# Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure*

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***Objective:*** **B-type natriuretic peptide (BNP) and N-terminal pro-BNP measurements are used for the diagnosis of congestive heart failure (HF). However, the diagnostic value of these tests is unknown under septic conditions. We compared patients with severe sepsis or septic shock and patients with acute HF to unravel the influence of the underlying diagnosis on BNP and N-terminal pro-BNP levels.**

***Design:*** **Prospective, clinical study.**

***Setting:*** **Academic medical intensive care unit (ICU).**

***Patients:*** **A total of 249 consecutive patients were screened for the diagnosis of sepsis or HF. Sepsis was defined according to published guidelines. HF was diagnosed in the presence of an underlying heart disease and congestive HF, pulmonary edema, or cardiogenic shock.**

***Interventions:*** **BNP and N-terminal pro-BNP were measured from blood samples that were drawn daily for routine analysis.**

***Measurements and Main Results:*** **We identified 24 patients with severe sepsis or septic shock and 51 patients with acute HF. At admission, the median (range) BNP and N-terminal pro-BNP levels were 572 (13–1,300) and 6,526 (198–70,000) ng/L in patients with sepsis and 581 (6–1,300) and 4,300 (126–70,000) ng/L in patients with HF. The natriuretic peptide levels increased during the ICU stay, but the differences between the groups were not significant. Nine patients with sepsis and eight patients with HF were monitored with a pulmonary artery catheter. Mean (SD) pulmonary artery occlusion pressure were 16 (4.2) and 22 (5.3) mm Hg ($p = .02$), and cardiac indexes were 4.6 (2.8) and 2.2 (0.6) L/min/m$^2$ ($p = .03$) in patients with sepsis and HF, respectively. Despite these clear hemodynamic differences BNP and N-terminal pro-BNP levels were not statistically different between the two groups.**

***Conclusion:*** **In patients with severe sepsis or septic shock, BNP and N-terminal pro-BNP values are highly elevated and, despite significant hemodynamic differences, comparable with those found in acute HF patients. It remains to be determined how elevations of natriuretic peptide levels are linked to inflammation and sepsis-associated myocardial dysfunction. (Crit Care Med 2006; 34:2140–2144)**

**KEY WORDS: natriuretic peptide; B-type natriuretic peptide; amino-terminal pro-B-type natriuretic peptide; sepsis; shock; myocardial dysfunction; heart failure; inflammation**

B-type natriuretic peptide (BNP) is a neurohormone that has been isolated first in the porcine brain and later in human ventricular cardiomyocytes (1). It derives from a pre-prohormone, which is clipped into pro-BNP. After stimulation, pro-BNP is released from the cell into the circulation as the active 32-amino acid long polypeptide BNP and an inactive 77-amino acid long fragment N-terminal pro-BNP (2–4). Because of its longer plasma half-life time and higher stability, the measurement of N-terminal pro-BNP has been introduced into routine clinical diagnostics (5, 6). BNP and N-terminal pro-BNP are used for the early diagnosis of heart failure (HF) in patients presenting to the emergency room with dyspnea (7–10). Additionally, in patients with chronic HF and acute and chronic coronary syndrome, both BNP and N-terminal pro-BNP are markers of unfavorable prognosis, being associated with increased mortality (11–14). Recently, elevated BNP levels have been measured in patients with septic shock and have been attributed to myocardial dysfunction due to sepsis (15–18). Because BNP synthesis is also induced by endotoxin and inflammatory mediators (19–21), the mechanisms leading to elevated BNP levels in patients with sepsis remain unclear. Little information is available concerning N-terminal pro-BNP levels in patients with critical illness, especially with sepsis.

To assess the clinical relevance of both BNP and N-terminal pro-BNP in intensive care unit (ICU) patients, we prospectively measured both markers in patients with severe sepsis and septic shock and compared them with natriuretic peptide levels obtained from patients admitted to our ICU with the diagnosis of acute congestive HF or low cardiac output syndrome.

*See also p. 2249.

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## MATERIALS AND METHODS

### Patient Population

Investigations were performed at the University Hospital Zurich, Switzerland. During a 4-month period, 249 patients who were consecutively admitted to the medical ICU were screened for the diagnosis of sepsis or HF. Patients were included into the analysis only once, even if they were readmitted during the observation period. Patients and/or their relatives gave their oral informed consent for the anonymous analysis of the collected routine clinical and laboratory data. The Institutional Review Board waives the need for informed consent in this particular condition.

*Septic Patients.* According to the published consensus, 24 of the 249 patients had systemic inflammatory response syndrome with infection, hence could be classified as septic (22). Severe sepsis was diagnosed in 16 patients and was associated with at least one of the following organ dysfunctions: arterial hypoxemia ($Pao_2/Fio_2$, <300 mm Hg), renal dysfunction (creatinine at admission, >2 mg/dL, or oliguria, <0.5 mL/kg body weight), arterial hypotension (systolic arterial blood pressure (BP), <90 mm Hg, or mean arterial BP, <60 mm Hg) responsive to fluid therapy, hyperlactatemia (>2 mmol/L), thrombocytopenia (platelet count, <100,000/μL), hyperbilirubinemia (total plasma bilirubin, >4 mg/dL), or signs of cerebral dysfunction with confusion or reduced consciousness (23). Septic shock was diagnosed in eight of the 24 septic patients and was accompanied by refractory hypotension (systolic arterial BP, <90 mm Hg, or mean arterial BP, <60 mm Hg) requiring vasopressors, despite adequate fluid therapy (23). Patients with sepsis due to endocarditis or after cardiovascular surgery were excluded from the study to avoid patients with both sepsis and heart failure.

*Heart Failure Patients.* In 51 of the 249 patients admitted to our ICU, we made the clinical diagnosis of acute decompensated HF. Therefore, an underlying heart disease and clinical signs of congestion (dyspnea, orthopnea, rales, elevated jugular venous pressure) or signs of low cardiac output with organ hypoperfusion and typical pulmonary infiltrates in the chest radiograph were required. Pulmonary edema was diagnosed in the presence of rales covering all lung fields and alveolar infiltrates in the chest radiograph. Cardiogenic shock was diagnosed in 20 of the 51 patients; all of them were in a low output state and needed inotropic drugs with or without additional vasopressors to have a mean arterial BP >60 mm Hg and a cardiac index >2.2 L/min/$m^2$.

### Measurement of Cardiovascular Functional Parameters

Arterial BP was measured noninvasively or invasively by catheters inserted into the radial or femoral arteries. If available, central venous pressure was measured through a catheter inserted into either the internal jugular or the subclavian vein (the correct position was assessed by a chest radiograph). In patients with prolonged shock, need of high-dose vasopressor therapy, or the presence of an acute respiratory distress syndrome, a pulmonary artery catheter (PAC) was inserted to measure pulmonary artery occlusion pressure and cardiac index with Baxter Vigilance Monitors (Edwards Lifesciences, Irvine, CA). All pressures were measured in the supine patient using Hellige SM 611 pressure transducers (Hellige GmbH, Freiburg im Breisgau, Germany). The zero reference was the middle axillary line. The median (range) time intervals from ICU admission to PAC insertion were 22 (5–66) and 7 (0–148) hrs ($p = .200$) and the median (range) time intervals from the initial hemodynamic measurement by PAC to blood sampling were 1 (0.8–3.0) and 0.9 (0.3–2.0) hrs ($p = .200$) in patients with sepsis and HF, respectively. Because echocardiography was acquired in only a limited number of patients and at very different time points, the results were not further analyzed for this study.

### Measurement of BNP and N-terminal pro-BNP Values

BNP and N-terminal pro-BNP levels were measured from blood samples that were drawn for routine laboratory analysis. Values at admission were obtained within 24 hrs. Subsequently, BNP and N-terminal pro-BNP were measured daily as long as the patient was hospitalized in the ICU. The values at admission, as well as the maximum value of the following days during the ICU stay, were used for the analysis. Physicians in charge of the patients were not blinded for the results. BNP was measured in blood using a fluorescence immunoassay kit (Triage, Biosite), and the cutoff level recommended by the manufacturer is 50 ng/L. N-terminal pro-BNP was measured in heparanized plasma using an electrochemiluminescence assay (Roche Diagnostics). The cutoff levels were set according to the manufacturer's recommendations and according to age and gender (men: age, <50 yrs—88 ng/L, >50 yrs—227 ng/L; women: age, <50 yrs—153 ng/L, >50 yrs—334 ng/L). The upper detection limits of the two assays were at 1,300 ng/L (BNP) and 70,000 ng/L (N-terminal pro-BNP). All values higher than these levels were included in the analysis and labeled 1,300 and 70,000 ng/L, respectively.

### Statistical Analysis

All data were collected from the patients' charts and entered into a database. Median (range), mean (SD), or percentages were calculated for the overall sample and subgroups. Comparisons were made with the use of the Mann-Whitney U test, Fisher's exact test, Student's *t*-test, or the chi-square test, as appropriate. Because the upper BNP and N-terminal pro-BNP values were limited by the dynamic range of the assay, we did not expect a normal distribution and used nonparametric procedures for the laboratory values. Box plots show median, 25th and 75th percentiles, as well as the range (without outliers or extremes). The null hypothesis was rejected with a two-sided $p < .05$. All analyses were performed with the use of SPSS 12.0 for Windows.

## RESULTS

### Patient Characteristics

Twenty-four patients with severe sepsis or septic shock and 51 patients with HF were included in the analysis. Baseline characteristics are shown in Table 1.

*Patients with Sepsis.* The following sources of infections were identified in the septic patients: six (25%) pneumonia; six (25%) skin/wound; four (17%) intestinal tract; three (13%) urogenital tract; one

**Table 1.** Baseline characteristics at admission to the intensive care unit

| | Patients with Severe Sepsis or Septic Shock (n = 24) | Patients with Heart Failure (n = 51) | *p* Value |
|---|---|---|---|
| Age, yrs, mean (SD) | 60 (18) | 66 (13) | .123 |
| Male sex, n (%) | 14 (58) | 39 (77) | .173 |
| SAPS II, median (range) | 45 (18–106) | 35 (13–72) | .261 |
| Shock, n (%) | 8 (33) | 20 (39) | .799 |
| Temperature, °C, mean (SD) | 37.6 (1.4) | 36.7 (0.9) | .015 |
| Systolic BP, mm Hg, mean (SD) | 112 (29) | 110 (25) | .881 |
| Mean BP, mm Hg, mean (SD) | 78 (20) | 78 (19) | .957 |
| Diastolic BP, mm Hg, mean (SD) | 62 (16) | 60 (16) | .583 |
| Heart rate, per min, mean (SD) | 106 (20) | 89 (23) | .002 |
| Troponin T, μg/L, median (range) | 0.03 (0.01–0.56) | 0.46 (0.01–27.39) | <.001 |
| CRP, mg/L, median (range) | 221 (36–438) | 29 (2–254) | <.001 |
| Creatinine, μmol/L, median (range) | 141 (47–590) | 127 (59–413) | .174 |

SAPS, simplified acute physiology score; BP, blood pressure; CRP, C-reactive protein (norm, <5).

Table 2. Hemodynamic parameters in patients monitored with a pulmonary artery catheter

| | Patients with Severe Sepsis or Septic Shock (n = 9) | Patients with Heart Failure (n = 8) | *p* Value |
|---|---|---|---|
| MAP, mm Hg, mean (SD) | 65 (7.8) | 67 (10) | .689 |
| CVP, mm Hg, mean (SD) | 14 (4.0) | 15 (3.9) | .463 |
| PAOP, mm Hg, mean (SD) | 16 (4.2) | 22 (5.3) | .016 |
| CI, L/min/$m_2$, mean (SD) | 4.6 (2.8) | 2.2 (0.6) | .034 |
| $Smvo_2$, %, mean (SD) | 69 (11) | 60 (10) | .101 |

MAP, mean arterial blood pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; $Smvo_2$, mixed venous oxygen saturation.

All values were obtained directly after insertion of the pulmonary artery catheter.

(4%) meningitis. One (4%) patient had a generalized herpes simplex infection with involvement of the gastrointestinal tract. Three patients (13%) had a bloodstream infection without a detectable source of infection, and one (4%) had *Plasmodium falciparum* infection. The isolated bacteria were as follows: seven (29%) patients, Gram-positive; eight (33%) patients Gram-negative; and three (13%) patients, mixed Gram-positive and Gram-negative. In three (13%) patients with pneumonia and one (4%) patient with cholangitis, no pathogen could be isolated, despite an explicit clinical suspicion of infection. Five (21%) patients with sepsis had established coronary artery disease, seven (29%) had a history of elevated BP, two (8%) had intermittent atrial fibrillation, and two (8%) had a cor pulmonale due to severe chronic obstructive lung disease.

*Patients with HF.* Seventeen of the 51 (33%) HF patients presented with pulmonary edema and six (12%) were admitted after successful resuscitation. Forty-one (80%) patients with HF had an established coronary artery disease, and acute coronary syndrome was the cause leading to HF in 23 (46%) patients, ten (20%) of them suffering from a ST-elevation myocardial infarction. Twenty-three patients with HF (45%) had a history of elevated BP.

*Patients with a Pulmonary Artery Catheter.* A PAC was inserted in nine patients with sepsis and in eight patients with HF. Five septic patients with PAC had neither a history of elevated blood pressure nor a preexisting cardiopathy. Hemodynamic parameters of patients monitored with a PAC are shown in Table 2.

## BNP and N-Terminal Pro-BNP Values

In patients with severe sepsis or septic shock, the median (range) BNP level at admission was 572 (13–1,300) ng/L and increased to 1,080 (135–1,300) ng/L during the ICU stay ($p = .09$). These values did not differ from BNP levels of patients with HF, which were 581 (6–10,300) and 965 (201–1,300) ng/L, respectively (Fig. 1*A*). In patients with severe sepsis or septic shock, the median (range) N-terminal pro-BNP level at admission was 6,526 (198–70,000) ng/L and increased to 16,013 (613–70,000) ng/L during the ICU stay ($p = .3$), and in patients with HF, the N-terminal pro-BNP values were 4,300 (126–70,000) and 8,005 (526–70,000) ng/L, respectively (Fig. 1*B*). Only seven (29%) and two (9.1%) septic patients had a maximum BNP level during the ICU stay <400 ng and N-terminal pro-BNP level <1000 ng/L, respectively. In patients with sepsis, there was a trend to higher BNP and N-terminal pro-BNP levels in women, whereas in patients with HF, no difference in terms of gender could be found. In septic patients, BNP and N-terminal pro-BNP levels at admission and during the ICU stay were not different between those with (n = 12) and those without (n = 12) a history of heart disease or elevated blood pressure.

In patients admitted with circulatory shock (need for vasopressors) independently of its origin, BNP and N-terminal pro-BNP values at admission were not different from those without shock. Thereafter, BNP and N-terminal pro-BNP levels increased more in patients with shock ($p = .047$ for BNP and $p = .019$ for N-terminal pro-BNP). In patients monitored with a PAC, the BNP ($p = .3$) and N-terminal pro-BNP ($p = .6$) levels were not statistically different between patients with sepsis and those with HF (Fig. 2).

## Outcome

Median (range) lengths of ICU stay were 7 (1–46) days in patients with sepsis and 4 (1–23) days in patients with HF ($p = .049$). Median (range) lengths of stay from ICU admission to hospital discharge were 16 (1–127) and 11 (1–66) days in patients with sepsis and HF ($p = .041$), respectively. ICU mortalities were 17% in patients with sepsis and 14% in those with HF ($p = .7$), and in-hospital mortalities were 29% and 24% ($p = .8$), respectively. BNP and N-terminal pro-BNP values at admission as well as the maximum levels during the ICU stay were not different between survivors and nonsurvivors independently of whether the patients had sepsis or HF (Fig. 3).

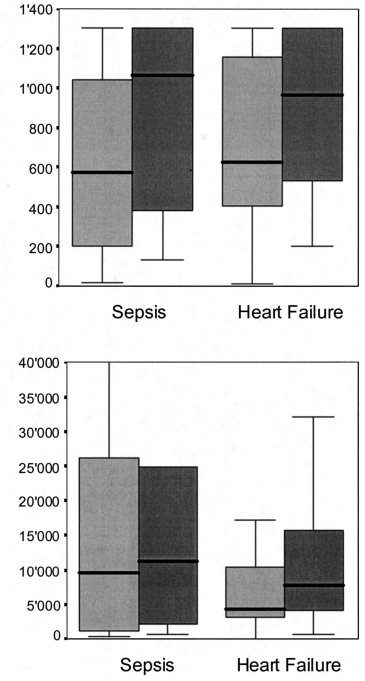


Figure 1. Natriuretic peptide levels at intensive care unit (ICU) admission and maximum values during the ICU stay in patients with severe sepsis and septic shock or heart failure (HF). *Panel A* demonstrates the B-type natriuretic peptide (BNP) levels at admission (*light gray*) and the maximum BNP levels during the ICU stay (*dark gray*). *Panel B* demonstrates the N-terminal pro-BNP levels at admission (*light gray*) and the maximum N-terminal pro-BNP values during the ICU stay. Neither the values at admission nor the maximum levels during the ICU stay were statistically different between patients with sepsis and HF for both BNP and N-terminal pro-BNP. However, the values increased during the ICU stay nonsignificantly in patients with sepsis (BNP, $p = .094$; N-terminal pro-BNP, $p = .279$) and significantly in patients with HF (BNP, $p = .014$; N-terminal pro-BNP, $p = .015$).

## DISCUSSION

The present study shows that BNP and N-terminal pro-BNP values are similarly elevated in both patients with severe sep-

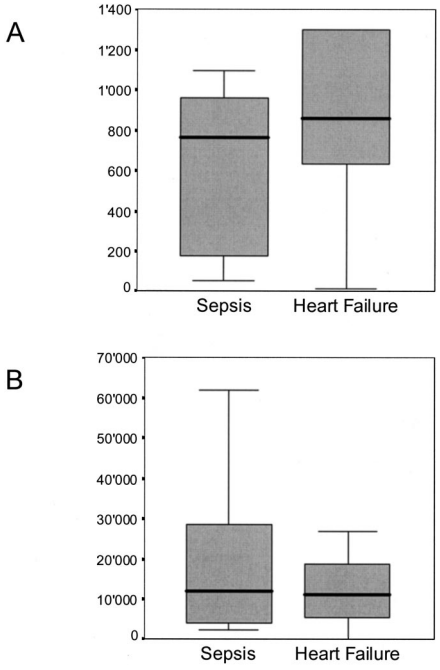


Figure 2. Natriuretic peptide levels after insertion of a pulmonary artery catheter in patients with severe sepsis and septic shock or heart failure. *Panel A* shows the B-type natriuretic peptide (BNP) values; *panel B* demonstrates the N-terminal pro-BNP levels. There were no statistically significant differences between the two groups of patients (BNP, $p = .321$; N-terminal pro-BNP, $p = .574$).

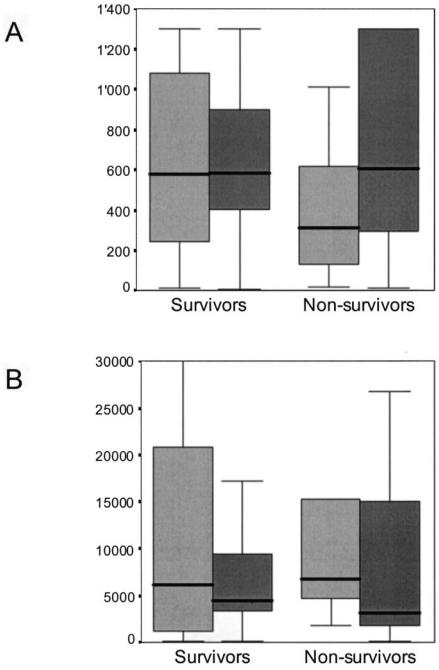


Figure 3. Natriuretic peptide levels in patients with severe sepsis and septic shock or heart failure (HF) independent of their hospital outcome. *Panel A* shows the B-type natriuretic peptide (BNP) values at hospital admission in patients with sepsis (*light gray*) and patients with HF (*dark gray*). *Panel B* demonstrates N-terminal pro-BNP values at admission in patients with sepsis (*light gray*) and HF (*dark gray*). The natriuretic peptide values were similar between hospital survivors and nonsurvivors (BNP sepsis, $p = .354$; HF, $p = .789$; N-terminal pro-BNP sepsis, $p = .590$; HF, $p = .263$).

sis or septic shock and acute congestive HF, independently of whether they presented with or without shock at ICU admission. Moreover, in a subset of patients monitored with a PAC, BNP and N-terminal pro-BNP values were not different between patients with severe sepsis or septic shock and patients with decompensated HF, despite significant hemodynamic differences between the two groups. Thus, results of our study suggest that neither BNP nor N-terminal pro-BNP can be used for the diagnosis of congestive heart failure in patients with severe sepsis or septic shock.

The results of the present study confirm previous studies indicating that BNP and N-terminal pro-BNP levels are elevated in patients with HF. Large multicenter studies have proven that elevated BNP levels are indicative for congestive HF in patients presenting with dyspnea to the emergency room (7–10). These results made many clinicians think that elevated BNP levels are equal to the diagnosis of congestive HF. Unfortunately, less clear is its clinical relevance in patients admitted to an ICU with sepsis, severe sepsis, and septic shock. Our study confirms that both BNP and N-terminal pro-BNP values are elevated in patients with severe sepsis and septic shock (15–18). It also clearly indicates that natriuretic peptides may be similarly elevated, despite significant hemodynamic differences as were found in our patients with severe sepsis and septic shock or acute HF. Recently, elevated natriuretic peptide levels have been found to be an indicator of myocardial dysfunction in septic patients (18). Since the first day patients with myocardial dysfunction (fractional area contraction, <50%) had elevated BNP levels, the BNP values measured were comparable with our values. Charpentier and coworkers (18) also measured cardiac index and found similar values between septic patients with and without myocardial dysfunction, the reported cardiac index values, despite the different methods used, being probably close to those obtained in our patients. Accordingly, several other studies indicated that the hyperdynamic state of these patients does not exclude cardiac dysfunction (24–27). Thus, we cannot exclude that our septic patients had myocardial dysfunction, despite normal cardiac index and an adequate fluid resuscitation (as it can be assessed using pulmonary artery occlusion pressure). On the other hand, however, our study clearly indicates that elevated BNP and N-terminal pro-BNP levels may not necessarily imply a low cardiac output state and/or elevated left ventricular filling pressures as indicated by the hemodynamic differences between patients with severe sepsis and acute HF. This result is supported by previous measurements performed in ICU patients, with cardiogenic and noncardiogenic shock showing no correlation between cardiac output and pulmonary artery occlusion pressure, as well as cardiac output and BNP blood levels (28). Thus, our study adds further evidence to the principle that BNP levels cannot be surrogates for the use of additional invasive hemodynamic monitoring or fluid restriction in septic patients.

Pathophysiological mechanisms other than myocardial dysfunction may also contribute to increased BNP and N-terminal pro-BNP levels in patients with sepsis. Clinical studies suggest that natriuretic peptide levels are, at least partly, elevated in response to either increased secretion or decreased degradation due to inflammation (18, 29). Accordingly, results from animal studies and tissue cultures show increasing evidence that both the production and the secretion of natriuretic peptides are activated by endotoxin and inflammatory mediators. Tomaru et al. (19) described a transcriptional activation of the BNP gene in cardiac myocytes after treatment with endotoxin. This effect was mediated through a pathway involving CD 14, Racl, p38 MAPK, and GATA elements. Others have demonstrated a dose-dependent stimulation of BNP messenger RNA expression and secretion in cultured rat myocytes by interleukin-6, interleukin-1β, and tumor necrosis factor-α (20, 21). Yet, a decade ago, Vollmar and Schulz (30) found natriuretic peptides expressed in mouse macrophages, suggesting a role for BNP during inflammation.

In the present study, natriuretic peptide values were not predictive for ICU or in-hospital mortality, neither in patients with sepsis nor in patients with HF. This stands in contrast to reports from others (18, 28), which could be explained by a lower mortality in our septic patients and a larger proportion of patients with a BNP

level >300 ng/L. Differences related to age, gender, or renal function, which are factors influencing BNP and N-terminal pro-BNP values, may add to this discrepancy (31–33). Other confounding factors that may alter the levels of natriuretic peptides are the different treatment modalities, such as fluid application or catecholamine therapy. Because the number of cases in our study was small, we were not able to control for all these factors. Therefore, large clinical studies are needed to better define the role of natriuretic peptides in critically ill patients with inflammation and sepsis.

## CONCLUSIONS

In patients admitted to the ICU with severe sepsis or septic shock, BNP and N-terminal pro-BNP values are highly elevated and, despite significant hemodynamic differences, comparable with those found in acute HF patients. Irrespective of the underlying mechanisms, elevated BNP and N-terminal pro-BNP levels must not be seen as an indication to withhold volume therapy in patients with severe sepsis or septic shock. It remains to be determined how elevations of BNP and N-terminal pro-BNP levels are linked to inflammation and sepsis-associated myocardial dysfunction.


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## Natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure

**To the Editor:**

We read with great interest the article by Rudiger et al (1). They showed that in patients with severe sepsis, brain natriuretic peptide (BNP) and amino terminal pro-B-type natriuretic peptide values were highly elevated and comparable with those found in heart failure patients. We have several comments. First, as they stated in the method section, the physicians in charge of the patients were not blinded for the levels of natriuretic peptides, which could have biased the results (2). Second, they confirmed that despite significant hemodynamic differences (mean pulmonary artery occlusion pressure was 16 in the septic shock patients vs. 22 mm Hg in the heart failure group; $p = .02$), BNP and N-terminal (NT) pro-BNP levels were not significantly different between the two groups. It should be noted that their conclusions are based on homodynamic data for only 17 of 75 patients; we do not know if the characteristics (previous history of cardiac and respiratory diseases, volume of fluid infusion, dose of dobutamine, etc.) of the patients with pulmonary arterial catheter are the same as those of patients without, in each group. Forfia et al. (3) reported a stronger correlation between natriuretic peptides and pulmonary artery occlusion pressure in intensive care unit (ICU) patients with preserved (BNP, $r = .58$; NT-proBNP, $r = .73$) vs. impaired renal function (BNP, $r = .48$; NT-proBNP, $r = .34$). We also reported the main importance of creatinine clearance in the elevation of natriuretic peptides (4). Unfortunately, Rudiger et al. reported on only the creatinine level, which was slightly higher in the sepsis group, not the creatinine clearance (1, 4). Rudiger et al. did not report on the level of positive end-expiratory pressure in the two groups. Thus, the application of positive end-expiratory pressure should result in overestimation of transmural left ventricular end-diastolic pressure, because the associated increase in pericardial pressure is not accounted for (5). Furthermore, right ventricle failure also leads to release of natriuretic peptides in the bloodstream, and it should be of interest to compare the values of pulmonary artery pressure in the two groups. Therefore, the rate of acute respiratory distress syndrome patients and chronic obstructive pulmonary disease in the sepsis group should be reported. Other factors influence natriuretic peptide levels, such as obesity and hypertension (6). Finally, despite differences in cardiac output, mixed venous oxygen saturation was similar in both groups, with surprisingly low mixed venous oxygen saturation (69%) in the sepsis group, which makes hemodynamic interpretation in regard to natriuretic levels difficult.

In fact, we agree that natriuretic peptides are probably less useful in the ICU than in the emergency department because of confounding factors (see above) (1, 7). However, we believe that the study by Rudiger et al. is not strong enough (lack of data) to demonstrate it.

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**The authors reply:**

We thank Drs. Ray and Riou for their interest in our article (1) and for their comments. Physicians in charge made the diagnosis of sepsis or acute heart failure (HF) according to their best knowledge, possibly including natriuretic peptides at least in HF patients. We agree that the lack of blinding might have influenced the diagnostic approach, promoting the clinical diagnosis of heart failure. The fact that severe sepsis and septic shock were diagnosed, despite elevated brain natriuretic peptide (BNP) levels, is reassuring in terms of diagnostic certitude.

We agree that not all of our patients were monitored with a pulmonary artery catheter (PAC). This monitoring device is usually reserved for the most ill patients in our institution. Hence, we assumed that discrepancies between HF and septic patients would be most prominent in this subpopulation. In patients monitored with a PAC, we found no differences in age, Simplified Acute Physiology Score II, and creatinine levels between the two groups. However, men were more common in the HF group (100% vs. 44%; $p = .029$). Four of the nine septic patients monitored with the PAC had a history of stable coronary artery disease ($n = 1$), intermittent atrial fibrillation ($n = 2$), and a history of elevated blood pressure ($n = 3$). Chronic obstructive lung disease was diagnosed in two septic patients. Because we did not perform echocardiography in our septic patients, we cannot exclude that right heart failure may have influenced our results; however, on average, central venous pressure was similar to pulmonary artery occlusion pressure in septic patients, which exclude overt right heart failure (2).

The fact that the mixed venous oxygen saturation was only 69% in our septic patients was not surprising to us. We reported the first measurement after insertion of the PAC, and it is known that early sepsis goes along with low central venous saturation (3), mostly because of an incomplete fluid resuscitation. Thus, this result may even reinforce our results, indicating that despite clear hemodynamic differences, BNP and N-terminal pro-BNP levels did not differ between patients with severe sepsis or septic shock and patients with acute HF.

We agree that various therapeutic interventions, such as fluid loading, treat-

ment with inotropes, and invasive ventilation, might have influenced natriuretic peptides levels in our critically ill patients. As we stated in the text, renal dysfunction is probably another important factor influencing BNP and N-terminal pro-BNP levels (4). In our population though, median (range) creatinine clearances were 57 (16–137) mL/min and not significantly different between patients with severe sepsis or septic shock and patients with acute HF. Finally, laboratory and clinical evidence is evolving and suggests that natriuretic peptides are directly influenced by inflammation (5). Thus, our results, despite all the potential confounders mentioned above, suggests that neither BNP nor N-terminal proBNP can be used as a maker of congestive HF in patients with severe sepsis or septic shock. We anticipate future studies elucidating the different mechanism of BNP and N-terminal pro-BNP elevations and the clinical role of these biomarkers in critically ill patients, especially in those with sepsis.

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