B-type natriuretic peptide as a predictor of outcome in a general intensive care unit

P. Grassi[1], C. Calderan[1], M.C. Vassallo[1], D. Cageggi[1], E. Stenner[2], B. Biasioli[2], G. Berlot[3]

[1]Department of Anesthesia and Intensive Care; [2]Department of Laboratory Medicine; Ospedale di Cattinara; [3]Trieste University School of Medicine, Trieste, Italy

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ABSTRACT

Background: B-type natriuretic peptide is a hormone secreted by the heart in response to ventricular wall stress. Increased B-type natriuretic peptide plasma levels are also found as a consequence of noncardiac conditions including sepsis, surgery-induced systemic inflammatory response syndrome and kidney failure. Since these conditions are common in general intensive care unit patients, we hypothesized that B-type natriuretic peptide could be a helpful marker in predicting outcome in this setting.
Methods: We measured plasma B-type natriuretic peptide concentrations in 228 patients at admission to our general intensive care unit. The primary aim of the study was to investigate the relationship between B-type natriuretic peptide and hospital mortality. The secondary aim of the study was to investigate the association between B-type natriuretic peptide and severity of disease, quantified by the Simplified Acute Physiology Score II.
Results: Logistic regression revealed a positive association between B-type natriuretic peptide level and in-hospital death (OR = 1.59; 95 % CI 1.30 to 1.95; $p < 0.0001$) and a Cox proportional hazards regression model showed that B-type natriuretic peptide was significantly associated with the risk of death (HR = 1.27; 95 % CI 1.11 to 1.46; $p = 0.0005$). B-type natriuretic peptide was higher in patients who died in the hospital than in those who survived (371.20 pg/ml vs. 127.10 pg/ml; $p < 0.0001$). There was a positive correlation between B-type natriuretic peptide and Simplified Acute Physiology Score II ($r = 0.50$; 95 % CI 0.40 to 0.59; $p < 0.0001$).
Discussion: B-type natriuretic peptide on admission is an independent prognostic marker of outcome in an unselected cohort of critically ill patients.

Keywords: *natriuretic peptides, intensive care units, multiple trauma, heart failure*

INTRODUCTION

Outcome prediction is a key issue in modern medicine. The possibility to estimate in advance and with reasonable precision the probability of a given disease to evolve in a certain direction once optimal care is delivered is crucial for both physicians and patients. The formers are expected to communicate healing possibilities, to promptly decide which intensity of care will optimize outcome and to correctly allocate resources also avoiding futile diagnostic or therapeutic procedures. For the latters and their families, the knowledge of future implications of patients' condition is the backbone of the recovery process or of the approach to the end of life.

In critical care medicine, outcome estimation is particularly important because of

Corresponding author:
Paolo Grassi, MD
Department of Anesthesia and Intensive Care,
Azienda Ospedaliero-Universitaria,
Ospedale di Cattinara,
Strada di Fiume, 447 - 34149 Trieste, Italy.
e.mail: paolo.grassi@aots.sanita.fvg.it

high costs and resource paucity. In this setting, severity scores have been developed as an aid in physiology derangement evaluation, risk stratification, study comparison and performance monitoring. Since the probability of dying in the hospital is an important parameter for clinical decision-making, the possibility to derive it from severity scores has been tested and confirmed: the Simplified Acute Physiology Score (SAPS) II, one of the most commonly used intensive care unit (ICU) classification systems, has been shown to be a reliable tool in predicting in-hospital death (1). However, its computation is relatively time-consuming and implies to consider multiple variables and their worst values in the first 24 hours of ICU stay. Hence, it is unavailable in the very first hours after admission, when the most critical decisions have to be taken. Finding a simpler and more readily-obtainable indicator of severity to assist in ICU decision-making would be of paramount importance. Ideally, it should be available in a short-time period after admission, it should be obtained through routinely-implemented procedures and its calculation should not impose additional tasks on clinical staff. B-type natriuretic peptide (BNP) is a widely recognized independent predictor of outcome in cardiac disease like heart failure (2, 3) acute coronary syndromes, (4, 5) pulmonary embolism (6, 7) and aortic stenosis (8). In critical illness BNP is frequently elevated on a multifactorial basis and independently from primary cardiac pathologies (9,10). Nonetheless, BNP measurement is advocated in this setting, mainly as an aid in the differential diagnosis of respiratory failure (11). The hypothesis that BNP could be used as a predictor of unfavorable outcome in ICU patients has been previously explored (9, 12-17). However, the evidence about this subject remains controversial with some studies confirming the association between BNP or N Terminal -pro-BNP (NT-pro-BNP) levels and in-hospital mortality (9, 13, 15-17) and others denying it (12-14). Furthermore, most of the existing studies used some form of entry selection, either at the level of ICU admission or of patient eligibility. Probably, increased BNP levels found in general medical/surgical ICU patients is an aspecific final common pathway shared, through different mechanisms, by many failing organs (9) and is also part of the neuroendocrine response to severe inflammation (18,19). We hypothesized therefore that it could be seen as an objective and easy-to-obtain marker that reflects the severity of a patient's global physiology derangement. The primary aim of the study was to investigate the relationship between BNP and hospital mortality. The secondary aim was to investigate the association between BNP and SAPS II.

METHODS

Study design

We prospectively included all patients admitted to a general, 13 bed ICU between March 2008 and February 2009. The unit admits trauma, medical and surgical patients (except cardiac surgery patients). The general ICU also admits patients with primary heart conditions if they are supposed to need prolonged mechanical ventilation or therapeutic hypothermia after cardiac arrest. Exclusion criteria were age less than 18 years and ICU admission for routine, short-term postoperative monitoring after uncomplicated surgery, admission during the week end (when the laboratory did not perform BNP determinations). Age, gender and admission diagnosis were recorded. In addition to standard laboratory assessment, blood samples for determination of BNP were obtained in all patients on ICU admission. Severity of disease was quantified by

SAPS II. ICU survival and hospital survival were recorded in all patients. BNP plasma levels were measured by the Triage BNP Test (Biosite Inc., San Diego, CA, USA) run on an Access 2 analyzer (Beckman Coulter, Fullerton, CA, USA). All samples were analyzed within 3 hours from being drawn and made available to the attending physician. The protocol respected the Declaration of Helsinki, was approved by the Ethical Committee and patients or next of kin signed a written consent.

Statistical analysis

After natural logarithm transformation of BNP values (log BNP) to reduce variability and to normalize, the association between BNP and the risk of in-hospital death was investigated by univariate logistic regression. BNP was also entered after SAPS II in a forward stepwise logistic regression to verify if it independently adds predictive power. Survival analysis was performed using a univariate Cox proportional hazards regression model with the hospital length of stay as the time variable; data were censored at hospital discharge. Graphical methods, the Hosmer-Lemeshow and Therneau-Grambsch tests were used, when appropriate, for assessment of log-linearity, calibration and proportional hazard assumption. Variance inflation factor analysis excluded multicollinearity and other model assumptions were not violated. Pearson correlation coefficient was used to verify the correlation between log BNP and SAPS II. Receiver operating characteristic (ROC) curves with in-hospital death as classification variable were produced and analyzed for both log BNP and SAPS II. Differences in raw BNP values between patients who survived and those who died in the hospital were further explored with the Mann-Whitney test. Two-sided p values < 0.05 were considered statistically significant. All statistical tests were performed with Stata/MP (StataCorp, College Station, Texas, USA) or MedCalc 11.1 (MedCalc, Mariakerke, Belgium) software.

RESULTS

We studied 228 patients. Their main demographic and clinical characteristics are summarized in Table 1. Raw BNP values followed a lognormal distribution while the Kolmogorov-Smirnov test allowed to accept normality for log BNP.

Patients who survived until hospital discharge had significantly lower raw BNP values at admission than patients who died in the hospital (median 127.10 pg/ml vs. 371.20 pg/ml, respectively, $p < 0.0001$, Mann-Whitney test).

Logistic regression analysis showed that log BNP was a significant predictor of in-hospital death (OR = 1.59; 95 % confidence interval [CI] 1.30 to 1.95; $p < 0.0001$). Moreover log BNP entered in a forward stepwise logistic regression after SAPS II determined a significant change in the likelihood-ratio, proving to be an independent predictor of in-hospital death risk (OR = 1.28; 95 % CI 1.02 to 1.61).

In the univariate Cox proportional hazards regression model, log BNP predicted the relative hazard (hazard ratio per unit increase in log BNP = 1.27; 95 % CI 1.11 to 1.46; $p = 0.0005$), thus confirming its capability in predicting in-hospital death risk.

The scatter plot of log BNP against SAPS II showed acceptable linearity (*Figure 1*). Pearson coefficient confirmed a positive correlation between the two variables ($r = 0.50$; 95 % CI 0.40 to 0.59; $p < 0.0001$).

The area under the ROC curve was 0.75 for SAPS II (95 % CI 0.68 to 0.80) and 0.69 for log BNP (95 % CI 0.62 to 0.75). The two curves were not significantly different (difference between areas 0.05; 95 % CI -0.01 to 0.13; $p = 0.13$; DeLong method; *Figure*

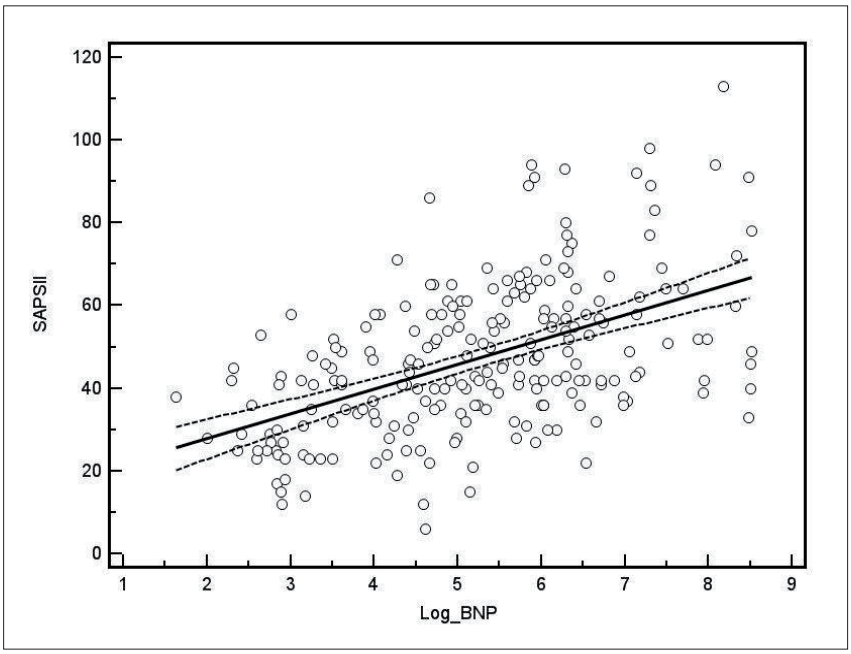

Figure 1
Scatter plot of log B-type natriuretic peptide vs Simplified Acute Physiology Score II with regression line and 95% confidence interval.

2). The cut-off point with the best compromise between sensitivity and specificity for log BNP was 4.68 (sensibility = 85.5%, specificity = 47.6%, Youden index), corresponding to a raw BNP value of 107.6 pg/ml. In a post-hoc analysis we stratified cases according to admission diagnosis (*Table 1*) to allow a more detailed characterization of the patients. All the groups were far too small to allow any conclusive inference,

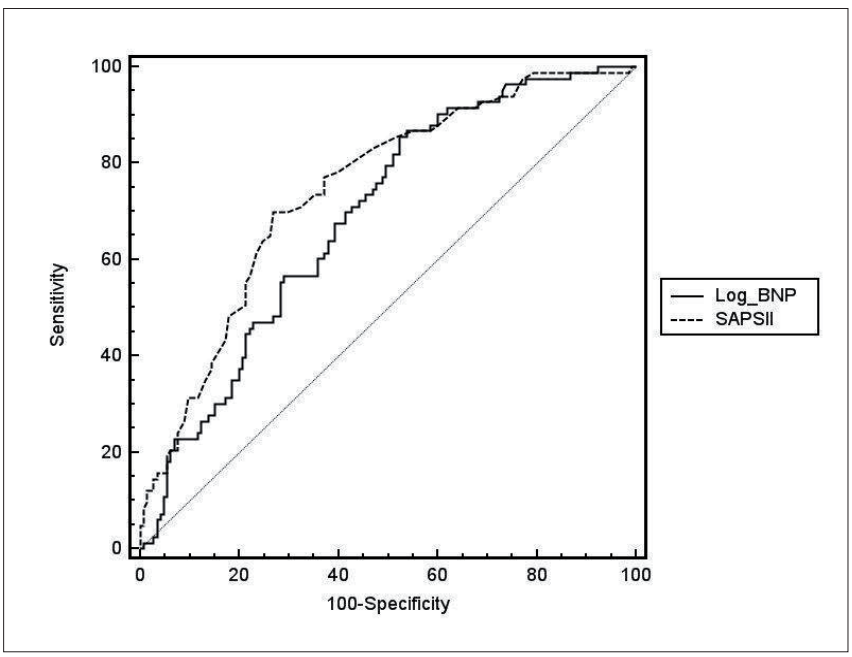

Figure 2
Simplified Acute Physiology Score II and log B-type natriuretic peptide Receiver operating characteristic curves for in-hospital death. The curves were not significantly different (p = 0.13).

but we noted that log BNP had predictive power in trauma patients, the largest of the groups (OR = 2.3, 95 % CI 1.24 to 4.29, p = 0.008; area under the ROC curve 0.75, 95 % CI 0.61 to 0.86). Odds ratio across the groups were not homogeneous (p < 0.001). Particularly, among patients admitted with a cardiac diagnosis in-hospital death rate was high (53 %), BNP levels were high (median 543 pg/ml; interquartile range 245 to 1260) and BNP did not predict the odds nor the relative hazard of in-hospital death.

The central laboratory at our institution provided a double cut-off for BNP: normal below 100 pg/ml, abnormal above 500 pg/ml, indeterminate between the two values. BNP was above the normality threshold (100 pg/ml) in 153 of the 228 studied patients (67 %) although most of the patients in our cohort did not suffer from a primary cardiac pathology (*Table 1*).

DISCUSSION

Our findings are consistent with previously published data showing that BNP plasma level at admission is an independent predictor of hospital mortality in adult ICU patients. When BNP was compared with SAPS II in terms of area under the ROC curve, they were not statistically different. Furthermore, BNP entered in a logistic regression model after SAPS II, independently adding predictive power.

The results from this study add further strength to the existing evidence in favor of a potential role of BNP as a marker of prognosis in critically ill patients. Although other studies previously held similar results, they often used some form of patients' selection. In some of them, patients with acute or chronic cardiac conditions or renal failure were excluded; (14, 15, 17) in oth-

Table 1 - *Main demographic and clinical characteristics of the studied patients.*

		Discharged alive	Died in hospital
Total	228	146(64 %)	82(36 %)
Males	143(63 %)	91(64 %)	52(36 %)
Females	85(37 %)	55(65 %)	30(35 %)
Age (years)	68(51-77)	61(43-73)	74(63-81)*
SAPS II	45(35-58)	41(30-50)	55(44-65)*
BNP (pg/ml)	205(64-542)	127(33-395)	371(146-773)*
Log BNP	5.32(4.16-6.29)	4.84(3.51-5.98)	5.92(4.98-6.65)*
Admission diagnosis			
Trauma	52(23 %)	42(19 %)	10(4 %)
Neurological/neurosurgical	44(19 %)	23(10 %)	21(9 %)
Cardiac	39(17 %)	18(8 %)	21(9 %)
Complicated surgery	37(16 %)	24(10 %)	13(6 %)
Respiratory	25(11 %)	19(8 %)	6(3 %)
Severe sepsis/septic shock	15(7 %)	8(4 %)	7(3 %)
Intoxication	6(3 %)	6(3 %)	0(0 %)
Hemorragic shock	5(2 %)	3(1 %)	2(1 %)
Others	5(2 %)	3(1 %)	2(1 %)

Data are expressed as absolute values and percentage or median and interquartile range.
*p < 0.05 vs. survivors.
SAPS II = Simplified Acute Physiology Score; BNP = B-type natriuretic peptide

ers, ICU admission criteria narrowed the spectrum of considered conditions, for example excluding multiple-trauma patients from the case-mix (16).

This study was conducted in a general ICU which admits adult patients with a very wide range of admission diagnosis including acute-on-chronic COPD, high-risk postoperative neurosurgical and abdominal surgery patients, multiple trauma and septic shock cases. The aim was to conduct a very pragmatic study to explore the BNP prognostic potential in a real-life general ICU scenario: for this reason we planned to enroll all admitted adult patients without any exclusion criteria. In a post-hoc analysis log BNP had predictive power in trauma patients. Among patients admitted with a cardiac diagnosis in-hospital death rate was high (53 %), BNP levels were high (median 543 pg/ml; interquartile range 245 to 1260) and BNP did not predict the odds nor the relative hazard of in-hospital death. Post-hoc, subgroups analysis-derived data, however, should be considered with extreme caution and viewed only as hypothesis-generating.

The studied form of the hormone is, in our opinion, a point of uncertainty in the published literature. Most existing trials on this subject considered NT-pro-BNP while only a few measured BNP, the 32 amino acides biologically active portion of the hormone. While the two molecules, secreted in equimolar proportion, could probably be considered equivalent from a diagnostic and prognostic point of view, although with different cut-off points, it is interesting to note that previous trials yielding negative results were all performed with BNP: Berendes (12) and Cuthbertson (14) found no association between hormone levels and mortality in ICU patients. We believe the discrepancy of results between these two studies and others showing positive results using NT-pro-BNP should not be ascribed to the different studied molecule. More likely, this could be due to an unusually low ICU mortality rate (7.9 %) in one case (12) and to the small sample size (49 patients) in the other (14).

Our findings seem to confirm this hypothesis, showing that also BNP, and not only NT-pro-BNP, holds prognostic capability in critically ill patients. BNP was above the normality threshold (100 pg/ml) in 153 of the 228 studied patients (67 %) although most of the patients in our cohort did not suffer from a primary cardiac pathology. This is consistent with the results of previous trials showing no difference in BNP or NT-pro-BNP between cardiac or noncardiac ICU patients (18, 20). However, the standard normality range could be inappropriate for mechanically ventilated critically ill patients (11) and the adoption of an ICU-specific cut-off has been recently advocated (21). Increased BNP secretion or reduced BNP elimination are found in many clinical noncardiac conditions which are per se associated with an increased risk of death. Pro-inflammatory cytokines and bacterial endotoxin are known to upregulate BNP gene expression and to lead to elevated BNP plasma levels independently of myocardial depression (18, 19). Inflammatory conditions with high mortality rates like severe sepsis/septic shock and systemic inflammatory response syndrome (SIRS) after major surgery are indeed common indications to ICU admission (22) and BNP has been previously shown to provide prognostic informations in septic (23-25) and postoperative patients (26). It is therefore possible and plausible that BNP levels in our mixed ICU population were, in general, more often influenced by the inflammatory burden than by myocardial systolic or diastolic dysfunction. However, for this study, we did not systematically collect hemodynamic data and we cannot exclude, therefore, that patients admitted with a "non-

cardiac" diagnosis suffered, at the time of admission, from some form of unrecognized myocardial depression. In a recently published study, echocardiographic assessment of diastolic dysfunction expressed as E/e'(peak early diastolic transmitral/peak early diastolic mitral anular velocity) was shown to be a more accurate predictor of outcome than BNP in septic shock patients (27). However, in the same study, the area under the ROC curve for BNP was 0.78, which is above the threshold considered to define a biomarker with good discriminative properties (0.75) (28). E/e' measurement implies the availability of tissue Doppler imaging, an advanced echocardiographic technique which, for complexity and costs, will probably not be widely implemented across ICUs in the near future. BNP determination instead can be accomplished with the same technology used for standard laboratory tests and is operator-independent. Renal failure is associated with poor outcome in critically ill patients (29) and BNP plasma levels are elevated in renal failure because of reduced excretion (30, 31). Consequently, renal failure could have contributed to determine the association between mortality and BNP in our patients. On the basis of these considerations, increased BNP levels could be seen as a feature shared by many clinical conditions associated with an increased risk of death: heart failure, coronary artery and valvular disease, severe sepsis and septic shock, SIRS and renal failure.

This study has methodological limitations. First of all it was a single center, small-sample study. A large multicenter trial would be needed to draw definitive conclusions. The study design lacked of "a priori" power analysis. Furthermore, this was not a blinded trial and attending physicians had access to BNP values: this could have led to a bias that possibly influenced therapeutic choices. We did not measured interleukins and we did not collect repeated BNP measurements in the same patient. In the logistic regression analysis we did not take into account variables known to affect BNP concentrations, but many of these variables are included in the SAPS II.

CONCLUSIONS

Our findings show that BNP plasma levels at ICU admission predict the risk of in-hospital death in a cohort of patients with a very wide range of diagnosis. This adds strength to the existing evidence supporting the utility of BNP as a practical prognostic tool in the critical care setting.

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