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Marked elevations in N-terminal brain natriuretic peptide levels in septic shock

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Abstract

Introduction N-terminal pro brain natriuretic peptide (NT-proBNP) is a cardiac biomarker that has recently shown to be of diagnostic value in a diagnosis of decompensated heart failure, acute coronary syndromes and other conditions resulting in myocardial stretch. We sought to study whether sepsis-induced myocardial dilation would result in an elevation of NT-proBNP.
Method Serum NT-proBNP measurements were made in six consecutive patients with septic shock within 6 hours of admission to the intensive care unit.
Results Markedly elevated levels of NT-proBNP were found in all six patients.
Conclusions NT-proBNP levels can be markedly elevated in critically ill patients presenting with septic shock. An elevated NT-proBNP level in a critically ill patient is not specific for decompensated heart failure.

Keywords: brain natriuretic peptide, N-terminal pro brain natriuretic peptide, septic shock

Introduction

Brain natriuretic peptide (BNP) is a hormone synthesized in the ventricular myocardium. The stimulus for its release is increased ventricular wall tension. Gene expression is the main regulator of BNP secretion, and can increase very rapidly in response to an appropriate stimulus. It is produced in the prohormone form (proBNP), which before secretion by cardiomyocytes is split into the inactive 76-residue N-terminal fragment (NT-proBNP) and the biologically active 32-residue C-terminal fragment (BNP) [1].

BNP has been shown to be a useful cardiac biomarker for the identification of patients with suspected heart failure [2]. Elevated serum levels have also been described in left ventricular systolic and diastolic dysfunction and right ventricular pressure overload states such as pulmonary embolism, cor pulmonale and primary pulmonary hypertension [3].

In a recent study by Witthaut and colleagues [4], both atrial natriuretic peptide (ANP) and BNP were found to be significantly elevated in patients with septic shock in comparison with controls.

More recently, Charpentier and colleagues [5] made a similar observation for BNP in patients with severe sepsis or septic shock who had echocardiographic evidence of systolic myocardial dysfunction.

A similar elevation of NT-proBNP in septic shock has, to our knowledge, not been described before. We sought to study

ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; ICU = intensive care unit; NT-proBNP = N-terminal pro brain natriuretic peptide.

NT-proBNP because it had been found in the context of heart failure to increase in concentration more strikingly and to have better sensitivity and positive predictive value than BNP [6].

Methods

Patient population

We describe six patients admitted to the Medical Intensive Care Unit (ICU) in our institution in July 2003 with septic shock. None had a prior history of hypertension. Septic shock was defined in accordance with the criteria of the consensus conference of the American College of Chest Physicians and Society of Critical Care Medicine [7]. Severity of disease was quantified by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [8].

Blood sampling and determination of NT-proBNP levels

All patients had blood samples taken for serum NT-proBNP measurement within 6 hours of admission. Serum NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The analytical range extends from 20 ng l^{-1} to 35 μg l^{-1}.

Ethics

Approval was obtained from our hospital's Institutional Review Board.

Results

The clinical details of the six patients are summarized in Table 1. All were in septic shock requiring vasopressors. None had pre-existing hypertension, ischemic heart disease or cor pulmonale.

The initial hemodynamic profile of patient 1 is described in further detail. After fluid resuscitation comprising 2.5 litres of colloids, the patient required intravenous dopamine (15 μg kg^{-1} min^{-1} to maintain a mean blood pressure of 70 mmHg. The cardiac index was 3.06 l min^{-1} m^{-2}. Intrathoracic blood volume index (ITBVI) was 816 ml m^{-2} (normal range 850–1000 ml m^{-2}) and stroke volume index was 25 ml m^{-2} (normal range 40–60 ml m^{-2}). These hemodynamic data were measured with the PiCCO® (Pulsion Medical Systems, Munich, Germany). The data demonstrate no obvious excess of intravascular volume.

Discussion

Cardiac dysfunction is often present in patients with septic shock. In a recent study by Charpentier and colleagues [5], systolic myocardial dysfunction (as defined by a fractional area contraction of less than 50% on echocardiography) was present in 44% of a cohort of patients with severe sepsis or septic shock, on the second day of their stay in the ICU. It is now evident that myocardial depression has a clear role in septic shock. Septic myocardial depression is characterized by reversible biventricular dilation, decreased systolic contractile function, and decreased response to both resuscitation with fluids and stimulation with catecholamines [9]. This myocardial depression occurs in the presence of an overall hyperdynamic circulation. This phenomenon is linked to the presence of a circulating myocardial depressant factor, which is probably due to tumour necrosis factor-α and interleukin-1β acting in synergy. These effects are mediated by mechanisms that include the generation of nitric oxide and cyclic GMP [10].

Our results show clearly that NT-proBNP levels can be markedly elevated in critically ill patients presenting with septic

Table 1

Clinical data for patients

Case	Cause of septic shock	Sex	Age (years)	APACHE II score	Vasopressor and dose	Mechanical ventilation	NT-proBNP (ng l^{-1})	TropT (μg l^{-1})	CK (U l^{-1})	CK-MB (μg l^{-1})	Procalcitonin (μg l^{-1})	Creatinine (μM)
1	Lung abscess	Male	55	20	Dopamine 15μg kg^{-1} min^{-1}	Yes	4997	0.01	42	3	3.88	45
2	*Acinetobacter baumanii* pneumonia (bacteremic)	Female	62	32	Noradrenaline 2.0 μg kg^{-1} min^{-1}	Yes	11,157	0.19	80	4	19.50	84
3	Leptospirosis	Male	28	11	Dopamine 10 μg kg^{-1} min^{-1}	No	6502	0.01	694	12	99.01	75
4	*Escherichia coli* pyelonephritis (bacteremic)	Female	59	8	Dopamine 10 μg kg^{-1} min^{-1}	No	2163	0.01	278	3	26.71	80
5	Gall-bladder empyema	Female	75	40	Noradrenaline 0.7 μg kg^{-1} min^{-1}	Yes	35,000	0.23	214	8	44.92	184
6	*Escherichia coli* pyelonephritis	Male	31	33	Noradrenaline 0.7 μg kg^{-1} min^{-1} + vasopressin 2 U h^{-1}	Yes	35,000	0.15	440	4	28.76	329

APACHE II, Acute Physiology and Chronic Health Evaluation II; CK, creatine kinase; CK-MB, creatine kinase MB fraction; TropT, troponin T.

shock. To our knowledge, our study is the first to describe this observation. We postulate that this marked elevation of NT-proBNP in our patients is a reflection of sepsis-induced ventricular dilation. The important diagnostic implication of our results is that an elevated NT-proBNP level in a critically ill patient is not specific for decompensated heart failure.

The magnitude of elevation of NT-proBNP seen in our patients was much greater than the twofold increase in BNP and fourfold increase in ANP described by Witthaut and colleagues [4]. This might be due to the longer half-life of NT-proBNP. NT-proBNP might therefore be a more sensitive marker of septic cardiomyopathy.

It remains to be seen whether the magnitude or trend of NT-proBNP elevation in septic shock holds any prognostic value. Further studies should be done to address this issue. What is also unanswered at this time is which of the cardiac biomarkers – BNP, NT-proBNP or ANP – is the best biological marker of myocardial dysfunction in patients with severe sepsis or septic shock.

Authors' contributions

Both authors contributed to the study design, implementation of the study and the final version of the report. GC collected and interpreted the data and wrote the report.

Key messages

- NT-proBNP elevations are seen in severe sepsis.
- There are non-heart-failure causes of NT-proBNP elevations in the ICU.

Competing interests

None declared.

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