Heart failure (HF) is a common condition and carries a considerable age-dependent all-cause mortality. As a leading cause of hospitalization in adults, ~50% of patients discharged with a diagnosis of HF are readmitted within six months, and the one-year mortality rate is 20% after an initial diagnosis is established. There is currently a chronic HF epidemic with a rapidly expanding prevalence pool of HF patients, which has accounted for increased rates of hospitalization over the past two decades. Accordingly, much effort has been directed toward understanding the pathophysiology of HF, as well as improving diagnostic and therapeutic strategies. The recognition of the natriuretic peptides, in particular B-type natriuretic peptide (BNP), as a marker for the diagnosis, prognosis, and severity of HF has been a major breakthrough. This article will focus on the latest advances in the clinical utility of BNP in a variety of applications (see Figure 1).

**Natriuretic Peptides—Important ‘Heart Hormones’**

There are three major natriuretic peptides, all sharing a common 17-amino-acid ring structure—atrial natriuretic peptide, BNP, and C-type natriuretic peptide. B-type natriuretic peptide is synthesized and stored in the ventricular myocardium as a precursor prohormone. Cleavage of the 32 amino acid sequence by the enzyme corin from the C-terminal end of ProBNP results in the active BNP peptide hormone and the inactive N-terminal fragment of proBNP (NT-proBNP). B-type natriuretic peptide is secreted into the circulation in a pulsatile fashion through the coronary sinuses in response to left ventricular (LV) wall stretch and multiple neurohumoral factors. It has a half-life of 22 minutes and is metabolized by neutral endopeptidase (~30%), and receptor-mediated endocytosis (~70%), which occurs predominantly in the kidney. Normally, BNP levels are slightly higher in women compared with men. Additionally, in the obese, BNP levels are 30% to 50% lower than those of normal body weight, either because of impaired BNP production or increased peripheral clearance of BNP. Both BNP and NT-proBNP have been found in urine. NT-proBNP is not cleared by neutral endopeptidase or by the clearance receptors, hence its clearance is more dependent on glomerular filtration with incomplete resorption, resulting in considerable quantities found in the urine. These urinary levels are high enough to be used as a urinary test for HF. Plasma BNP levels reflect the decompensated state of circulatory congestion and correlate with LV end diastolic pressure and pulmonary capillary wedge pressure. Due to the fact that BNP reflects volume status and has a short half-life, levels reflect dynamic changes in volume attributed to diuresis, making the assay an attractive marker for a variety of conditions associated with LV and right ventricular (RV) dysfunction. The majority of the published studies on clinical applications have utilized BNP; BNP levels will therefore be considered the focus of this article.

**Population Screening**

As a general rule, a normal BNP value should be less than half the chronological age of the patient. Multiple population screening studies indicate that a cut-point of 20pg/ml would be appropriate for a population with a mean age in the fourth or fifth decade. Although the reason for mild elevations in BNP in women compared with men is unknown, it is speculated that ventricular stiffening is more pronounced in women at all ages. All current studies of screening support the notion that clinical information such as cardiac risk factors, age, gender, and subtle symptoms should trigger the BNP test in practice. Blanket asymptomatic population screening with BNP would likely lead to over-utilization of resources including cardiology consultation and echocardiography (ECG).

** Decompensated HF**

HF has two major subtypes, systolic and diastolic failure, which each account for half the cases in the HF prevalence pool. The pivotal Breathing Not Properly Multinational Study (BNPMS) evaluated 1,586 patients who presented to the emergency department (ED) with acute dyspnea and demonstrated that BNP >100pg/ml or more had a sensitivity of 90%, and a specificity of 76% in differentiating between dyspnea due to HF (either systolic or diastolic), and dyspnea related to other
Causes. In determining the correct diagnosis, adding BNP to clinical judgment would have increased the diagnostic accuracy from 74% to 81%. A proposed algorithm for using BNP in the acute evaluation of dyspnea is given in Figure 2. Due to the fact that BNP levels were found to correlate negatively with estimated glomerular filtration rate (eGFR), the optimum cutpoint for diagnosing HF rose to 200 pg/mL for patients with eGFR less than 60 ml/min.

Due to the fact that BNP is a reflection of LV wall tension, it follows that BNP levels would identify patients with dyspnea related to HF with diastolic HF, where the primary abnormality is decreased LV compliance and increased end-diastolic pressure. Lubien et al. reported on BNP levels in 294 patients referred for ECG to evaluate ventricular function with careful classification of diastolic filling patterns. Transmitral pulsed Doppler velocity recordings were used to derive the deceleration time. Short deceleration times are known to be highly associated with LV end diastolic pressures >25 mmHg. In this analysis, BNP levels were higher in patients with deceleration times <160 ms (249 ± 43 pg/mL), in comparison with the near normal BNP levels (70 ± 13 pg/mL) in patients with normal deceleration times. Similarly, the BNPMS reported the median BNP of patients with diastolic HF was 413 pg/mL, in comparison with 34 pg/mL in patients with dyspnea not due to HF. B-type natriuretic peptide levels did not separate patients with systolic HF from those with diastolic HF, although levels trended higher in patients with systolic HF (821 pg/mL), likely related to this cohort’s higher New York Heart Association (NYHA) functional classification status.

Prognosis of HF

Prognosis in HF is dictated by the complex interplay of neurohumoral, mechanical, electrical, and multi-organ derangements. Koglin et al. evaluated the prognostic power of BNP in 78 patients referred to their HF clinic. Levels of BNP were significantly correlated with the HF survival score. Patients with high levels of BNP were much more likely to develop clinical deterioration or die over a median 398-day follow-up period. As nearly half of the HF mortality in these and other trials is felt to represent sudden cardiac death, Berger et al. investigated the association of BNP with future cardiac death in 452 patients with LV ejection fraction (LVEF) ≤ 35%. Forty-four (10%) of the patients developed sudden death over a period of 592 days, with equal distribution between ischemic and non-ischemic HF etiology. Among all baseline variables, BNP was the most important predictor of sudden death. The sudden-death free survival rate among patients with high BNP levels (defined as log BNP > 130 pg/mL) was 81%, compared with 99% in patients with low BNP levels. B-type natriuretic peptide has consistently been found to be the best predictor of survival in HF; when compared with all other clinical variables.

Multiple blood marker approaches have recently been reported for HF prognosis. Horwich et al. studied the combination of BNP and cardiac Troponin I (cTnI) levels upon initial heart transplantation evaluation in 98 patients with ischemic and non-ischemic cardiomyopathy. Independently, detectable levels of blood cTnI due to accelerated myocyte apoptosis were associated with a two-fold increased mortality risk. The combination of detectable cTnI and high BNP levels (> 485 pg/mL) portended a 12-fold relative risk of death. These studies support the notion that a multi-marker approach may provide incremental prognostic information in patients with advanced HF.

Predicting Treatment Outcomes and Guiding the Management of HF Patients

Several recent studies support the usefulness of changes in BNP levels, as well as predischarge BNP levels, as important markers to optimize the care of patients hospitalized with HF. Bettencourt et al. investigated the ability of changes in BNP levels during hospitalization to track clinical outcomes in 50 consecutive patients hospitalized with decompensated HF. B-type natriuretic peptide levels decreased in most patients, although to a significantly greater degree in those who remained free of readmission for CV causes and death. Of the seven patients with increases in BNP levels during hospitalization, only one patient was event-free at six months. Within the
These compelling data raise the argument that neurohormonal levels, in particular BNP levels, may be useful in actively guiding the treatment of patients with HF. Mueller et al. randomized 452 patients who presented to the ED with acute dyspnea, to a diagnostic strategy including a single measurement of BNP level versus the use of a standard diagnostic strategy without the aid of BNP level.27 Serial measurements of BNP were not performed in either group. The measurement of BNP level in the ED resulted in reduced time to presentation to the in-patient care of patients with dyspnea.26

Importantly, change from baseline and the per cent change of BNP level over a four- and 12-month period were also evaluated. This analysis demonstrated a direct relationship between per cent change from baseline BNP levels and four-month mortality. Highest mortality was seen in patients with the largest per cent increase in BNP, while the lowest mortality was observed in those with the largest per cent decrease in BNP.26

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In this out-patient setting, self-reported quality of life has little relation to the blood BNP level, since quality of life is continually resetting to lower levels as disease progresses. BNP is therefore a useful and independent measure of disease severity obtained in the out-patient clinic. To date, there have been three small randomized controlled trials supporting the out-patient use of BNP to guide the medical management of HF. As an example, the first trial of 69 patients with symptomatic HF (NYHA class II-IV; LVEF <40%) hospitalized with decompensated HF or referred from cardiology clinics were randomized between N-BNP guided treatment (BNP group) and standardized clinically guided (clinical group) treatment. The treatment target in the BNP group was an N-BNP level <70pg/ml, and the target for the clinical group was based upon an objective standardized HF scoring system. If patients did not meet target, pharmacotherapy (ACE inhibitors, diuretics, digoxin, and vasodilators) was up-titrated in a prespecified protocol, with repeat assessment in two weeks. In the BNP group, BNP levels fell by an average of 273.5pg/ml from baseline, in comparison with a 10.4pg/ml rise in the clinical group. More importantly, after a 9.5-month follow-up there were more events (CV death, hospital admission for any CV event, and out-patient decompensated HF) in the clinical group than the BNP group (54 compared with 19 events, respectively, (p=0.02)). The improvement in outcome seen in the BNP group was attributed to a statistically significant increase in dosage of conventional, oral HF medications. These important studies suggest that there may be an active role for a neurohumoral guided approach to titration of drug therapy in HF.

**Mortality in Acute Coronary Syndromes, Pulmonary Embolism, and Sepsis**

It has been reported in multiple studies that BNP can be elevated in acute cardiopulmonary emergencies that have cardiac dysfunction as part of the syndrome. In these circumstances, BNP is elevated in only a minority of cases; however, when found, the elevated BNP level indicates a higher mortality rate in ACS, pulmonary embolism, and sepsis.

De Lemos et al. found that a BNP level >137.8pg/ml occurred only in 25% of ACS patients (fourth quartile), but when at this level predicted higher rates of all-cause mortality at 30-days and six months. Above a threshold of 80pg/ml, there were higher rates of death, new or progressive HF, and recurrent MI. It has been shown that BNP can be elevated in cases of unstable angina without evidence of infarction, and again, it is predictive of acute and longer term mortality. It is believed that BNP elevations reflect underlying cardiac decompensation due to the size of the infarct or ischemic zone and/or the overall lack of compensatory hyperkinesis of the reference segments, and therefore these processes are critically linked to the survival of the patient. Acute pulmonary embolism is known to increase levels of BNP produced from the RV. Wolde et al. found BNP was elevated (>75.1pg/ml) in one-third of 110 patients with angiographically proven pulmonary emboli. It was this group that had the highest mortality (25%) over the next 80 days. Conversely, those patients with BNP levels <8.7pg/ml had no deaths reported. Echocardiographic evaluation has correlated RV
dysfunction with elevations in BNP and subsequent mortality. In 50 patients with confirmed pulmonary embolism, Kruger found that the mean BNP levels were 340pg/ml and 55pg/ml for those with and without RV dysfunction, respectively (p<0.0001). The best discriminating mortality level for BNP in pulmonary embolism was found to be 90pg/ml.

In sepsis, endotoxin has been shown to induce the synthesis of mRNA for BNP. Sepsis is known to be a cardiotoxic state with subtle reductions in LV performance attributed to circulating cytokines and myocardial depressants. In sepsis, BNP levels are correlated to the severity of the sepsis state and short-term mortality. There are too few data to identify a critical cut-point for BNP and survival in sepsis to date. In the population of patients with dyspnea, sepsis is fairly uncommon. In the BNPMS, there were 717 patients without HF and only 40 (5.6%) of those had BNP levels >500pg/ml, with the majority having underlying renal dysfunction. Sepsis was thought to be a cause of the elevation in a minority of cases.

**BNP and Cardiac Surgery**

All of the cardiac natriuretic peptides rise acutely with cardiac surgery, and then decline over the following three to five post-operative days. Atrial natriuretic peptide is best correlated with moment-to-moment elevations in left atrial and pulmonary capillary wedge pressure and are not predictive of outcomes. Elevated pre-operative BNP levels have been associated with the development of atrial fibrillation and death after coronary artery bypass surgery (CABS). Wazni et al. measured BNP pre-operatively in 187 patients (mean ejection fraction 42%) and found the mean BNP was 615pg/ml and 444pg/ml in those who did and did not develop post-operative atrial fibrillation, respectively. The pre-operative BNP was the strongest predictor of post-operative atrial fibrillation. Hutfless reported higher pre-operative BNP levels in patients who died within one year (357pg/ml compared with 184pg/ml). Finally, Chello et al. reported on 31 patients with LV dysfunction, and found that BNP dropped from 133.2pg/ml to 77.5pg/ml, as the mean ejection fraction improved from 29% to 39%, pre-operatively and at 10 months, respectively. These data suggest that BNP is not only predictive of post-operative complications, but that a fall in BNP measured in the months after surgery indicates recovery of LVEF after revascularization.

**Chronic Valvular Heart Disease**

The chronic valvular lesions of aortic stenosis (AS), aortic regurgitation (AR), and mitral regurgitation (MR) have all been associated with elevations of BNP. In general, if the baseline BNP value is known over time, then a significant increase in BNP value is thought to precede ECG changes in LV function, and hence might be a useful guide in the timing of valvular surgery. Gerber et al. found that BNP levels were 31.2pg/ml and 96.9pg/ml for those with asymptomatic (aortic valve area=0.99cm²) and symptomatic (aortic valve area=0.71cm²) AS, respectively (p<0.0001). A cut-point of 48.5pg/ml was the best discriminator for symptomatic AS. Qi et al. demonstrated that the BNP levels more closely reflected the pulmonary capillary wedge pressure and LV function than the severity of AS. Importantly, it has recently been shown that a pre-operative BNP level >130pg/ml predicted higher event rates and need for aortic surgery in patients with severe AS by ECG (see Figure 5). In patients with AI, the data are similar, with BNP levels averaging 152.3 and 24.2pg/ml in symptomatic and asymptomatic patients with moderate to severe AI. There are analogous data in the setting of chronic MR where Sutton et al. reported the mean BNP values were 58.5pg/ml and 24.6pg/ml in those with and without symptoms. The chronology of how BNP rises over the course of chronic valvular heart disease is unclear, but it likely rises before there are changes seen on the ECG and possibly before symptoms develop. As a general rule, a doubling of BNP over time may be the first signal in AS, AR, or MR that a clinician could detect indicating cardiac decompensation; however, there are too few data to identify critical cut-points for each lesion. When a patient has been selected for valvular surgery, then the pre-operative BNP level predicts long-term symptom-free survival, much like the way LVEF predicts outcome.

**Caveats**

While data continue to emerge with respect to the clinical meaning of BNP levels in given patients, the
following caveats need to be emphasized. The blood level should be interpreted in context with the patient, their gender, age, renal function, degree of adiposity, and underlying LVEF. It appears that BNP at particular cut-points may be useful for predicting or anticipating clinical events but does not replace clinical judgement.

These caveats and suggestions for clinical use have been summarized in the 2004 BNPMS Consensus Panel document and in the most recent update to the American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure Guidelines.15,48 An integrated approach to using BNP in the continuum of HF, a disease process, is shown in Figure 6.

**Conclusion**

BNP levels can facilitate the proper diagnosis of patients with HF and add valuable information to the physician faced with the assessment of patients with and without known HF. When BNP is elevated in acute coronary syndromes, pulmonary embolism, and sepsis, subclinical LV and/or RV dysfunction is present and a higher mortality can be expected. Elevated BNP levels before cardiac surgery are associated with higher rates of atrial fibrillation and death. After bypass surgery, as LV function improves, the BNP level can be expected to fall. Lastly, in patients with AS, AR, and MR, BNP elevates and is associated with the development of symptoms—it can possibly serve as a trigger for additional evaluation or intervention.

**References**


Clinical Utility of Blood Natriuretic Peptide Levels


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