PERSPECTIVE

Brain natriuretic peptide: a potential marker for mortality in septic shock

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Introduction

Brain natriuretic peptide (BNP), a cardiac neurohormone, is the second member of a family of polypeptides secreted by the cardiac ventricles in...
response to volume expansion and pressure over-load. Physiologically, BNP promotes natriuresis and diuresis, as well as vasodilatory actions via antagonism of the renin-angiotensin-aldosterone system.1,2

As a diagnostic test, BNP is an accurate marker for left ventricular dysfunction from different causes such as ischemic and non-ischemic dilated cardiomyopathies.3 Elevated plasma levels of BNP are associated with multiple echocardiographic parameters of systolic and diastolic dysfunction.3,4 Prior studies in symptomatic and asymptomatic patients found that a BNP level of 18 pg/mL or more had a sensitivity of 92% and a specificity of 72% for a diminished left ventricular ejection fraction (LVEF) of 30% or less.5

Sepsis and septic shock represent an increasingly important clinical problem. It has been recently estimated that severe sepsis causes more than 200,000 deaths per year, the majority of which are due to cardiovascular collapse.6 As a systemic inflammatory response to infection, sepsis induces the endogenous release of a wide spectrum of mediators with deleterious cardiovascular effects. When this response is severe, alterations in cardiovascular homeostasis lead to septic shock. One of the most important manifestations of septic shock is myocardial dysfunction.7

The early assessment of myocardial depression and its severity, as well as the prediction of mortality in patients with septic shock, usually involves cumbersome techniques that require special equipment and expertise. Thus, readily measurable circulating biomarkers could facilitate the diagnosis and possibly even the prevention of cardiovascular collapse in these patients.

**Myocardial depression in septic shock**

Myocardial depression is well recognized as an early feature of human septic shock, causing absence of appropriate oxygen supply to peripheral tissues and subsequent death. Early systolic dysfunction has been identified in these patients and seems to be inversely related to mortality.8,9 Prior work with radionuclide cineangiography demonstrated that in survivors of septic shock, the left ventricular cavity acutely increases in size, as evidenced by an increase in the left ventricular end-diastolic volume index (LVEDVI), and the LVEF decreases transiently, returning to normal in seven to ten days.10 In contrast, patients with septic shock who die maintain a normal LVEF and LVEDVI throughout the course of their illness. Studies in septic and non-septic critically ill patients showed a decreased left ventricular stroke work index (LVSWI) in response to equivalent increments in the LVEDVI.11 Similarly, right ventricular systolic dysfunction with transient dilatation and a decrease in right ventricular ejection fraction has also been described.12,13

As regards diastolic function in sepsis, previous reports have shown a concordance between the pulmonary artery wedge pressure and the left ventricular end-diastolic volume. Some studies using echocardiography, however, have demonstrated slower left ventricular filling and abnormal relaxation in septic patients, suggesting that impaired compliance may also play a role.14-16

Various invasive studies with hemodynamic measurements have reported that the inability to acutely dilate the left ventricle and to decrease the LVEF along with a persistently low LVEDVI may be markers for increased mortality.7,9 In addition, a persistently low cardiac index (CI) and systemic vascular resistance, as well as a progressive increase in the heart rate, have been related to subsequent death.9,11 Similarly, right ventricular dysfunction has also been associated with a poor outcome but the data supporting this association are less convincing.12,13,17,18 Thus, both echocardiographic and invasive hemodynamic parameters of systolic and diastolic dysfunction may be helpful in predicting outcomes in sepsis. Nonetheless, acquisition of these data may be expensive, time-consuming and not always technically reliable.

**Natriuretic cardiac neurohormones in sepsis and septic shock**

The role of neurohormonal markers of myocardial dysfunction in sepsis has been reported in both animal and human models. Hartemink et al.19 found that right and left systolic dysfunction correlated with an increase in plasma levels of α-atrial natriuretic peptide (α-ANP) and its second messenger cyclic guanosine monophosphate (cGMP) during the first 72 hours after the diagnosis of septic shock. In measurements of hemodynamic variables with a pulmonary artery catheter, both the right ventricle stroke work index and the LVSWI correlated inversely with the serum levels of α-ANP and cGMP. The optimum cutoff values of these markers for a prediction of a LVSWI <35 g/m² were 172 pg/mL and 4.5 mg/mL respectively, with a sensitivity and specificity of 68% and 82%, respectively for αANP and 77% and 93%, respectively for cGMP. Further, levels of ANP and cGMP were also found to be significantly lower in survivors than in non-survivors.

The precursor of α-ANP, pro-ANP, has been studied as a novel hormone marker of cardiac depres-
sion caused by sepsis, and has been suggested to be a potential predictor of acute respiratory distress syndrome (ARDS). Atrial plasma concentrations of pro-ANP were measured in 17 septic patients, showing a negative correlation with CI. Further, higher values resulted in patients who developed ARDS. C-type natriuretic peptide (CNP) has also been associated with sepsis. Septic patients had a markedly elevated serum level of CNP (13.2 ± 10 fmol/mL; normal 1.4 ± 0.6 fmol/mL) when compared to patients with congestive heart failure and hypertension.

Currently there is only one retrospective study that has evaluated BNP production in the peripheral circulation in relation to cardiovascular function and systemic inflammation. In a group of 17 patients with septic shock and 19 controls in the intensive care unit (ICU), elevated blood levels of α-ANP (82.7 ± 9.9 vs. 14.9 ± 1.2 pg/mL) and BNP (12.4 ± 3.6 vs. 5.5 ± 0.7 pg/mL) were demonstrated. α-ANP was found to correlate directly with levels of IL-6 (r = 0.73, p < 0.01) and BNP to correlate inversely with the CI (r = −0.56, p < 0.05). BNP showed the highest levels in patients with septic shock on day 0 (12.4 ± 3.6 pg/mL) without significant differences up to day four (9.8 ± 2.1 pg/mL). As has been previously reported in other studies, a decrease in the LVSWI was observed in these patients, suggesting a diminished LVEF. A compensatory increased filling volume of the left ventricle, along with the consequent rise in the ventricular distension and the plasma levels of BNP were also proposed. No relationship with mortality was found.

In a recently presented study (Abstract presented at the AHA Annual Meeting, 10 November 2003, Orlando, FL) 13 critically ill and mechanically ventilated patients with septic shock, as well as 18 age-matched controls, had levels of BNP followed during their ICU stay. Comparison of ICU admission BNP plasma levels between patients (849.4 ± 154.8 pg/mL) and healthy individuals (100 ± 9.4 pg/mL) showed that plasma levels of BNP in patients with septic shock were significantly higher (p < 0.05). For patients who recovered from septic shock (n = 9), plasma BNP levels after recovery (351.7 ± 136.6 pg/mL) were significantly lower than on admission to the ICU, but remained significantly higher than BNP levels in healthy subject levels (p < 0.05). Mortality was not evaluated.

BNP is a relatively inexpensive and simple test, which is now widely available in clinical practice. BNP is also a predictor of both echocardiographic parameters of ventricular dysfunction as well as clinical outcomes in patients with acute and chronic heart disease. BNP has also been hypothesized to be a marker for ventricular dysfunction in patients with the human immunodeficiency virus. The relationship of BNP with myocardial dysfunction and mortality in septic shock has not yet been evaluated in a prospective study.

Hypothesis

The hypothesis here assumes that BNP is a marker for mortality in septic shock-associated myocardial dysfunction. It is believed that ventricular dilatation and decreases in both the LVEF and the RVEF in the initial phase of myocardial depression during septic shock will cause plasma levels of BNP to rise. Among patients with septic shock who will survive, BNP will return to normal within the first ten days. Among patients with septic shock destined to die, however, BNP will remain within normal limits because their cardiac ventricles will not increase in size and their ejection fraction remains normal.

Testing the hypothesis

To test this hypothesis, an initial observational study is needed in patients with septic shock in whom echocardiographic and hemodynamic parameters (mainly LVEDVI, LVSWI and CI) were measured in the initial phases and throughout the course of their illness. Plasma levels of BNP will be measured at the time of diagnosis and sequentially during the course of the septic shock. The inter-relationship of BNP, ventricular dilatation, and mortality will also be evaluated. Furthermore it may be informative to evaluate BNP, echocardiographic and hemodynamic parameters in non-septic critically ill patients.

At the present time, the hypothesis that BNP is a marker of mortality in septic shock is plausible. If, in the future, a body of evidence emerges to support this hypothesis, utilization of BNP as a marker for mortality in septic shock would have major clinical and public health implications.

Conflict of interest: The authors do not have any potential conflict of interest regarding the development of this research hypothesis.

References