Positive End-Expiratory Pressure and Renal Function Influence B-Type Natriuretic Peptide in Patients with Severe Sepsis and Septic Shock

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Summary

Background: Myocardial dysfunction is a complication associated with a poor prognosis in septic patients. A biomarker of cardiac function providing prognostic information is of paramount interest.

Objective: We sought to determine the value of B-type natriuretic peptide in patients with severe sepsis/septic shock.

Methods: We performed a prospective study in patients with severe sepsis/septic shock in a medical intensive care unit. B-type natriuretic peptide level was determined within 24 hours after the diagnosis of severe sepsis/septic shock. We also analyzed mortality, and presence of association between B-type natriuretic peptide and clinical, hemodynamic and respiratory variables.

Results: 23 (9 women; 14 men) patients with ages ranging from 20-79 (mean 51.3±18.6) years old and APACHE score of 22.6±11.8 were included; 15 (65.2%) patients received pulmonary artery catheters, and 20 (87%) were mechanically ventilated. Multivariate analysis disclosed inverse association between B-type natriuretic peptide values with positive end-expiratory pressure values, and direct association with creatinine (beta 0.548 and 0.377, p 0.02 and 0.002, respectively), but not with mortality, clinical and hemodynamic parameters.

Conclusion: This is the first report on an inverse association between positive end-expiratory pressure and BNP levels in patients with severe sepsis and septic shock. BNP and creatinine levels should be taken into consideration when analyzing B-type natriuretic peptide levels in this setting. (Arq Bras Cardiol 2008;91(2):107-112)

Key words: Positive-pressure respiration; natriuretic peptide, B-type; shock; sepsis; cardiac output, low.

Introduction

Sepsis is a frequent cause of patient admission in intensive care units, accounting for over 200,000 deaths per year in the United States[1] alone. The occurrence of myocardial dysfunction is a long known complication in septic patients occurring in up to 50% of patients with severe sepsis and septic shock[2,3]. In this setting, myocardial depression is presumed to play a central role in the development of tissue hypoxia and multiple organ dysfunction and is associated with poor prognosis despite advances in therapy[4]. There is no consensus as to the possible reasons for the occurrence of myocardial dysfunction in septic patients. These include circulating myocardial depressant substances, increased myocardial apoptosis, and myocardial hypoxia.

In this setting, cardiovascular support is a pivotal part of current treatment strategy, and hemodynamic monitoring is considered crucial in septic patients. However, the value of the use of pulmonary artery catheters (PAC) has been questioned by recent studies, as no survival benefit could be demonstrated from PAC-guided therapy[5]. Considering that other methods of non-invasive hemodynamic monitoring, such as echocardiography or esophageal Doppler monitoring, require a high degree of training, and are not promptly available in many institutions, the development of a biomarker of cardiac function providing prognostic information in septic patients is of paramount interest.

B-type natriuretic peptide (BNP) is a member of a family of proteins produced by the human heart in response to myocardial stretch that carries natriuretic, diuretic and vasodilating properties[6]. BNP has been shown to be an accurate marker of ventricular systolic and diastolic function, as well as an important diagnostic, prognostic and monitoring tool for patients with heart failure[7], acute coronary syndromes[8] and hypertension[9]. In these conditions, plasma level of BNP correlates with hemodynamic data, such as elevation of pulmonary artery occlusion pressure, elevation of the left-ventricle end-diastolic pressure and reduction in the ejection fraction[10]. However, studies on the value of BNP in critically ill patients revealed conflicting results regarding its association

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with hemodynamic variables, and mortality[11]. In addition, methodological flaws[12] and the absence of a representative number of septic patients in these studies[13-15] prevent us from drawing final conclusions on the subject.

Thus, we sought to determine the prognostic value of BNP levels in patients with severe sepsis and septic shock, and to study the influence of different clinical, hemodynamic and respiratory parameters on BNP levels.

Patients and methods

Patients

Patients consecutively admitted to a medical intensive care unit (ICU) in a university hospital from March 2004 through February 2006 were screened for diagnosis of severe sepsis or septic shock, according to current guidelines[16]. Inclusion criteria required the diagnosis of severe sepsis or septic shock either as the reason for ICU admission or as a complication during ICU stay, in patients over 18 years old. Written informed consent from all participants or their closest relative, when appropriate, was required before study entry. Patients were excluded from study if they had one of the following conditions: brain hemorrhage, renal replacement therapy, evidence of current or previous heart disease, acute coronary syndromes, or post-operative status. Patients were included in the study within 24 hours after diagnosis of severe sepsis/septic shock. Patient status at ICU discharge was registered.

The local ethics committee approved the study protocol. A decision regarding the use of invasive monitoring with pulmonary artery catheter, as well as therapeutic decisions were not influenced by the investigators, and were left to ICU team discretion.

Clinical variables

Patients included in the study had their medical charts reviewed as well as their history and physical examination. Severity of disease was quantified by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score[17]. Clinical variables analyzed included demographic data, water balance, and ICU mortality. Arterial blood samples were obtained for gas analysis, pH, base-excess and bicarbonate determinations. Another blood sample was drawn from a central vein in the neck for routine measurements of sodium, potassium, creatinine, BUN, hemoglobin, leucocytes and platelet counts. Part of this blood sample was immediately centrifuged and stored in plastic tubes under -70º C for later analysis; and in April 2006 these samples were used to measure BNP levels. We performed a microparticle enzyme immunoassay (MEIA –Abbott Diagnostics) whose upper limit of detection of BNP is 4000 pg/ml.

Hemodynamic and respiratory variables

The following hemodynamic and respiratory variables were registered at the time of blood sampling: heart rate, blood pressure, central venous pressure, positive end-expiratory pressure, and the arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2). Arterial blood pressure was measured both noninvasively and invasively by catheters inserted into the radial or femoral arteries. Central venous pressure was measured through a catheter inserted into a central vein. All pressures were measured in the supine position, and the zero reference was the middle axillary line. In patients monitored with PAC, information on pulmonary capillary wedge pressure, pulmonary vascular resistance, systemic vascular resistance[18], and cardiac index (as determined by thermodilution technique in triplicate) were also recorded.

Mechanical ventilation

Patients submitted to mechanical ventilation had the positive end-expiratory pressure (PEEP) titrated until optimal oxygenation was achieved, tidal volume was kept up to 6 ml per kilogram, and driving pressures of less than 20 cm of water above PEEP value. Recruiting maneuvers were used at the discretion of the attending team; BNP was not collected during, immediately before or after recruiting maneuvers.

Statistical analysis

The Student's *t* test was applied for comparison of means of normally distributed data. Deviations from a Gaussian distribution were tested by Kolmogorov-Smirnov test. BNP data were log transformed, thereby promoting normality. Noncontinuous variables were analyzed by use of a 2x2 table and Fisher's exact test. Pearson correlation test was applied for univariate association between variables, and further analysis was performed with a stepwise multiple linear regression. Values of $p<0.05$ (2 tailed) were considered significant. Tests were performed with SPSS 12.0 software for Windows.

Results

We included 23 patients (9 women and 14 men) in the study. Their clinical characteristics are described in Table 1; 9 patients were discharged alive from the ICU (ICU mortality 60.9%). Older age, higher APACHE score, increased water balance, higher levels of creatinine and lactate, and lower hemoglobin level were found in non-survivors (Tables 2 and 3). Pulmonary artery catheters were used in 15 (65.2%) patients, and the hemodynamic parameters are depicted in table 3. Seven (30.4%) patients had acute respiratory distress syndrome and six (26.1%) patients had acute lung injury. The site of infection was determined on a clinical or microbiological basis in 17 cases; in six patients the site of infection could not be established, and five of these patients had some degree of immunodepression (rheumatological disease in one patient, acute leukemia in 2 patients, lymphoma in 1 patient, myelodysplasia in one patient).

Patients had BNP, hemodynamic and respiratory data collected at least once during ICU stay. In 16 patients a second analysis was performed the following day; furthermore, in 7 of these patients a third set of data was also collected within 24 hours after the second one. Altogether, 46 analyses were performed in 23 patients during three consecutive days (Table 4).

Mean BNP level was 280.3 ± 286.2; BNP level was 261.7 ± 220.7 pg/ml on the first day, 275.3±.279.6 pg/ml on the second day, and 352.6±482.6 pg/ml on the third day (p =

Table 1 - Baseline characteristics of the patients

Variable	N / Mean ± SD	%/ Range
Sex		
Male	14	60.9
Female	9	39.1
Age (years)	51.3 ± 18.6	20-79
APACHE score	22.6 ± 11.8	7-41
SOFA score	10 ± 3.2	3-16
Septic shock	19	82.6
Severe sepsis	4	17.4
Positive culture	12	52.2
Site of infeccion		
Lungs	10	43.5
Skin	3	13
Urinary tract	2	8.7
Biliary tract	1	4.3
Blood stream	1	4.3
Not detectable	6	26.1
Mechanical ventilation	20	87
PEEP (cm H_2O)	14.1 ± 5.7	5-25
PAC	15	65.2
Dobutamine	12	52.2
Dose of dobutamine (µg/Kg/min)	8.9 ± 6.7	1-18
Norepinephrine	19	82.6
Dose of Norepinephrine (µg/Kg/min)	0.34 ± 0.3	0.01-1
BNP (pg/ml)	280.3 ± 286.2	23.3-1405.7
Troponin (ng/ml)	0,15 ± 0,12	0,02-0,36
Na (mEq/L)	140.7 ± 7.2	122-154
Creatinine (mg/dL)	1.5 ± 1.4	0.4-6.0
Base excess (mEq/L)	-9.5 ± 5.6	-23.5-0.7
Lactate (mg/dL)	15.3 ± 6.7	6-28
Platelet count (/mm^3)	194,478 ± 143,823	11,000-518,000
Hemoglobin (g/dL)	9.4 ± 1.8	6,3-13
Leucocytes count (/mm^3)	18,480 ± 20,580	3,450-105,000
Water balance 24h (ml)	4,409 ± 3,387.5	100-11000
ICU mortality	14	60.9
In-hospital mortality	15	65.2

PAC - pulmonary artery catheter; ICU - intensive care unit; APACHE - Acute Physiology and Chronic Health Evaluation II; BNP - B-type natriuretic peptide; PEEP - positive end-respiratory pressure.

0.9). There was no statistically significant difference in the BNP levels regarding gender (181.5 ± 2.6 pg/ml in men; 203.2 ± 1.9 pg/ml in women), dobutamine administration (194.1 ± 2.6 pg/ml in those who received dobutamine *vs* 162.3 ± 2.6 pg/ml in those who did not), norepinephrine

Table 2 - Comparison of baseline (first day) clinical characteristics of survivors and non-survivors

Variable	Survivors	Non-Survivors	p value
Sex			
Male	6 (66.7%)	8 (57.1%)	ns
Female	3 (33.3%)	6 (42.9%)	ns
Age (years)	43.2 ± 20.3	56.6 ± 16.0	0.09
APACHE score	17.2 ± 1.5	26.1 ± 11.7	0.07
SOFA score	10.6 ± 3.2	9.9 ± 3.2	ns
BNP *	2.24 ± 0.27	2.3 ± 0.43	ns
Septic shock	7 (77.8%)	12 (85.7%)	ns
Severe sepsis	2 (22.2%)	2 (14.3%)	ns
Mechanical ventilation	8 (88.9%)	12 (85.7%)	ns
PEEP (cm H_2O)	15.2 ± 5.0	13.4 ± 6.0	ns
PO_2/FiO_2 ratio	262.4 ± 70.7	249.2 ± 100.1	ns
Dobutamine	4 (44.4%)	8 (57.1%)	ns
Dose of dobutamine (µg/Kg/min)	9.9±6.3	8.4 ± 7.2	ns
Norepinephrine	7 (77.8%)	12 (85.7%)	ns
Dose of Norepinephrine (µg/Kg/min)	0.25 ± 0.3	0.4 ± 0.4	ns
PAC	6 (66.7%)	9 (64.3%)	ns
Water balance 24h (ml)	2720 ± 2100	5670 ± 3670	0.03
Troponin elevation	4 (44.4%)	8 (66.7%)	ns
Troponin level (ng/mL)	0.19 ± 0.16	0.13 ± 0.11	ns
Creatinine (mg/dL)	0.9 ± 0.4	1.9 ± 1.6	0.05
Base excess (mEq/L)	-8.3 ± 4.0	-10.4 ± 6.7	ns
Lactate (mg/dL)	11.7 ± 2.6	17.9 ± 6.7	0.007
Hemoglobin (g/dL)	10.4 ± 1.6	8.8±1.6	0.03

*PAC - pulmonary artery catheter; ICU - intensive care unit; APACHE - Acute Physiology and Chronic Health Evaluation II; BNP - B-type natriuretic peptide; PEEP - positive end-respiratory pressure. * BNP values were log transformed.*

Table 3 - Baseline hemodynamic characteristics of survivors and non-survivors

Variable	Survivors	Non-Survivors	p value
Heart rate (bpm)	92.2 ± 24.7	101.5 ± 28.1	ns
Mean arterial blood pressure (mmHg)	84.7±14.0	78.8 ± 15.6	ns
Mean pulmonary pressure* (mmHg)	31.0 ± 5.9	31.4 ± 4.7	ns
Pulmonary wedge pressure* (mmHg)	19.2 ± 3.0	17.1 ± 4.1	ns
Central venous pressure (mmHg)	15.1 ± 4.2	14.2 ± 4	ns
Cardiac index* L/min/m^2	4.8 ± 1.5	4.9 ± 2	ns
SVO_2 (%)	77.1 ± 6.3	68.9 ± 11.3	0.06

SVO_2 - central venous hemoglobin saturation.

Table 4 - Evolution of variables over time

Variable	Day 1	Day 2	Day 3
Number of patients	23	16	7
SOFA score	10.2	10.2	9
BNP (pg/ml)	261.8	275.3	352.0
PEEP (cm H_2O)	14.5	16.6	17
PO_2/FiO_2 ratio	254.4	249.8	290.3
Dobutamine	12	11	5
Dose of dobutamine (µg/Kg/min)	8.9	12.7	15.7
Norepinephrine	19	9	1
Dose of Norepinephrine (µg/Kg/min)	0.3	0.4	0.4
Water balance 24h (ml)	4409.8	5225	3584.3
Creatinine (mg/dL)	1.5	1.3	1.0
Hemoglobin (g/dL)	9.5	8.9	8.2
Heart rate (bpm)	97.9	98.4	105.8
Mean arterial blood pressure (mmHg)	81.0	91.9	87.5
Mean pulmonary pressure* (mmHg)	31.3	33.3	29.5
Pulmonary wedge pressure* (mmHg)	17.9	17.9	21.5
Central venous pressure (mmHg)	14.5	16.6	16
Cardiac index* L/min/m^2	4.9	4.2	4.1
SVO_2 (%)	72.1	68.5	72.4

SVO_2 - Hemoglobin Saturation of Central Venous Blood; BNP - B-type natriuretic peptide; PEEP: positive end-respiratory pressure.

Table 5 - Univariate and multivariate analysis of variables and BNP level

Variable	Univariate analysis		Multivariate analysis	
	Pearson's coefficient	P value	Standard Beta	P value
Age	0.206	0.171		
APACHE score	0.206	0.169		
SOFA score	0.159	0.296		
Hemoglobin (g/dL)	-0.130	0.388		
Platelet count (/mm^3)	-0.134	0.373		
Creatinine (mg/dL)	0.235	0.116	0.377	0.002
Reactive Protein C	-0.142	0.575		
Base excess (mEq/L)	0.043	0.774		
Lactate (mg/dL)	-0.177	0.250		
Heart rate (bpm)	-0.190	0.211		
Mean arterial pressure*	0.021	0.892		
Mean pulmonary pressure*	0.185	0.338		
Pulmonary wedge pressure*	-0.011	0.954		
Central venous pressure*	-0.309	0.075		
Cardiac index (L/min/m^2)	0.001	0.997		
SVO_2 (%)	-0.057	0.714		
Water balance 24h (ml)	-0.008	0.959		
Dose dobutamine**	-0.463	0.012	-0.20	0.32
Dose Norepinephrine**	0.151	0.418		
PEEP	-0.457	0.003	-0.548	0.024
pO_2/FiO_2	-0.002	0.988		

*APACHE - Acute Physiology and Chronic Health Evaluation II; BNP - B-type natriuretic peptide; PEEP - positive end-respiratory pressure; pO_2/FiO_2 - ratio of arterial oxygen pressure to fraction of inspired oxygen. * mmHg. **µg/Kg/min.*

administration (207.5 ± 2.9 pg/ml in those who received norepinephrine *vs* 149.3 ±1,9 pg/ml in those who did not), mechanical ventilation (191.4 ± 2.7 pg/ml in those who received mechanical ventilation and 130.3±1.8 pg/ml in those who did not) or ICU mortality (173.8±1.8 pg/ml in survivors *vs* 199.5±2.7 pg/ml in nonsurvivors).

Results of the univariate and multivariate analysis of the association between BNP values and clinical and hemodynamic variables are shown in table 5, and indicate that BNP levels were inversely associated with the PEEP level, directly associated with creatinine levels, but not with hemodynamic parameters.

Discussion

The present study shows that BNP values are elevated in patients with severe sepsis and septic shock, and correlate with PEEP values as well as creatinine. To the best of our knowledge, this is the first report on the existence of an inverse association between BNP levels and a respiratory variable, namely PEEP.

The results of the present study are in accordance with previous reports, indicating that BNP levels are elevated in septic patients[19-22]. The first of these reports analyzed 17 patients with severe sepsis and septic shock, all of them were mechanically ventilated and received vasopressors. Although an increase in BNP was found, the absolute value of BNP was very low (12.4±3.6pg/ml *vs* 5.5 ± 0.7pg/ml)[16]. Following studies found higher levels of BNP, ranging from 95pg/ml up to 905pg/m[23-25], depending on the patient's status; most studies report BNP values from 200-500pg/ml[15], which confirms our findings.

In our study neither ventricular filling pressures, nor the cardiac index were associated to BNP levels. In heart failure patients most studies report that BNP values correlate with hemodynamic variables[12-14]. However, recent reports on correlation between measurements of N-terminal pro BNP and ambulatory filling pressures in outpatients with chronic heart failure have challenged this belief[22]. Data are also conflicting in septic patients as well. Two studies analyzed the correlation between natriuretic peptides levels and echocardiographic variables. In a study with 34 consecutive patients with severe

sepsis and septic shock, the level of BNP was higher in patients with myocardial dysfunction, defined as an fractional area contraction of less than 50%[24]. Another study found that NT-proBNP level correlated with the severity of reduction in left ventricular function (classified as slight, moderate and severe) as determined by echocardiography[23]. Data on the association between natriuretic peptides and hemodynamic variables obtained from pulmonary artery catheterization are scarce. In a pilot study with 17 patients, the authors found that BNP was inversely correlated to cardiac index ($r=0.56; P<0.05$)[16]. In another study, however, that compared the levels of pro-BNP in patients with severe sepsis, septic shock and acute heart failure in 24 patients, the level of the peptide was similar among groups, despite different hemodynamic patterns[25]. More recently a prospective case series study[23] of 22 patients with septic shock, 11 patients with severe sepsis, and 20 healthy volunteers measured BNP at days 1, 2, and 4. BNP was markedly elevated in patients with septic shock/severe sepsis compared with controls; only BNP on day 2 in patients with septic shock significantly correlated with hemodynamic variables, namely right atrial pressure, pulmonary arterial pressure, pulmonary arterial wedge pressure, left ventricular stroke work index, and with poor prognosis. Altogether, the current available data does not warrant the existence of a predictable association between BNP values and hemodynamic variables.

Pathophysiological mechanisms other than myocardial dysfunction may have influenced the results found in the present study, such as BNP clearance and cytokine levels. It has been suggested that pro-inflammatory cytokines may raise BNP levels, and that cytokine removal can reduce plasma BNP[26]. Additionally, endothelial pathways involved in BNP clearance may be inhibited in septic patients[27].

The present study also analyzed the correlation between BNP levels and respiratory variables, namely PEEP and the PaO_2/FiO_2 ratio. Our findings indicate an inverse correlation between BNP and PEEP. In our study, patients were submitted to an open lung strategy of treatment, and PEEP levels used were high as compared to other reports[24]. This peculiarity of patient care may have disclosed an association never reported before. Mechanical ventilation is known to have multiple influences in the vascular system[25], and we hypothesize that PEEP may determine a lower level of BNP by reducing transmyocardial pressure. Transmyocardial pressure is defined as the pressure gradient between ventricular chamber and the pressure applied to the heart surface (roughly considered as the pleural pressure); the higher the pressure gradient, the higher the myocardial work load. Increasing pleura pressure by the application of PEEP can reduce transmyocardial gradient and, thus, improve myocardial function and reduce myocardial strech[28]. The pathophysiological nature of the association between BNP and PEEP is, so far, merely speculative and awaits rigorous demonstration.

Our study also found a correlation between BNP and creatinine. Elevated BNP levels have been found in patients with end-stage renal failure[26]. In addition, a substudy of the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation trial revealed that patients with kidney disease had higher BNP levels than patients without kidney disease[27]. Studies on patients admitted to intensive care units also report greater BNP levels in patients with impaired renal function[28-30]. However, specific data on septic patients are scarce, some authors reporting significant association of NT-proBNP levels and creatinine levels in patients with severe sepsis[23]. We believe that the influence of renal function on BNP measurement should be taken into account when interpreting BNP levels in septic patients.

Finally, we found similar levels of BNP in survivors and nonsurvivors. Thus no association could be demonstrated between BNP and prognosis. A prognostic impact of BNP was found by other authors[17,30]. In contrast, a recent study analyzing 78 patients who had been admitted to a general ICU (35 patients with sepsis) revealed higher BNP levels in survivors as compared to nonsurvivors, the same trend being observed when analysis was restricted to the patients with sepsis[31]. Other studies did not find any prognostic information from BNP levels in critically ill patients[32]. Currently available data does not support an association between BNP levels and prognosis in patients with severe sepsis and septic shock.

Limitations

Although the BNP levels we found are in accordance with findings from literature, this is a non-controlled study that enrolled a small number of patients. In addition, BNP measurements were conducted up to the third day after ICU admission, meaning that information from different stages of the disease were included in our analysis. It is possible that due to the relatively small number of patients included in our study, some differences (such as mortality and the influence of hemodynamic variables) may have been underestimated. The present studied evaluated a high risk group of septic patients, as expressed by the high number of patients requiring mechanical ventilation, and high mortality rate; and therefore caution should be taken when considering other populations. Additionally, the inclusion of repeated measurements from the same patients in our analysis and grouped data from different sites of the disease increase the heterogeneity of our variables.

Conclusions

Taken together, our results indicate that BNP levels are elevated in patients with septic shock and severe sepsis. Moreover, BNP levels are influenced by therapeutic interventions, (namely PEEP level), and by comorbidities (as indicated by the association with creatinine levels), but not by hemodynamic parameters. These findings suggest that the influence of PEEP level should be taken into account when interpreting BNP measurements in patients with severe sepsis and septic shock.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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