

## Commentary

# New horizons: NT-proBNP for risk stratification of patients with shock in the intensive care unit

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## Abstract

B-type natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP) are promising cardiac biomarkers that have recently been shown to be of diagnostic value in decompensated heart failure, acute coronary syndromes and other conditions resulting in myocardial stretch and volume overload. In view of the high prevalence of cardiac disorders in the intensive care unit, the experience of elevated natriuretic peptide levels in the critically ill might be of enormous diagnostic and therapeutic value. BNP and NT-proBNP levels rise to different degrees in critical illness and may also serve as markers of severity and prognosis in diseases beyond acute or chronic heart failure. The diagnostic and prognostic use of natriuretic peptides in the intensive care setting for patients with various forms of shock could be an attractive alternative as noninvasive markers of cardiac dysfunction that could obviate the need for pulmonary artery catheterization in some patients.

In a recent issue of *Critical Care*, Januzzi and coworkers [1] report the results of a prospective cohort study, evaluating natriuretic peptides in various shock patients in the intensive care unit (ICU). The authors found no correlation between elevated levels of amino-terminal pro-BNP (NT-proBNP) and high filling pressures among patients with shock within the ICU, but higher values were reported to be strongly associated with death. A low level of NT-proBNP, however, identified low risk patients, who were less likely to benefit from pulmonary artery catheterization (PAC). The authors posed the question, therefore, whether NT-proBNP measurements can replace the need for PAC in ICU patients.

Brain natriuretic peptide (BNP) has been shown to be a useful cardiac biomarker for the identification of patients with suspected heart failure [2]. Elevated serum levels have been described in both left ventricular (LV) systolic and diastolic dysfunction as well as in right ventricular pressure overload

states, such as pulmonary embolism, cor pulmonale and primary pulmonary hypertension [3]. BNP and its amino-terminal fragment NT-proBNP are markers of LV dysfunction, and elevated levels aid in discriminating cardiac from non-cardiac dyspnea [2]. Peptide levels also correlate with LV filling pressures (LVFP) in patients with depressed systolic function [4]. However, it is unclear whether BNP or NT-proBNP correlate with pulmonary capillary wedge pressure in a population of critically ill patients with a broad range of life-threatening diagnoses. Many critically ill patients have clinical and radiographic findings that cast doubt on LVFP. PAC has been used to measure LVFP and guide patient management. However, given its cost, complications, and evidence from recent studies that it has either a neutral or negative effect on ICU patient outcome, a reliable non-invasive method or parameter for the estimation of LVFP is needed [5,6].

Patients with various forms of shock have a high mortality in the ICU [7]. One method of evaluating patients with shock is invasive hemodynamic monitoring with PAC. In the modern era, however, non-invasive methods for estimating cardiac filling pressures and hemodynamics in ICU patients with shock, such as biomarkers capable of predicting prognosis, are coming to light. Several studies have shown that levels of the neurohormones BNP and NT-proBNP are increased in patients with cardiac dysfunction and severe sepsis or septic shock [8-12]. Moreover, these studies have shown that NT-proBNP can serve as an early marker of prognosis in this patient population [8,11].

Similar to previous examinations [13], Januzzi and coworkers [1] demonstrated that elevated levels of NT-proBNP were strongly associated with the risk of death in the ICU, and were even stronger predictors of death than APACHE II

BNP = brain natriuretic peptide; ICU = intensive care unit; IL = interleukin; LV = left ventricular; LVFP = left ventricular filling pressures; NT-proBNP = amino-terminal proBNP; PAC = pulmonary artery catheterization.

scores. It is doubtful, however, whether BNP or NT-proBNP correlate with invasively measured hemodynamic parameters, such as pulmonary capillary wedge pressure or low cardiac output in patients with various types of shock in the ICU [1,14]. In agreement with the findings reported by Jannuzzi and coworkers in the present issue of *Critical Care* [1], previous investigators reported that lower levels of NT-BNP identified patients with lower risk and better prognosis and that they may differentiate survivors from non-survivors in the ICU [8,11]. Thus, Januzzi and coworkers suggested that low NT-proBNP concentrations may be useful indicators to avoid PAC in low risk patients in the ICU.

Several mechanisms account for increased natriuretic peptide levels in shock patients and for the observed lack of association between natriuretic peptides and cardiac filling pressures and hemodynamics. First, lipopolysaccharide [15] and proinflammatory cytokines such as interleukin-1 $\beta$  [16] and cardiotrophin-1 [17] up-regulate transcription of the gene encoding BNP. Second, wall stretch can activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway in cardiomyocytes; this activation augments IL-6 mRNA expression and consecutively IL-6 release [18]. According to Witthaut and colleagues [10], who found a correlation between levels of natriuretic peptides and interleukin-6 plasma levels, the upregulation of IL-6 may effect cardiac release of natriuretic peptides. Thus, plasma levels of natriuretic peptides are not only affected by LV function, but also by secretion of inflammatory cytokines such as IL-6 in ICU shock patients. However, future studies evaluating the precise mechanisms responsible for enhanced natriuretic peptide secretion in critically ill patients are still needed.

In critically ill patients, the use of PAC neither increases overall mortality or days in hospital nor confers benefit. Despite almost 20 years of randomized clinical trials, a clear benefit leading to improved survival from the use of PAC has not been proven. The neutrality of PAC for clinical outcomes may result from the absence of effective evidence-based treatment regimens according to PAC information across the spectrum of critically ill patients. Further clinical trials should lead to the establishment of treatment protocols for the use of PAC in this patient population. The additional measurement of NT-proBNP in critically ill patients may provide promising decision support for the application of PAC and may help to identify candidates who might benefit from PAC measurements or be harmed by PAC.

## Competing interests

The authors declare that they have no competing interests.

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