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Critical Care

BMC

Crit Care. 2007 Apr 13;11(2):122. doi: [10.1186/cc5728](https://doi.org/10.1186/cc5728)

What does high NT-proBNP mean in septic shock patients? A part of the puzzle

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PMCID: PMC2206461 PMID: [17442126](https://pubmed.ncbi.nlm.nih.gov/17442126/)

Abstract

B-type natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP) plasma levels are commonly high at the early phase of septic shock and have been suggested to be prognostic markers for this condition.

It is uncertain, however, whether this increase reflects sepsis related cardiac dysfunction. In a recent issue of *Critical Care*, Mokart and coworkers showed the accuracy of NT-proBNP in predicting intensive care unit mortality in cancer patients with septic shock, which could help in identifying high risk cancer patients. Results from repeated transthoracic echocardiographs show that NT-proBNP on day 2 after admission was higher in patients presenting with cardiac dysfunction, whereas NT-proBNP on day 1 did not predict cardiac dysfunction. These data suggest that after an initial overexpression of NT-proBNP in all septic patients, patients with cardiac dysfunction will present persistent high levels of NT-proBNP.

In a this issue of *Critical Care*, Mokart and coworkers [1] report the results of a prospective cohort study evaluating plasma amino-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker of prognosis and cardiac dysfunction in cancer patients with septic shock. They included 51 patients, mainly with hematological malignancies. By univariate analysis, Logistic Organ Dysfunction score, early NT-proBNP level and recent hematopoietic stem-cell transplantation were associated with intensive care unit (ICU) mortality. In a multivariate analysis, NT-proBNP level on day 2 was the unique parameter associated with mortality. The area under the curve was 0.87. Transthoracic echocardiography was repeated in 45 patients. NT-proBNP level on day 2 but not on day 1 was significantly higher in patients presenting a left or right cardiac dysfunction during the course of the septic shock.

BNP and its amino-terminal fragment, NT-proBNP, are mainly produced by myocytes in response to a ventricular volume expansion or pressure overload. Their levels in blood are, therefore, accurate markers of ventricular dysfunction and have been shown to be associated with mortality in various cardiac diseases. In ICU patients, although BNP and NT-proBNP are not correlated with filling pressures [2,3], low levels of BNP have been shown to have a high negative predictive value for the presence of cardiogenic shock [2]. In septic shock patients, several studies have reported very high levels of BNP and NT-proBNP [4-7] and have suggested that NT-proBNP is an independent marker of prognosis in this population [6,7]. It remains unclear, however, whether NT-proBNP is high in these patients because they all present with a certain degree of cardiac dysfunction and whether the NT-proBNP level is associated with mortality by reflecting the intensity of this dysfunction. Firstly, experimental studies have shown that endotoxin and some cytokines are able to upregulate the transcription of the gene encoding BNP [8,9]; therefore, the extent of the inflammatory response could account, at least in part, for the dramatically high levels of NT-proBNP reported during septic shock. Secondly, cardiac dysfunction during sepsis is complex and can be associated with left and right as well as systolic and diastolic dysfunctions [10,11]; therefore, the respective contribution of these dysfunctions to an increase in NT-proBNP is difficult to determine. However, knowledge of the determinants of the secretion of natriuretic peptides during septic shock is necessary prior to considering NT-proBNP as a potential tool to guide therapy of these patients.

Like previous reports, Mokart and coworkers show that all patients at the early phase of septic shock exhibit high levels of NT-proBNP. They also confirm the prognostic value of early NT-proBNP measurement and show that this also applies to cancer patients. As for other reports, it is noteworthy that the samples of patients are small and that the odds ratios for the effect of NT-proBNP on mortality are large.

Moreover, the role of anthracyclin treatment in the myocardial dysfunction deserves further investigation. Mokart and coworkers also confirm the association of NT-proBNP level with cardiac dysfunction. In a seminal paper, Charpentier and coworkers [5] reported higher BNP levels in septic patients with altered left ejection fraction. In the study by Mokart and coworkers, NT-proBNP on day 1 did not predict cardiac

dysfunction; however, a key result from this study is that NT-proBNP continued to rise on day 2 in patients developing cardiac dysfunction whereas it quickly decreased in the others. This result suggests that mechanisms other than cardiac wall stress (such as inflammatory mediators or neurohormonal activation) could be involved in the initial upregulation of BNP and NT-proBNP secretion, whereas cardiac dysfunction could contribute to persistent high NT-proBNP levels.

A limitation of the study by Mokart and coworkers is the lack of serial measurements of NT-proBNP over several days, which could help to confirm this tendency. To date, the relationship observed between BNP or NT-proBNP and sepsis related myocardial dysfunction remains insufficiently described to propose them as markers of cardiac failure during septic shock. Left dysfunction could be predominant in some patients whereas right dysfunction could complicate respiratory failure in others. Mokart and coworkers show that NT-proBNP could not discriminate these patients.

Future studies will have to precisely identify the determinants of the secretion of natriuretic peptides during human sepsis as well as the confounding factors affecting their levels in ICU patients. The great sensitivity of NT-proBNP in predicting prognosis could be largely counterbalanced by a lack of specificity for cardiac depression. Studies with larger samples of patients should also determine whether NT-proBNP or BNP measurement can contribute to risk stratification of septic shock patients.

Abbreviations

BNP = B-type natriuretic peptide; ICU = intensive care unit; NT-proBNP = amino-terminal pro-BNP.

Competing interests

The authors declare that they have no competing interests.

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