Assessment (SOFA) score in septic patients.

Material/Methods: NT-proBNP, SOFA score, and survival were evaluated in 20 consecutive septic patients. They were prospectively included in the study when the sepsis criteria according to the ACCP/SCCM definitions (modified by the Polish Working Group for Sepsis) were fulfilled. Blood serum NT-proBNP concentrations were determined in each patient at given time intervals and the severity of organ dysfunction was estimated according to the SOFA score. The first measurement was performed within 12 h after the patient's inclusion into the study, the second, third, and fourth at 12, 24, and 48 hours after the first, and then every 48 hours thereafter.

Results: The mean NT-proBNP concentration and the mean SOFA score were 140.80±84.65 pg/ml and 6.31±3.75 points, respectively. The correlation coefficient between NT-proBNP level and SOFA score was R=0.5164 ($p<0.05$). The mortality in the studied group was 30%.

Conclusions: NT-proBNP levels correlate with the severity of organ dysfunction as assessed by the SOFA score in septic patients.

Key words: **Keywords: N-terminal brain natriuretic propeptide • Sepsis-related Organ Failure Assessment score • sepsis • severe sepsis**

Abbreviations: **ACCP/SCCM** – American College of Chest Physicians/Society of Critical Care Medicine; **ANP** – atrial natriuretic peptide; **NT-proANP** – N-terminal atrial natriuretic peptide; **APACHE II score** – Acute Physiologic and Chronic Health Evaluation II score; **BNP** – brain natriuretic peptide; **LOD score** – Logistic Organ Dysfunction score; **MOD score** – Multiple Organ Dysfunction score; **NT-proBNP** – N-terminal brain natriuretic propeptide; **SOFA score** – Sepsis-related Organ Failure Assessment score.

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Introduction

In clinical practice, various scales are used to estimate the level of organ dysfunction in septic patients. In the case of sepsis, severe sepsis, or septic shock, the Sepsis-related Organ Failure Assessment (SOFA) score, the Brussels scale, the Multiple Organ Dysfunction (MOD) score, and the Logistic Organ Dysfunction (LOD) score have demonstrated their usefulness. The SOFA and Brussels were worked out during numerous coordinating conferences, whereas MOD and LOD are based on complex statistical analyses.

The Sepsis-related Organ Failure Assessment score is a multiorgan dysfunction score system and estimates organ dysfunction (Table 1) [2,10–12,15,16]. The estimation comprises six major systems on a scale of 0–4. In the literature, various applications of this assessment are found for further prognostication of morbidity, duration of hospitalization, hospitalization costs in the ICU, or mortality (the score on the first day of hospitalization, the mean score during hospitalization in the ICU, the highest score during hospitalization in the ICU, the sum of the worst scores of the particular six components of the SOFA score during hospitalization).

Myocardial dysfunction often accompanies severe sepsis and septic shock [9,17]. In order to evaluate this dysfunction in practice, echocardiographic examinations are performed [9] or specific markers are determined, e.g. atrial natriuretic peptide (ANP) [17], brain natriuretic peptide (BNP) [6,9,17], N-terminal atrial natriuretic peptide (NT-proANP) [8], and N-terminal brain natriuretic propeptide (NT-proBNP) [7,8].

In a recent study by Witthaut et al, both ANP and BNP were found to be significantly elevated in patients with septic shock in comparison with controls [17]. Charpentier et al. made a similar observation for BNP in patients with severe sepsis or septic shock who had echocardiographic evidence of systolic myocardial dysfunction [9].

N-terminal brain natriuretic propeptide, diagnostically serving for the size of BNP synthesis evaluation, is the least known and investigated marker of cardiac dysfunction.

A few studies have demonstrated increased NT-proBNP levels in septic patients [4,7,8], but their relationship with organ dysfunction and failure has not been evaluated.

We hypothesized that NT-proBNP concentration correlates with the severity of organ dysfunction as assessed by the Sepsis-related Organ Failure Assessment score in septic patients.

We therefore investigated this relationship.

Material and Methods

Study population

Having obtained approval from the Bioethics Committee of the Medical University in Łódź, Poland (No. RNN/26/03/KB),

Table 1. The sepsis-related organ failure assessment (SOFA) score evaluation system of multiple organ dysfunction. Six organ systems are evaluated on a scale of 1–4 each. The arithmetical sum of these six systems is the value of the SOFA score

Score points	1	2	3	4
Respiration				
PaO_2/FiO_2	<400	<300	<200	<100
			with respiratory support	with respiratory support
Cardiovascular				
Hypotension*	MAP <70 mmHg	Dopamine ≤5 or	Dopamine >5 or	Dopamine >15 or
		dobutamine in any dose	epinephrine ≤0.1 or	epinephrine >0.1 or
			norepinephrine ≤0.1	norepinephrine >0.1
Liver				
Bilirubin mg/dl	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Renal				
Creatinine mg/dl	1.2–1.9	2.0–3.4	3.5–4.9	5.0
or urine output			or <500ml/2 4h	or <200ml/24 h
Coagulation				
Platelets $\times 10^3/mm^3$	< 150	< 100	< 50	< 25
Central nervous system				
Glasgow Coma Scale	13–14	10–12	6–9	< 6

* Adrenergic agents administered for at least 1 h (doses are given in μg/kg/min)

Table 2. Assay characteristics and precision of NT-proBNP determinations

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%

20 patients were qualified for the study, i.e. 15 men and 5 women. The subjects were recruited consecutively from patients attending the ICU from July 1, 2003, to July 31, 2004. The patients were prospectively included in the study when sepsis criteria according to the ACCP/SCCM definitions [1,3] (modified by the Polish Working Group for Sepsis) [14] were fulfilled. The investigations were carried out in each patient until they stopped meeting these same criteria of sepsis or when the patient died.All the patients were given verbal and written information about the potential risks and benefits of participation in the study. They gave their consent in writing prior to the study.

Study protocol

All the patients were treated by the same team of physicians and care of the patients was conducted according to the same 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.

Serum determination

Blood serum NT-proBNP concentrations were determined in each patient at given time intervals and the severity of organ dysfunction was estimated using the Sepsis-related Organ Failure Assessment. The first measurement was performed within 12 h after the patient's inclusion into the study, the second, third, and fourth at 12, 24, and 48 hours after the first, and then every 48 hours thereafter.

The quantitative determination of NT-proBNP (in pg/ml) was based on an immumoenzymatic method, a test based on the competitive EIA method (the precision of this method: coefficient of variation (CV) ca. 4.7% on average). The reading was performed on an ETI Max 3000 analyzer (Dia Sorin) using Biomedica reagents. This competitive EIA test kit is designed to measure 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 to NT-proBNP (8-29) immobilized on the surface of a well of a microtiter plate. The assay is based on the competitive reaction of the unlabelled peptide in the standards or samples and the horse radish peroxidase labeled peptide (tracer) for the limiting binding sites of the NT-proBNP (8-29)-specific antibody. The concentrations of the tracer and 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 proBNP (8-29) microplate well 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.

Statistical analysis

Statistical analysis was performed with Statistica 5.1 PL (StatSoft, Poland) and Office 97 programs (Microsoft, Poland).To determine correlations, correlation coefficients were calculated: the Pearson's correlation coefficient in the case of a normal distribution and the Spearman's correlation coefficient when at least one sample had a distribution different from normal. The result was given in the form of $p<max$ ($p<0.05$). This means that the correlation was statistically significant at the specified level of significance. The assay characteristics and precision of NT-proBNP determination are presented in Table 2.

Results

Twenty consecutive septic patients were included in the study. The basic data on the investigated group are presented in Table 3.

In total, 128 measurements (a mean of 6.4 in each patient) were performed in the investigated group. The mean NT-proBNP concentration and mean SOFA score were respectively 140.80±84.65 pg/ml and 6.31±3.75 points. The correlation coefficient of the NT-proBNP level and the SOFA score was $R=0.5164$ ($p<0.05$) (Figure 1).

Mortality in the investigated group was 30%.

Discussion

This study should be treated as a preliminary examination owing to the small number of samples. N-terminal brain natriuretic propeptide may serve as a useful laboratory marker to indicate myocardial dysfunction in septic patients [8]. Pereira-Barretto et al. suggest that serum NT-proBNP concentrations exceeding 100 pmol/l allow for identification of patients with heart failure, whereas concentrations >270 pmol/l are observed in patients with severe heart failure [13]. Chua et al. described significantly elevated levels of NT-proBNP in patients in septic shock [7]. In the Biomedica method, the reference values for NT-proBNP are below 600 pg/ml (250 fmol/ml) in healthy persons. In

Table 3. Basic data on the studied group

Patient number	Sex	Age (years}	Time in ICU/ Length of hospital stay (days)	Basis of inclusion into the study *	Infection site	Microbial etiology	Number of scores in APACHE II score at the start of the study	The highest number of organ failure	Death in the course of the study	Cause of death
1	Male	49	4/59	Sepsis	Abdominal cavity	–	7	0	No	–
2	Male	39	44/44	Sepsis	Abdominal cavity	Pseudomonas aeruginosa	14	3	No	–
3	Female	90	7/31	Severe sepsis	Abdominal cavity	–	17	1	No	–
4	Female	29	14/14	Sepsis	Abdominal cavity	Enterobacter aerogenes	9	5	Yes	MODS, DIC
5	Male	33	13/88	Severe sepsis	Abdominal cavity	–	10	2	No	–
6	Male	49	55/55	Severe sepsis	Lungs/ Abdominal cavity	MRSA, Stenotro-phomonas maltophilia	19	4	No	–
7	Female	53	5/11	Sepsis	Abdominal cavity	–	3	1	No	–
8	Male	22	14/14	Sepsis	Lungs	MRSA	12	1	No	–
9	Male	70	11/11	Severe sepsis	Lungs	Pseudomonas aeruginosa	14	1	No	–
10	Female	50	16/18	Severe sepsis	Abdominal cavity	Enterobacter cloacae, MRSA	17	4	Yes	MODS
11	Male	47	7/16	Severe sepsis	CNS	–	11	2	No	–
12	Male	51	3/11	Severe sepsis	Abdominal cavity	–	8	1	No	–
13	Male	71	4/18	Severe sepsis	Abdominal cavity	Pseudomonas aeruginosa	12	3	Yes	Respiratory – circulatory failure
14	Female	88	5/6	Severe sepsis	Abdominal cavity	–	10	1	No	–
15	Male	67	8/14	Severe sepsis	Abdominal cavity	MRSA	13	3	Yes	Respiratory – circulatory failure
16	Male	51	3/3	Severe sepsis	Lungs	–	24	4	Yes	Respiratory – circulatory failure
17	Male	59	6/31	Severe sepsis	Abdominal cavity	MRSA	7	2	No	–
18	Male	41	19/54	Severe sepsis	Abdominal cavity	MRSA	4	2	No	–
19	Male	30	14/15	Severe sepsis	Abdominal cavity	Escherichia coli, Enterococcus faecium	11	2	No	–
20	Male	55	5/5	Severe sepsis	Lungs	–	17	4	Yes	Respiratory – circulatory failure

* Sepsis criteria according to the ACCP/SCCM definitions, modified by the Polish Working Group for Sepsis.

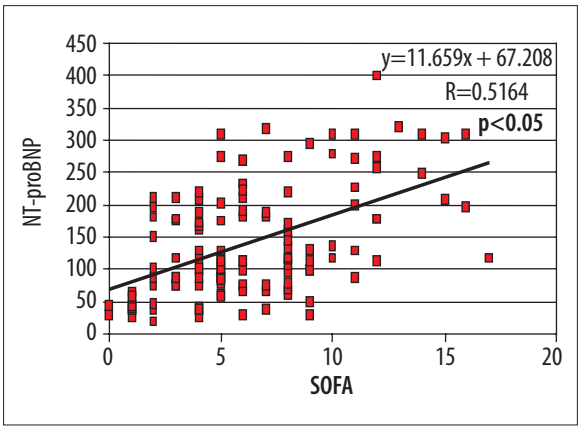

Figure 1. The correlation between NT-proBNP concentration and the severity of organ dysfunction as assessed by the Sepsis-related Organ Failure Assessment score in the investigated group (128 measurements)

our study the mean NT-proBNP concentration was below 200 pg/ml (140.80±84.65 pg/ml). This suggests that cardiac failure was not very significant in our septic patients.

In this study, NT-proBNP levels correlated with the severity of organ dysfunction as assessed by the Sepsis-related Organ Failure Assessment score in septic patients. To our knowledge, this is the first study to describe such correlation. In the studies of Brun-Buisson and colleagues concerning patients with severe sepsis in intensive care units in France, the mean value of, among others, the SOFA scores was found to be 9. In this group, mortality analyzed within a period of 30 days was 35% [5]. In our studies the mean value of the SOFA scores was 6.31±3.75 points and mortality analyzed within a period of 28 days was 30%.

Conclusions

NT-proBNP levels correlate with the severity of organ dysfunction as assessed by the Sepsis-related Organ Failure Assessment score in septic patients.

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