B-Type Natriuretic Peptide

A Biomarker for the Diagnosis and Risk Stratification of Patients With Septic Shock

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Background: The importance of cardiomyocyte damage during sepsis has been a recent subject of interest. The progression of sepsis results in the upregulation of proinflammatory cytokines, which act in concert to damage cardiomyocytes and produce cardiac contractile dysfunction. B-type natriuretic peptide (BNP) is a neurohormone released from the ventricles of the heart in response to myocardial dysfunction. The goal of this study was to examine the relationship between BNP levels and the severity of sepsis independent of congestive heart failure.

Design: Prospective, nonrandomized control study.

Setting: University hospital.

Patients: Forty-nine patients were divided into 3 groups: 13 patients with septic shock, 18 with early sepsis, and 18 age-matched healthy control subjects. We excluded patients with septic shock who had comorbid conditions (congestive heart failure or renal failure); sepsis severity was determined using the Sequential Organ Failure Assessment scoring system. Patients with sepsis were followed up for 21 days.

Main Outcome Measures: Serum BNP levels, determined at the time of diagnosis of sepsis and on patient improvement or deterioration.

Results: Patients with septic shock had significantly higher BNP levels on admission compared with the other 2 groups ($P < .05$). The BNP levels were not significantly elevated in patients with early sepsis. Plasma BNP levels for patients with septic shock were positively correlated with Sequential Organ Failure Assessment scores ($r^2 = 0.74$, $P < .05$) and prognosticated survival.

Conclusions: This study confirms the relationship between BNP level elevation and severity of sepsis independent of congestive heart failure. It also supports the utility of BNP level as a marker for mortality in septic shock.

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B-Type Natriuretic Peptide (BNP) is a neurohormone released from cardiomyocytes in response to increased wall stress and left ventricular dysfunction.1,2 B-type natriuretic peptide belongs to the group of cardiac natriuretic hormones shown to have natriuretic, diuretic, vasodilator, and antimitogenic effects on cardiovascular tissue. Through these effects, BNP is postulated to play an important role in cardiovascular homeostasis and fluid volume regulation.3 In patients with congestive heart failure (CHF), increased secretion of BNP partially counteracts the effects of norepinephrine, endothelin, and angiotensin II, limiting the degree of vasoconstriction and sodium retention and thus lowering the effective vascular volume and decreasing the load on the heart.4 Furthermore, increased BNP levels have been shown to be valuable predictors of the short-term and long-term risks of cardiac dysfunction and death in many critical care settings, including acute coronary syndrome and CHF.4,9 This led to approval for using BNP level to determine risk stratification in acute coronary syndrome10 and the proposal to use serial BNP measurements during patient follow-up because they may aid in prognostic assessment and determination of response to therapy.9

Sepsis and septic shock continue to pose clinical and diagnostic challenges. Severe sepsis has been reported to cause more than 200,000 deaths per year, most of which are attributed to cardiovascular collapse.11 Patients with septic shock were shown to have reversible left ventricular systolic dysfunction with an associated elevation in cardiac index.12 It was also de-
tended that myocardial depression persists in patients with septic shock until death or recovery. The early assessment and diagnosis of cardiovascular dysfunction and its severity in patients with septic shock requires special equipment and expertise. Thus, a readily measurable circulating biomarker would facilitate the assessment and perhaps prevent cardiovascular dysfunction in these patients. To our knowledge, only 1 retrospective study has shown a relationship between an increase in BNP levels and septic shock. Other studies have examined N-terminal (NT) prohormone forms of atrial natriuretic peptide (ANP) (NT-proANP) and BNP (NT-proBNP) as potential markers for sepsis. These analytes represent residual fragments of proANP and proBNP. Those studies showed that NT-proANP and NT-proBNP may serve as useful laboratory markers of myocardial dysfunction and may help differentiate between survivors and nonsurvivors of severe sepsis. The role of BNP during early sepsis and septic shock, specifically with regard to a correlation between BNP levels and sepsis severity independent of CHF, has yet to be examined. In light of the association of myocardial dysfunction in sepsis, there may be additional utility for BNP level in a non-CHF setting, namely sepsis. Our aim was to determine the role of BNP level as a potential marker of outcome in septic patients independent of CHF.

**METHODS**

**STUDY PATIENTS**

Forty-nine patients were selected for this prospective, nonrandomized control study. The patients were divided into 3 groups: 13 patients were diagnosed as having septic shock, 18 were diagnosed as having early sepsis, and 18 served as age-matched healthy control subjects. The diagnosis of early sepsis or septic shock was made in accordance with criteria set forth by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. All septic patients had positive-growth cultures taken from blood, an indwelling catheter, sputum, or a urinary source. Congestive heart failure was ruled out in included patients by results of right heart catheterization and transthoracic echocardiogram. Renal and hepatic failure were also ruled out. Septic patients who were unable to undergo additional testing for CHF were excluded. Patient consent was obtained from the patient, the legal guardian, or the next of kin. This study was approved by the institutional review board at SUNY Downstate Medical Center.

All patients with septic shock were admitted to the intensive care unit and required mechanical ventilation for various lengths of time (range, 4–21 days). Laboratory, biochemical, hemodynamic, and physical variables were determined on the day of diagnosis (day 0) and on the first and fourth days after diagnosis. All patients with septic shock were followed up for 21 days, until the patients either improved or deteriorated and died.

Hemodynamic measures recorded included central venous pressure, cardiac output, cardiac index, positive airway pressure, pulmonary artery wedge pressure, systemic vascular resistance, heart rate, mean arterial pressure, body temperature, respiratory rate, and urinary output. The white blood cell count, hematocrit, platelet count, liver function test results, and electrolytes were also recorded, along with the time spent in the intensive care unit and the outcome of treatment.

Patients with septic shock were stratified according to the degree of their sepsis as measured by the Sequential Organ Failure Assessment (SOFA) scale. SOFA is a reliable outcome predictor in septic shock and is a better predictor of outcome in patients with cardiovascular dysfunction than other scoring systems.

**BLOOD SAMPLE COLLECTION AND BNP LEVEL MEASUREMENT**

Blood samples for the measurement of BNP level were obtained by venipuncture and collected in EDTA tubes. The BNP level for patients with septic shock and early sepsis was determined on the day of diagnosis and 21 days later. Blood was drawn from the 18 controls only once.

The BNP level was measured with a single-use fluorescence immunoassay (Triage BNP Test; Biosite Inc, San Diego, California) on the manufacturer’s meter (Triage Meter; Biosite Inc). This system determines the concentration of BNP in whole blood or plasma using EDTA as the anticoagulant. The specimen is added to the sample port of the test device with a transfer pipette. After the specimen is added, the device is inserted into the meter, which is programmed to automatically perform the BNP analysis after the sample has reacted with the reagents (stabilizers, murine BNP monoclonal antibodies, and BNP polyclonal antibodies labeled with a fluorescent dye) within the device. The BNP analysis is based on the amount of fluorescence detected; a greater amount of fluorescence indicates a higher BNP concentration in the specimen. The test should be performed within 4 hours of sample collection; otherwise, the plasma should be separated and stored at −20°C until it can be tested. The analytical sensitivity (or the lowest detectable concentration that is distinguishable from zero) for the immunoassay was determined by testing a zero calibrator 20 times each using 3 lots of reagents and 5 meters on 5 different days. The intrapatient and interpatient coefficient of variation for this test was approximately 10%. The average 95% confidence limit of the analytical sensitivity of the immunoassay was less than 5 pg/mL (to convert BNP to nanograms per liter, multiply by 1).

**CARDIOVASCULAR FUNCTION ASSESSMENT**

A Swan-Ganz catheter was placed via the jugular vein into the pulmonary artery. Hemodynamic factors included pulmonary artery wedge pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, systemic vascular resistance, and pulmonary vascular resistance. The arterial pressure was non-invasively determined by the following equation:

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\text{Mean Arterial Pressure} = \frac{\text{Systolic Pressure}}{\text{Diastolic Pressure}} + \left[\frac{2 \times \text{Diastolic Pressure}}{3}\right].
\]

All patients with septic shock were assessed for CHF using this method.

Echocardiography was also used to measure left ventricular dimensions from M-mode and 2-dimensional echocardiographic images in the parasternal long-axis view. Left ventricular volumes and ejection fractions were calculated by modification of the Simpson method with 2 apical views. We used this method to assess CHF in all patients with early sepsis. Patients were excluded from the study if CHF criteria were met by either of these tests.

**STATISTICAL ANALYSIS**

The data are presented as mean ± SD. Because most of the data were normally distributed, the t test was applied. Data were ana-
lyzed using a 2 × 2 table. Values of $P < .05$ (2-tailed) were considered statistically significant.

## RESULTS

### BNP LEVELS IN PATIENTS WITH SEPTIC SHOCK

The 13 patients diagnosed as having septic shock had elevated BNP levels at the time of diagnosis (mean level, 849.4 ± 154.8 pg/mL) ([Figure 1](#)), which were significantly higher than those of the age-matched healthy controls (mean level, 100.0 ± 9.4 pg/mL) ($P < .05$). The sepsis group was further subdivided into 2 groups on the basis of patient survival, and a second BNP measurement was obtained 21 days after the initial diagnosis. Those who improved clinically and survived (n = 9) had elevated BNP levels (mean level, 351.7 ± 136.3 pg/mL). Although these patients had lower BNP levels on day 21 than the levels obtained on day 0, they were still significantly higher than those of the control group ($P < .05$). The second group of patients with septic shock, who did not improve clinically within 21 days and who eventually died (n = 4), maintained elevated BNP levels (862.2 ± 160.0 pg/mL).

### LEVELS OF BNP IN PATIENTS WITH EARLY SEPSIS

In the 18 patients diagnosed as having early sepsis, the mean BNP level was 120.0 ± 11.2 pg/mL at the time of diagnosis. This value was not statistically significant when compared with that of the control group (mean level, 100.0 ± 9.4 pg/mL) ($P > .05$) (Figure 1). Subsequent BNP levels were also not significantly different from those of the controls.

### BNP AND SEVERITY OF SEPSIS IN PATIENTS WITH SEPTIC SHOCK

SOFA scores, and therefore the severity of sepsis, were higher in patients with sepsis (mean score, 7.0 ± 0.6) compared with scores of those recovering from sepsis (mean score, 2.4 ± 0.9) ($P < .05$). Our analysis demonstrated a significantly positive correlation between BNP levels and SOFA scores in our patient population ($P < .05$) ([Figure 2](#)). This positive correlation was consistent for late septic shock.

### COMMENT

### BNP LEVEL AND CARDIAC DYSFUNCTION IN SEPTIC SHOCK

The relationship between CHF and increased levels of BNP has been well described in the literature. Yasue et al.22 determined that BNP is secreted mainly from the left ventricle in healthy adults, as well as in patients with left ventricular dysfunction. They also showed that increased wall tension of the left ventricle results in an increase in the rate of BNP secretion.22 Because of this relationship, Yasue and colleagues proposed BNP level as a marker of the degree of left ventricular dysfunction.22 Myocardial dysfunction has an important effect on the morbidity and mortality of patients with sepsis and septic shock. In these patients, cardiac dysfunction is manifested by biventricular dilation and reduced ejection fraction.24-28 The underlying cause of sepsis-induced myocardial dysfunction remains unclear. One theory speculates on the presence of a circulating myocardial depressant substance13,29,30, one other investigators have shown a relationship between myocardial depression and different cytokines, including interleukin 1β and tumor necrosis factor α, as well as endotoxins from gram-negative microorganisms.13,30 The myocardial depressant effect of these cytokines has been linked to mechanisms involving nitric oxide generation.13

Other laboratory markers linked to cardiac dysfunction or myocardial cell damage in severe sepsis include cyclic guanosine monophosphate, ANP, NT-proANP, NT-proBNP, endothelin, and troponin I.14-16,31-33 Despite the numerous cardiac changes that occur during septic shock,

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**Figure 1.** Levels of B-type natriuretic peptide (BNP) on day 0 for age-matched healthy controls, patients with early sepsis, and patients with septic shock. Data represent mean ± SD. To convert BNP to nanograms per liter, multiply by 1.

**Figure 2.** Correlation between levels of B-type natriuretic peptide (BNP) and Sequential Organ Failure Assessment (SOFA) scores. The solid line represents the linear regression fit across all individuals. To convert BNP to nanograms per liter, multiply by 1.
the role of BNP during sepsis has yet to be determined. Our findings show that BNP levels not only are increased during septic shock but also may provide risk stratification of septic patients. Furthermore, we have provided evidence of the clinical use of BNP measurement outside CHF.

Our study demonstrates a clear elevation of BNP levels in septic shock. This finding is consistent with previously quoted studies\(^{11-13}\) that linked sepsis to cardiac dysfunction. Patients with early sepsis had no significant elevation in BNP levels. This may be owing to an absent or minimal effect of early sepsis on cardiac function. Additional patient studies will elucidate the utility of BNP level as a marker for early sepsis.

**BNP LEVEL AND PROGNOSIS IN SEPTIC SHOCK**

Morrow et al\(^{34}\) reported that elevated BNP levels in acute coronary syndrome constitute an independent predictor of new CHF and death. Our study demonstrates that BNP levels may also predict the prognosis of patients with septic shock: patients diagnosed as having septic shock whose BNP levels improved survived; those whose BNP levels remained elevated died. B-type natriuretic peptide was also positively correlated with the SOFA scoring system. This is the first report, to our knowledge, of a relationship between BNP levels, SOFA scores, and survival in patients with septic shock. Our study supports the use of serial BNP levels in the intensive care unit as a reliable biomarker for risk stratification of patients with septic shock. This correlation cannot be made for patients with early sepsis, possibly because of the absence of adverse outcomes in this group in our study.

The utility of BNP level in septic shock can be confounded by many factors. Our study demonstrates the prognostic value of BNP level in a group of patients diagnosed as having septic shock but without comorbid conditions such as CHF and renal failure. Although the mortality of patients with septic shock and comorbid conditions is high (upwards of 90%),\(^ {12}\) our patient group, in whom these factors were ruled out, may have a better survival outcome and these patients would benefit from BNP analysis.

B-type natriuretic peptide may be found in the blood only after significant myocardial dysfunction, which may occur in severe sepsis only. Results of a study by Parker et al\(^ {13}\) examining the relationship between outcomes and cardiac dysfunction in the setting of septic shock correlated well with our findings. In that study, survivors of septic shock demonstrated acute cardiac function changes that returned to normal within 10 days.\(^ {21}\) The change in cardiac function was mirrored in our study by the decrease in BNP levels for survivors of septic shock as they improved. On the other hand, the study by Parker and colleagues also demonstrated that some patients who did not survive septic shock had normal cardiac function that did not change throughout the study.\(^ {21}\) This finding was mirrored in our study by the continuous elevation of BNP levels in patients who died of septic shock.

In conclusion, we have demonstrated that BNP levels are significantly increased in patients in septic shock and may play an important role in risk stratification in these patients. Measurement of BNP level may serve as potential diagnostic and prognostic biomarkers for septic shock independent of CHF. This information may lead to BNP level serving as a valuable measure for determining reduced left ventricular function in patients with septic shock.

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**REFERENCES**


Kandil and colleagues purport a role for BNP level as a useful marker of ventricular function and mortality in sepsis. There were no demographic data provided for the groups, specifically age and the underlying disease. Also, the absence of any BNP data between days 1 and 21 precludes potential useful information about BNP activity in response to therapy. These investigators state that patients without renal and heart failure may benefit from measurement of BNP levels but do not present any supporting data, only concepts. They also state that BNP level determination may help with risk stratification, which is suspect because there was no significant difference between the control subjects and patients with early sepsis (100±9.4 vs 120±1.2 pg/mL). They further stated that BNP level may serve as “a valuable measure for determining reduced left ventricular function in patients with septic shock”; again, with no supporting data. Besides, there are much better tools for assessing left ventricular function (eg, thermistor-tipped, flow-directed pulmonary artery catheters and transesophageal echocardiography or even transthoracic echocardiography) because BNP level provides no quantitative data. The authors gave no information about the availability of this test in most hospitals: Is it a routine test, or a research study that must be sent to a reference laboratory? What does it cost, and will insurance companies pay for it? Elevation of BNP level in septic shock may well be just a measure of deteriorating myocardial function during end-stage sepsis after weeks of significant tachycardia and pressors, when the heart can no longer compensate. I was surprised to see a resurrection of an ancient term, myocardial depressant substance, which we used (and discarded) many years ago to explain observations we did not understand. In my view, their goal of determining a role for BNP in sepsis was not achieved, and their observations most likely represent a “true-true but unrelated” association between the two. As presented, they can say only that if BNP levels remain high, death is imminent; there is little one can do with such information except withhold treatment, which is not an option in this context.

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