Review

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# The Significance of Brain Natriuretic Peptide Levels in the Critically Ill

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## Abstract

**Brain natriuretic peptide levels (BNP) have been best studied in the heart failure (HF) literature and has been increasingly used in the critical care population as an estimate of cardiac function. BNP is secreted by cardiomyocytes in response to an increase in transmural ventricular pressure. The measurement of BNP is well known in the cardiac literature. Studies in the critical care population have looked at measuring BNP in different subsets of patients with sepsis, pulmonary embolism (PE), acute respiratory distress syndrome (ARDS), pulmonary hypertension (PH) and non-cardiogenic pulmonary edema (CPE). BNP has been used to differentiate HF syndrome from other causes of respiratory failure both in the acute and chronic settings. The measurement of BNP in the critical care population is fraught with difficulties only one of which is the significant effect of renal failure on our ability to interpret BNP levels effectively. This review summarizes the current literature on the utility and significance of measuring BNP in the critical care population.**

**Key words:** BNP, NT-proBNP, heart failure, critical care, sepsis

## Introduction

The official NIH definition of a biomarker is: "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [1]. Biomarkers that are widely used in critical care include troponins as a measure of cardiac ischemia, procalcitonin for ventilator associated pneumonia and sepsis, lactate for tissue hypoxia and C reactive protein in sepsis. BNP elevations have been found in several disease states in the critically ill.

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BNP: Synthesis, mechanism of action and kinetics

The 1981 landmark observation that the intravenous injection of supernatant from atrial tissue homogenates caused significant natriuresis and diuresis in rats was soon followed by the isolation of atrial natriuretic peptide (ANP) from the human cardiac atrium [(2]. Stimulated by atrial stretch, storage granules within cardiac myocytes release an ANP prohormone that is cleaved into ANP and three additional hormones, long-acting natriuretic peptide, vessel dilator, and kaliuretic peptide [2]. Three natriuretic peptide receptors (NPR- A, B, and C) have been identified in mammalian tissues. The physiologic actions of BNP are mediated by NPR-A, while NPR-C functions as a clearance receptor and NPR-B binds to CNP and to a much lesser extent, BNP [3].

BNP is mainly synthesized in humans in ventricular

cardiomyocytes. A gene in chromosome 1 encodes the prohormone proBNP, which is cleaved into the active BNP and the inactive N terminal (NT)-proBNP. The main stimuli for BNP release are an increase in ventricular wall stretch and volume overload, which promote rapid BNP gene expression. It is also secreted in response to increased angiotensin II and sympathetic tone [4]. Once released into the blood stream, BNP has a number of physiologic actions, the net effect being decreased preload and afterload. Specifically, BNP results in decreased vascular tone via smooth muscle relaxation resulting in decreased afterload. Additionally, it induces fluid shift to the interstitium, thus reducing preload [4]. BNP decreases smooth muscle and fibroblast cell proliferation, sympathetic nervous system activity, salt and water intake, release of antidiuretic hormone as well as decreasing aldosterone synthesis and release from the adrenal glands [5]. In the kidney, BNP increases glomerular filtration rate and renal blood flow via increased efferent arteriolar and decreased afferent arteriolar tone, and decreases renin release and sodium reabsorption, ultimately resulting in both diuresis and natriuresis [5]

BNP and NT-proBNP differ in terms of their secretion and excretion kinetics. The estimated in vivo half-life of BNP in blood is 20 minutes and between 1 and 2 hours for NT-proBNP and its related forms. BNP is cleared by a combination of receptors neural endopeptidases, proteolytic enzymes and renal clearance. Due to its longer plasma half-life time and higher stability, the measurement of NTpro-BNP has also been introduced into routine clinical diagnostics [6]. BNP is stable in whole blood at room temperature with the addition of EDTA for at least 24 h, whereas NT-proBNP is stable for at least 72 h in whole blood at room temperature and requires no additives. Both BNP and NT-proBNP are stable during freeze and thaw processes [6,7].

BNP: Measurement in the outpatient, emergency room and ICU

BNP levels have been best studies in the HF population and it is from this literature that BNP levels have been validated. The rapid point-of-care BNP test is a reliable and cost-effective diagnostic biomarker in differentiating dyspnea due to HF from that related to a non-cardiac cause and has been proposed as the first-line diagnostic complement in the emergency care setting. In the Breathing Not Properly study of HF patients, the optimal cut point BNP of 100 pg/mL had a NPV of 89%, while a cut point of 50 pg/mL, which is still higher than the upper limit of normal (20 pg/mL) for healthy subjects, showed an NPV of 96% [8]. In the PRIDE study, the data were even more impressive [9]. At a cut point for all persons (900 pg/mL), the NPV was 94%, while a ''rule out'' cut point of 300 pg/mL yielded an NPV of 99%. Both the Breathing Not Properly and PRIDE studies also had high positive predictive values with markedly elevated levels. The rule-out value of BNP (rule out HF) was also confirmed in a meta-analysis of 55 studies (16,730 patients), which showed a pooled negative likelihood ratio of 0.11 [10]. However, positive likelihood ratios were more heterogeneous making the reliability of BNP testing questionable for confirming the presence of HF. The wider range of values seen with NT-proBNP, which speaks to the much higher levels observed in vivo, may ultimately make it a more accurate test by allowing the clinician to differentiate between levels that would otherwise be in the so-called gray zone for BNP (100–500 pg/mL).

Kotaska *et al* used receiver operator characteristic (ROC) analysis on performed on 280 patients to determine the best cut off value to detect cardiac involvement as well as to assess the discrimination ability (by calculating the area under the ROC curve) of NT-proBNP to recognize patients with various types of heart disease. The area under ROC curve for the detection of cardiac involvement was high: 0.93 (95 % confidence interval 0.90 –0.95) .The appropriate cut off value for the diagnosis of cardiac involvement was 130 ng/L. With this cut off value, sensitivity was 98 % and specificity was 79 %. The values for NT- pro BNP and BNP correlated with New York Heart Association class 1 and 2 and not 3 and 4 [11].

A poorer performance has been suggested in elderly patients with preserved left ventricular (LV) systolic function. A similar study using the rapid point of care BNP test was done in ICU patients [12]. All patients

admitted to a combined medical and surgical ICU over a four-week period were included. BNP was measured at admission using a hand-held meter. Clinicians were blinded from the measurement at diagnoses as to whether or not the patients had clinically significant cardiac dysfunction. Patients with cardiac dysfunction had a significantly higher level of BNP when compared to the non-cardiac dysfunction group: 516±385 pg/mL (n =26) vs. 67±89 pg/mL (n =58) (P <0.0001). A BNP cut-off value at 144 pg/mL exhibited a 92% sensitivity, 86% specificity and 96% NPV. The sensitivity improved to 96% when the analysis was confined to patients >55 years.

Another study looked at whether cut-off values for BNP and NT-proBNP reliably diagnosed RV and/or LV failure in a heterogeneous population of patients admitted to the ICU for acute respiratory distress and/or shock, whether noncardiac factors led to an increase in these markers and, finally, whether these markers could be an alternative to echocardiography [13]. They compared plasma levels of BNP and NT-proBNP with echocardiographic signs of cardiac dysfunction. The ROC curve showed that BNP levels greater than 221 pg/mL predicted cardiac dysfunction with 68% sensitivity, 88% specificity, 89% PPV and 63% NPV. The ROC curve showed that a plasma NT-proBNP level greater than 443 pg/mL indicated cardiac dysfunction with 84% sensitivity, 75% specificity, 84% PPV and 75% NPV. There was no difference in plasma BNP and NT-proBNP levels with regard to vasoactive drugs, mechanical ventilation and death. There was a good correlation between plasma BNP and NT-proBNP levels. The ROC curves showed no significant difference between these two markers for the diagnosis of cardiac dysfunction. RV dysfunction with normal LV function was associated with a marked but non-significant increase in plasma BNP; in contrast, the increase was significant in patients with both LV and RV dysfunction. RV dysfunction was associated with a non-significant NT-proBNP increase in patients with or without LV dysfunction.

McLean *et al* [12] found a lower BNP cut-off (144 pg/mL) for LV and/or RV dysfunction in ICU patients, although their cardiac dysfunction definitions and BNP assay method were similar to those used in the above study; however, their report supplies no information on renal function. The cut-off of NT-proBNP for the diagnosis of cardiac dysfunction in the above study is different from that found by Jefic *et al* [14] (1550 pg/mL); however, in the study by Jefic *et al*, RV function was not evaluated, LV function was measured with a pulmonary artery catheter (PAC) with LV dysfunction being defined as an LV stroke index of less than 35 $g/m^2$ and, finally, the cohort of patients was different (only hypoxic respiratory failure)

BNP: Variations in measurement

Multiple studies have shown that only BNP changes of greater than approximately 113–130% and NT-proBNP changes of greater than 90–98% can reliably be considered to have overcome both inter and intraindividual variation and analytical variation [15,16]. In healthy subjects, BNP is related to age, gender, circadian rhythms and exercise; levels increase with age and are more elevated in females than males [17]. Race also plays a role, with wider variability seen in African Americans compared to Caucasians [17]. BNP levels are lower in obese versus non-obese patients. In a sub study from Breathing Not Properly, in patients diagnosed with CHF, a marked inverse correlation existed with approximately 10% of those with BMI ‡ 40.0 having BNP above 1000 pg/mL, while approximately 50% of those with CHF and BMI <20.0 had BNP levels >1000 pg/mL [18]. Despite this, BMI was not independently related to BNP levels in multivariate analysis. In another sub study of this population, those with morbid obesity had nearly a 100% lower cut point (54 pg/mL) to maintain the 90% sensitivity level seen for the entire population and using the standard cut point in morbidly obese patients yielded a nearly 20% false negative rate [19]. Genetics also has a role in BNP variability. Interestingly, genetic linkage analysis from the Framingham offspring study shows that the genetic variation in levels may actually be due to genes other than those for ANP, BNP or the natriuretic peptide receptors, suggesting a polygenetic basis for BNP variability [20]. At present, there are no known BNP gene mutations resulting in variable serum BNP levels. In patients with systolic heart

failure, higher levels of BNP tend to be associated with additional abnormalities such as advancing degrees of diastolic dysfunction, RV dysfunction, and valvular heart disease [21], as well as right HF and pulmonary diseases [22]. Renal function also affects BNP levels, with higher overall levels being noted in those with renal dysfunction. In patients on hemodialysis, there were significant abnormal rhythmic oscillations in BNP levels within individuals compared to healthy subjects [23]. In the Breathing Not Properly study, predictors of gray zone BNPs in the absence of HF included age, atrial fibrillation, low BMI, and anemia [24].

## Clinical Studies

BNP: Relationship with respiratory failure

Karmpaliotis *et al* prospectively tested the utility of BNP for discriminating ARDS vs. CPE [22]. They enrolled ICU patients with acute hypoxemic respiratory failure and bilateral pulmonary infiltrates who were undergoing right-heart catheterization to aid in diagnosis. Patients with acute coronary syndrome, end-stage renal disease, recent coronary artery bypass graft surgery, or preexisting LV ejection fraction ≤30% were excluded. BNP was measured at right heart catheterization. Median BNP was 325 pg/mL (interquartile range [IQR], 82 to 767 pg/mL) in acute lung injury/ARDS patients vs. 1,260 pg/mL (IQR, 541 to 2,020 pg/mL) in CPE patients ($p = 0.0001$). BNP offered good discriminatory performance for the final diagnosis (C-statistic, 0.80). At a cut point ≤200 pg/mL, BNP provided specificity of 91% for ARDS. At a cut point ≥1,200 pg/mL, BNP had a specificity of 92% for CPE. Higher levels of BNP were associated with a decreased odds for ARDS (odds ratio, 0.4 per log increase; $p = 0.007$) after adjustment for age, history of HF, and right atrial pressure. BNP was associated with in-hospital mortality ($p = 0.03$) irrespective of the final diagnosis and independent of APACHE (acute physiology and chronic health evaluation) II score.

Another study looked at using BNP and NT pro BNP to differentiate HF syndrome from other causes of respiratory failure [14] and tried to determine if BNP and NTproBNP could predict mortality in critically ill patients with respiratory failure. This study was a prospective observational study of 41 patients all but two of whom were intubated and the majority had more than one organ failure. The population had generally depressed left ventricular contractility, even though only half had known or suspected heart failure. Only 17% of their patients had near-normal cardiac contractility, judged by LV stroke work index. The authors concluded that using the cutoffs for natriuretic peptides established for ambulatory populations, or using them as a rule-out/rule-in test, may be problematic in determining the etiology of pulmonary infiltrates (ARDS vs. CPE) because of the high prevalence of preexisting cardiac impairment and unknown baseline levels of natriuretic peptides. The natriuretic peptide levels appear to be good surrogates of cardiac contractility and predictors of patients with respiratory failure who have additional cardiac dysfunction but cannot be used in the general critical care population due to a great variety of factors that influence their levels.

BNP: Relationship with pulmonary capillary wedge pressure (PCWP)

A prospective observational study examining the relationship between BNP and NT-proBNP and PCWP in critically ill patients requiring invasive hemodynamic monitoring showed that these levels were markedly elevated, but weakly correlated with invasive hemodynamics, most notably PCWP, in the setting of critical illness [25]. In this study the majority of patients (68%) had normal LV ejection fraction (>60%). Consistent with these results, a recent study showed that BNP levels weakly correlated with PCWP ($r = 0.32$, $p = 0.02$) in a mixed ICU cohort, with the optimal cutoff for BNP <60% specific for a PCWP >15 mmHg [26]. In the study by Karmpaliotis *et al* which attempted to use BNP levels to differentiate CPE and ARDS in a mixed population of patients admitted for hypoxic respiratory failure, the correlation between BNP and PCWP was modest ($r = 0.27$, $p = 0.02$) [22].

BNP: Relationship with precapillary PH

Andreassen *et al* looked at NT pro BNP in PH [27].

Compared with age-matched controls (n =10), plasma NT-pro-BNP was significantly greater in those with idiopathic PH (n =16), chronic precapillary PH associated with other diseases (n =26), and chronic thromboembolic disease (n =19) and was correlated with hemodynamic variables and functional capacity. In 17 medically treated patients, the significant decrease in NT-pro-BNP levels correlated with improved hemodynamics. During follow-up, 15 patients died from cardiopulmonary causes. Baseline NT-pro-BNP was an independent predictor of mortality. Kaplan-Meier survival analysis according to the median value of NT-pro-BNP (168 pmol/L) demonstrated a significantly higher mortality rate in those with supramedian values than in those with low plasma levels (p =0.010).

Leuchte *et al* evaluated circulating BNP levels as a parameter for the presence and severity of PH in patients with chronic lung disease [28] and levels were measured in 176 consecutive patients with various pulmonary diseases. Right heart catheterization, lung functional testing, and a 6-min walk test were performed. The mean follow-up time was nearly 1 yr. Significant PH (mean pulmonary artery pressure >35 mmHg) was diagnosed in more than one-fourth of patients and led to decreased exercise tolerance and life expectancy. Elevated BNP concentrations identified significant PH with a sensitivity of 0.85 and specificity of 0.88 and predicted mortality. Moreover, BNP served as a risk factor of death independent of lung functional impairment or hypoxemia in uni- and multivariate analysis.

BNP: Relationship with PE

In acute PE, the medical status depends on the hemodynamic compromise mostly determined by the level of RV overload [29]. BNP levels reflect the severity of acute HF in PE [30]. In 2005, there were two studies that proposed including biomarkers into risk assessment. Binder *et al* [31] observed that NT-proBNP cut-off level of 1000 pg/mL had a high NPV (95% for a complicated course, 100% for death), whereas troponin combined with echocardiography improved the prediction of outcome in intermediate-risk group. The second study also proved that low levels of NT-proBNP predict favorable outcome [32]. Interestingly, mortality related to PE in patients with elevated NT-proBNP and high troponin T was similar to the death rate observed in a group of patients with clinically massive PE and reached 33%. Importantly, both biomarkers helped to stratify 40-day prognosis in acute PE for both low and high-risk groups. Aujesky and colleagues described an 11-variable prognostic model for PE [33] including the patient's age, sex, pulse, blood pressure, respiratory rate, temperature, arterial oxygen saturation, an altered mental status (defined as the presence of disorientation, lethargy, stupor, or coma), and a known history of cancer, heart failure, or any chronic lung disease. The model was most useful in identifying low-risk patients with PE who are potential candidates for outpatient treatment with low-molecular weight heparins. Patients with the highest risk based on the model (risk class V) had a 30-day mortality between 10–25%, resulting in PPVs for mortality of 11–14% which is too low to accurately identify high-risk patients with PE.

BNP: Relationship with sepsis

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 [34]. 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 [35,36].

To assess the clinical relevance of both BNP and N-terminal pro-BNP in ICU patients, a study prospectively measured both markers in patients with severe sepsis and septic shock and compared them with levels obtained from patients admitted with the diagnosis of acute HF or low cardiac output syndrome [37]. Twenty-four patients with severe sepsis or septic shock and 51 patients with HF were included in the analysis. 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 =0.09). 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. 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 =0.3), 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. 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 =0.047 for BNP and p =0.019 for N-terminal pro-BNP). In patients monitored with a PAC, the BNP (p =0.3) and N-terminal pro-BNP (p =0.6) levels were not statistically different between patients with sepsis and those with HF. 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.

In another study the mean plasma level of BNP in septic shock was 47 times higher on admission, and it was 133 times higher on day 2 than those in controls [38]. Of note is that plasma level of BNP in nonsurvivors with septic shock on day 2 was even higher and reached 177 times higher than controls, whereas that in survivors with septic shock was only 81 times higher. The optimal cutoff point for predicting mortality was BNP level of 650 pg/mL on day 2, in which sensitivity and specificity for predicting mortality in septic shock were 92% and 80%, with area under the curve of 0.85. At this cutoff value, BNP level on day 2 is a strong predictor of mortality in patients with septic shock. Although plasma ANP levels were also elevated in patients with septic shock, this elevation was much less marked than that of BNP. The authors postulated that myocardial depression is the main cause of the BNP elevation in septic shock as they observed that plasma BNP levels in septic shock peaked on day 2 as myocardial depression occurred magnitudely [39]. They also showed that plasma BNP levels were best correlated with hemodynamic parameters such as PAWP, right atrial pressure and LV stroke work index.

Brueckmann *et al* looked at the prognostic value of natriuretic peptides in sepsis [40]. Fifty-seven patients with severe sepsis were included. Levels of NT-proANP and NT-proBNP were measured on the second day of sepsis by ELISA. Septic patients with NT-proBNP levels >1400 pmol/L were 3.9 times more likely (relative risk [RR], 3.9; 95% CI, 1.6 to 9.7) to die from sepsis than patients with lower NT-proBNP values (p <0.01). NT-proANP levels, however, were not predictive of survival. A highly significant correlation was found between troponin I levels and NT-proBNP levels in septic patients (r =0.68, p <0.0001). In addition, troponin I significantly accounted for the variation in NT-proBNP levels (p <0.0001), suggesting an important role for NT-proBNP in the context of cardiac injury and dysfunction in septic patients. Twenty-three septic patients who received treatment with drotrecogin alfa (activated) presented with significantly lower concentrations of NT-proANP, NT-proBNP, and troponin I compared with patients not receiving drotrecogin alfa (activated). Other investigators have also found similar utility of BNP in predicting mortality in septic shock especially in those with cardiac dysfunction [37,41,42].

BNP: Relationship with renal failure

Amongst the many factors that may influence BNP and NT-proBNP levels, renal function has been reported to have the greatest effect on the cut-offs for these two parameters [12]. Bal L *et al* found that BNP and NT-proBNP were higher in patients with than without renal dysfunction, and that the difference was significant only for those patients without cardiac dysfunction [13]. Similar results were found by Jefic *et a*l [14]. In a study of patients receiving emergency-room care for acute dyspnea, McCullough *et al* [43]

determined BNP cut-offs for different ranges of creatinine clearance (30, 30-60, 60-90 and >90 mL/min/1.73 $m^2$). The contribution of early renal failure to the increase in myocardial transmural pressure, and therefore to BNP (and NT-proBNP) elevation, is proportionally less marked in patients with than without cardiac dysfunction.

Natriuretic peptide levels >1,000 pg/mL (BNP) and 10,000 pg/mL (NT-proBNP) were more specific for a glomerular filtration rate <60 (BNP, 92%; NT-proBNP, 100%) than for PCWP >18 mmHg (BNP, 42%; NT-proBNP, 60%) [25]. Sommerer *et al* looked at BNP levels in chronic hemodialysis patients [44]. All hemodialysis patients had excessively high levels of NT-proBNP (median 4,524; interquartile range 2,000-10,250 pg/mL) and NT-proBNP was significantly higher in hypervolemic hemodialysis patients compared to euvolemic hemodialysis patients. ROC showed a threshold of NT-proBNP >5,300 pg/mL as a predictor of hypervolemia. Asymptomatic chronic hemodialysis patients with NT-proBNP >5,300 pg/mL were more likely to die due to cardiac events in the follow-up period.

## Conclusions

Natriuretic peptides have diverse actions across the brain, renal, cardiovascular and peripheral vascular systems and their functions include vasopressin suppression, natriuresis, peripheral vasodilatation and reduction of cardiac preload. The natriuretic peptide most often tested in the clinical setting is BNP. BNP is secreted by cardiomyocytes in response to an increase in transmural ventricular pressure and has found most of its applicability in cardiac disease (diagnosis and prognosis of acute coronary syndromes, heart failure, and valvular heart disease and in the post cardiac surgery and post heart transplant settings). BNP has also been tested in the critical care setting in acute respiratory failure with or without cardiac dysfunction, pulmonary hypertension, pulmonary embolism and in severe sepsis and septic shock. Its use is limited due to extreme variability across disease states and elevations associated with renal dysfunction.

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