Circulating Natriuretic Peptide Levels in Acute Heart Failure

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Natriuretic peptide (NPs) levels have achieved worldwide acceptance. They are excellent rule-in and rule-out biomarkers for patients presenting with dyspnea. In the hospital, NP levels may represent altered forms of B-type natriuretic peptide (BNP), including the inactive precursor molecule, pro-BNP. NP levels drop during hospitalization as the patient is decongested. In the future, NP levels may be used as a surrogate to titrate outpatient therapy.
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Natriuretic peptides (NPs) have become increasingly important markers for evaluation of the dyspneic patient and treatment of congestive heart failure (CHF). Although NPs are primarily used as a tool for diagnosing or ruling out acute CHF in the dyspneic patient, recent work suggests a much broader application for NPs. NPs are not only a useful adjunct for diagnosing and monitoring patients with heart failure (HF), but studies now suggest that they provide independent prognostic information for patients with acute and chronic HF as well as acute coronary syndromes (ACS).

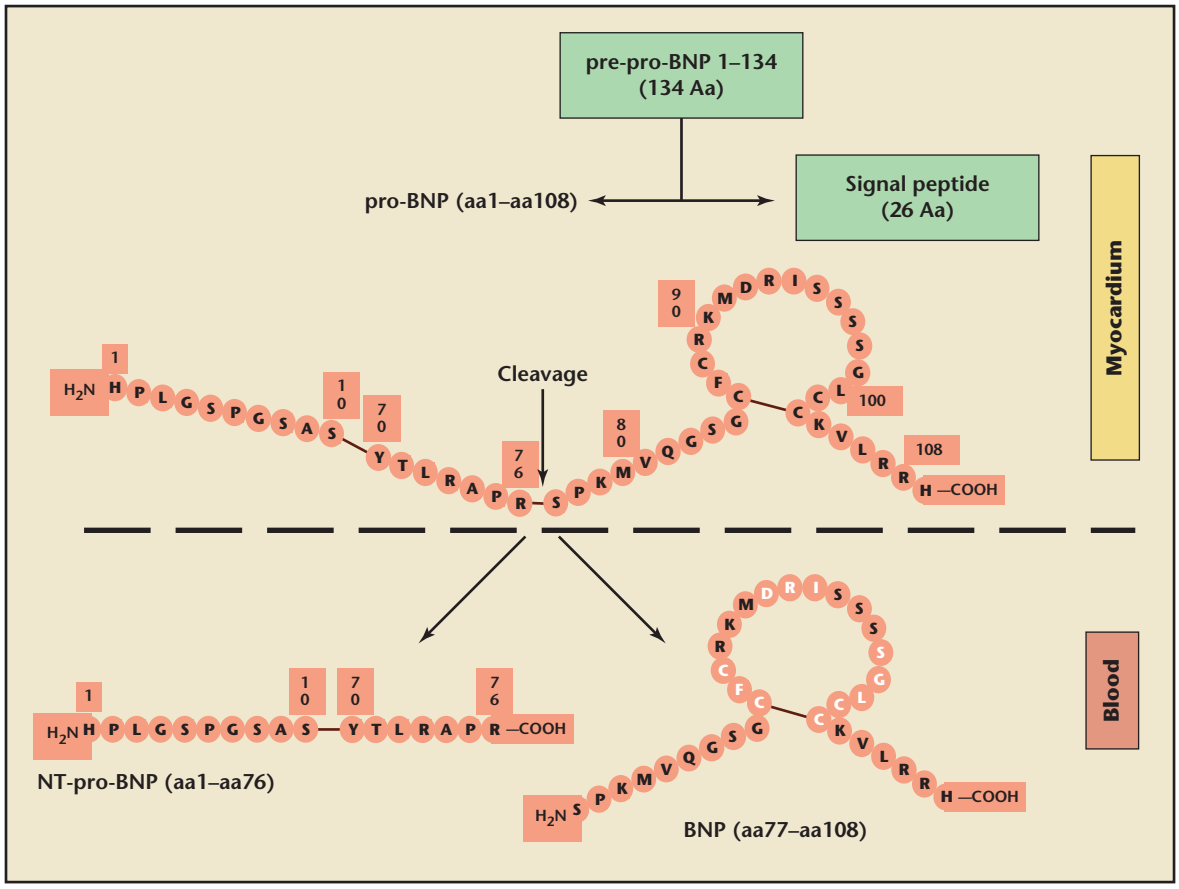

Figure 1. *Structure and function of B-type natriuretic peptide (BNP).*

Physiology of Natriuretic Peptides

B-type natriuretic peptide (BNP) and the amino-terminal fragment of pro-BNP (NT-pro-BNP) are secreted by the myocardium in response to increased end-diastolic wall stress (Figure 1). BNP, with a half-life of about 20 minutes, is quickly cleared via several mechanisms, including degradation and clearance by the NP receptor-C. In addition, BNP is degraded by neutral endopeptidase, and direct renal filtration and passive excretion may be responsible for some BNP clearance as well. NT-pro-BNP, on the other hand, has a longer half-life of about 1 to 2 hours. Despite 1:1 secretion of BNP and NT-pro-BNP, the long half-life of NT-pro-BNP (about 1-2 hours) leads to higher circulating levels and slower fluctuations compared with BNP.[1] Although values of BNP and NT-pro-BNP are not interchangeable, both NPs offer considerable value to the clinician. The final decision as to which NP will be used, BNP or NT-pro-BNP, is not necessarily based on the differences between the 2 peptides, but rather the presence of the pre-existing laboratory equipment necessary to run the assay, as well as the perceived need for point-of-care devices versus large laboratory platforms.

Diagnosis of HF

Diagnosing acute HF in the emergency setting is often difficult. In order to avoid the increased morbidity and mortality that parallels delayed and incorrect diagnoses, it is necessary to have tools with which to differentiate these diseases and make a rapid and accurate diagnosis. Several studies have established the role of NPs in the clinical diagnosis of acute HF. Dao and colleagues[2] performed the first clinical study using point-of-care BNP levels in 250 patients presenting to the emergency department (ED) with dyspnea. BNP values were shown to be the strongest predictors of acute HF, being both sensitive and specific for diagnosing HF. The mean BNP level in patients found to have HF was higher than in patients without HF (1,076 pg/mL vs 38 pg/mL; $P < .001$).[2]

These findings provided a foundation for the Breathing Not Properly multinational study,[3] a prospective study that used BNP levels to evaluate the causes of dyspnea. In this study of 1586 ED patients with acute dyspnea, BNP levels were found to be more accurate predictors of HF than any history, physical findings, or laboratory values.[3] A BNP cutoff value of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating HF from other causes of dyspnea, and a cutoff level of 50 pg/mL had a negative predictive value of 96%. A BNP level of more than 230 pg/mL was associated with a relative risk of 7.0 for a HF-related event in the absence of a correct diagnosis by the physician. BNP levels, had they been available to clinicians, would have reduced the rate of indecision from 43% to 11%. Incorporation of BNP into the clinical evaluation of the dyspneic patient was found to increase the absolute diagnostic accuracy by 10%.[4] A simple but useful algorithm for using BNP testing in the ED is presented in Figure 2.

The Pro-BNP Investigation of Dyspnea in the ED (PRIDE)[5] was a similar study performed with NT-pro-BNP, measured in 600 patients who presented to a single ED with dyspnea. In this study, NT-pro-BNP had a sensitivity and specificity similar to the Breathing Not Properly study. Patients with acute HF had a median NT-pro-BNP over 4000 pg/mL, compared with 130 pg/mL in those without acute HF. An NT-pro-BNP cutpoint of 300 pg/mL was proposed to rule out a diagnosis of HF, whereas higher age-dependent cutpoints were suggested to rule in HF (area under the receiver operator curve, 0.94).

The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT)[6] examined the relationship between perceived severity of disease by physicians and severity as indicated by BNP levels. Physicians were informed whether the BNP level was above or below 100 pg/mL, but were not given the actual value. Surprisingly, the patients who were discharged from the hospital had higher BNP levels than those admitted for treatment. The median BNP level for discharged patients was 976 pg/mL, compared with a mean BNP of 766 pg/mL for patients who were admitted to the hospital. Patients with BNP levels of less than 200 pg/mL had an excellent prognosis, with a mortality of 0% at 30 days and only 2% at 90 days. Therefore, BNP levels not only improve the accuracy of diagnoses of dyspnea, but also can be used to assess severity of the disease in individual patients.

The inclusion of NPs in clinical decision making has been shown to be cost effective and to improve quality of care in the emergency and hospital settings. The B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study[7] in Switzerland explored the cost effectiveness of using the BNP test as an adjunct to the standard clinical tools. Patients enrolled in the study were randomized to 1 of 2 groups: to receive or not to receive a BNP blood test upon arrival in the ED. Patients who received a BNP test upon presentation were shown to have 10% fewer admissions, decreased length of hospital stay by a mean of 3 days, and lower mean total cost of treatment.

Recently, data from the Canadian Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) study[8] confirmed that the findings of the BASEL study also apply in a universal health coverage system. A total of 500 patients presenting with dyspnea to 7 EDs were randomly

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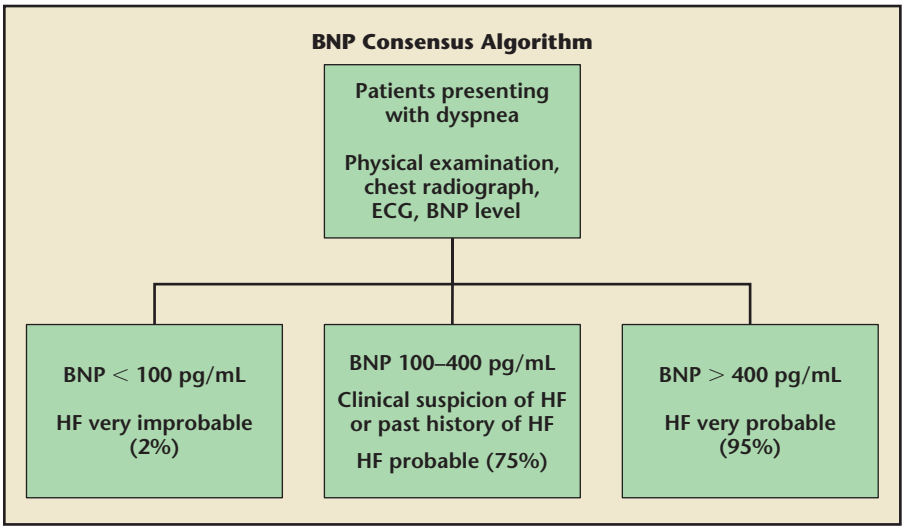
Figure 2. *B-type natriuretic peptide (BNP) algorithm for the emergency department. ECG, electrocardiogram; HF, heart failure. Adapted from Silver et al.*[51]



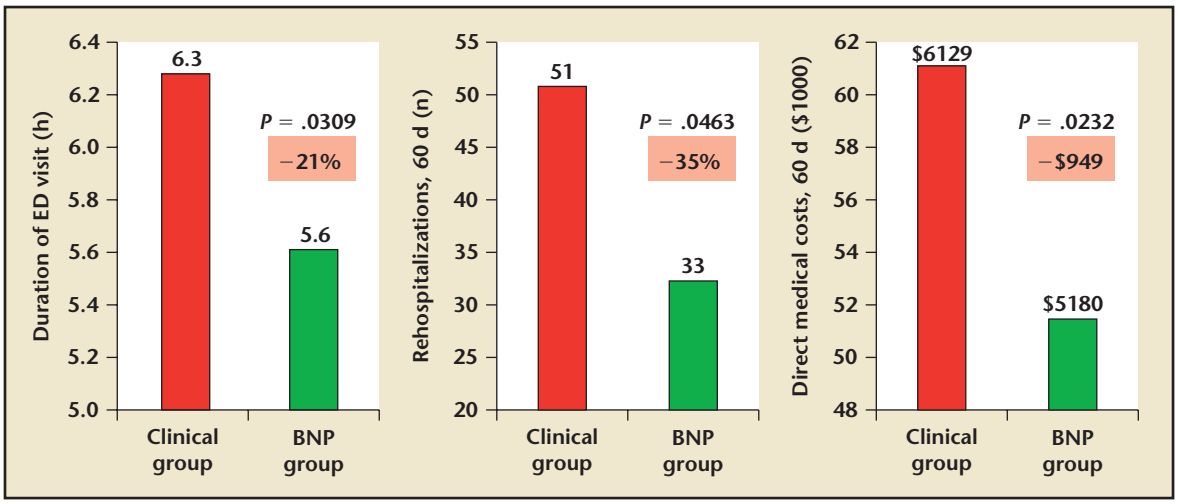


Figure 3. *Use of NT-pro-BNP reduces duration of ED visits, number of rehospitalizations, and direct medical costs. BNP, B-type natriuretic peptide; ED, emergency department. Data from Moe et al.*[8]

Table 1
Caveats When Using BNP Levels

Low BNP
Anemia
Obesity
Normal BNP
Flash pulmonary edema
Acute mitral valve rupture
Constrictive pericarditis
Cardiac tamponade
Raised BNP
Previous heart failure
Increasing age
Sex
Pulmonary hypertension
Pulmonary embolism
Renal insufficiency
Acute coronary syndromes
High-output states
Atrial fibrillation
Ascitic cirrhosis
Myocardial ischemia

BNP, B-type natriuretic peptide.

assigned to management with or without the knowledge of NT-pro-BNP levels. The knowledge of NT-pro-BNP levels reduced the duration of the ED visit by 21%, the number of patients rehospitalized over 60 days by 35%, and direct medical cost of all ED visits, hospitalizations, and subsequent outpatient services at 60 days by 15% (Figure 3).

Caveats and Special Issues in Using NP Levels

Raised NP Levels

A given level of an NP is a summation of many inputs and is reflective of the overall state of myocardial function. However, there are caveats and special issues that need to be considered when evaluating NP levels. These are illustrated in Table 1.

The "gray zone." The gray zone is defined as a BNP level between 100 and 400 pg/mL[9]; and an NT-pro-BNP level that falls between 300 and 450 pg/mL for those below 50 years of age, between 300 and 900 pg/mL for those between ages 50 and 75, and between 300 and 1800 pg/mL for those over 75 years of age.[5] Those who fall in the gray zone require extra physician attention and ancillary testing. Although the final diagnosis in most patients is mild to moderate HF,[9] other causes of a modest rise in NP level should be considered.

Previous HF. Patients with a history of HF often have NP levels above the suggested cutpoints, even when their volume status is optimal. This was demonstrated in the BNP trial, which showed that patients with a history of HF but without an acute exacerbation had intermediate levels of BNP in between those without HF and those with an acute diagnosis of HF.[3] For patients regularly followed in a clinic, it may be beneficial to establish their "optivolemic" or "dry-weight" NP level; that is, the BNP or NT-pro-BNP level that corresponds to their optimized fluid status. Significant deviations above this value could then be used in lieu of traditional cutpoints for diagnosing HF exacerbations, whereas values much lower than this optivolemic level might indicate that the patient is over-diuresed.

Advanced age. NP levels increase with age.[10,11] Increased prevalence of heart disease with age, including diastolic dysfunction, may contribute to this phenomenon, but is probably not the principal factor. One study that excluded patients with age-related diastolic dysfunction nonetheless found an association between

age and elevated levels of BNP.[10] Other possible contributors include altered renal function, increased production, reduced secretion, or altered metabolism. Nevertheless, in the acutely dyspneic patient, the cutpoint of 100 pg/mL for BNP was still found to be optimal.[11]

Sex. NP peptide levels are higher in women than in men at any age.[10,12] Although the reason for the higher levels in women is unknown, estrogen may play a role, because a community-based study showed that older women on hormone replacement therapy had higher BNP levels than women not on therapy.[10] However, use of estrogen had only a minimal effect on NT-pro-BNP levels in the same cohort.[13] Again, these small differences are likely unimportant when dealing with the acutely dyspneic patient.

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Pulmonary disease. Differentiation between cardiac and pulmonary causes of dyspnea is a great challenge faced by ED physicians. In a study of 321 patients with dyspnea who presented to the ED, BNP distinguished HF (mean BNP 759 ± 798 pg/mL) from pulmonary disease (61 ± 10 pg/mL) and other clinical presentations with a high specificity and sensitivity. Moreover, when patients with a history of HF but whose dyspnea was attributable to chronic obstructive pulmonary disease (COPD) (mean BNP 47 ± 23 pg/mL) were compared with patients who had a history of COPD but whose dyspnea was caused by HF (731 ± 764 pg/mL), a BNP value of 94 pg/mL yielded a sensitivity and specificity of 86% and 98%, respectively, and differentiated HF from lung disease with an accuracy of 91%.[14]

Secondary analysis of the Breathing Not Properly study demonstrated that measurement of BNP levels can expose underlying HF in patients with bronchospastic diseases such as asthma or COPD.[15] Of 417 patients studied who had a history of asthma or COPD and no history of HF, 87 (20.9%) were found to have a final diagnosis of new-onset HF. The mean BNP levels for patients with and without a history of HF were found to be 587.0 and 108.8 pg/mL, respectively. Thus, routine NP testing in patients with a history of asthma or COPD may increase the rate of new diagnosis of HF by as much as 20%.

Pulmonary embolism. Acute, hemodynamically significant pulmonary embolism can cause elevation of NP levels. In this setting, NP levels are indicative of right heart strain rather than left HF and elevated levels portend worse outcomes.[16] It is important to remember that elevated NP levels are not pathognomonic for HF in acutely dyspneic patients, and acute pulmonary embolism must still be excluded, especially with "gray-zone" levels of BNP (100-400 pg/mL).

Renal failure. Both BNP and NT-pro-BNP levels rise with worsening renal function, but it is unclear to what degree this rise is caused by concomitant heart disease in patients with chronic kidney disease, versus reduced clearance of NPs from the circulation via renal-mediated mechanisms. Several studies have found that NP levels begin to rise at a threshold of estimated glomerular filtration rate (GFR) of 60 mL/min/1.7 m^2, which is approximately the same level at which increased rates of both systolic and diastolic HF are seen.[17] Regardless, an evaluation from the PRIDE study showed that NT-pro-BNP levels, although higher in patients with worse renal function, were still the strongest independent predictor of outcome in patients with GFR under 60 mL/min/1.7 m^2 and suggested the higher cutpoint of NT-pro-BNP above 1200 pg/mL for such patients. Similarly, an analysis of the BNP trial also found a weak but significant correlation between GFR and BNP, and suggested a series of higher cutpoints for those with GFR under 60 mL/min/1.7 m^2.[18]

BNP in ACS. The accumulated body of evidence, derived by both clinical trials and registries, clearly shows that the levels of NPs are independent predictors of prognosis in ACS. Higher concentrations of NPs are associated with increased short- and long-term mortality and increased risk of HF, independently of other well-known clinical predictors of outcome in ACS, including infarct size and left ventricular (LV) function, as well as troponin and C-reactive protein levels.[19-22] Of note, this association is present even when troponin levels are normal, as in the case of unstable angina, or even in patients with stable coronary artery disease. However, NP levels do not appear to predict the occurrence of new nonfatal ischemic events.[23]

The reason for the prognostic significance of NP levels in ACS is not fully understood. Higher NP levels are associated with more severe underlying coronary artery disease, more extensive ischemic areas, and more affected left or right ventricular function.[24,25] All these reasons, and the fact that the NP levels may be indicators of comorbidities such as diabetes, hypertension, LV hypertrophy, repetitive symptomatic or silent ischemia, and renal dysfunction, could provide a potential pathophysiologic explanation of the observed prognostic significance of NPs in ACS.

The available evidence does not yet support a management strategy based on NP levels in ACS. However, it has been shown that the majority of patients with non–ST-elevation ACS and high NP levels failed medical therapy and needed cardiac catheterization.[23] Thus, one may suggest a more aggressive approach, with a lower threshold for invasive intervention, in patients with ACS and elevated NP concentrations.[25] However, in most published studies there was no difference in mortality by an invasive management strategy in patients with higher NP levels. Because NP levels are an independent predictor of mortality but not of atherothrombotic events, early invasive and antithrombotic strategies based on elevated NPs won't influence clinical course. Additional work is needed to identify therapies that may reduce the risk associated with increased NP levels.

High-output states. Patients with high-output states (including sepsis, cirrhosis, and hyperthyroidism) can all present with elevated NP levels in the absence of overt HF. In patients with severe sepsis or septic shock, for example, NP levels may be markedly elevated,[26,27] perhaps via induction by endotoxin and other inflammatory mediators,[28] or as a reflection of underlying myocardial dysfunction.[29] Similarly, patients with both alcoholic and nonalcoholic cirrhosis may have elevated NP levels, which may reflect cardiac dysfunction or their hyperdynamic circulatory state.[30] NP levels may be elevated in patients with hyperthyroid when compared with those with hypothyroid, and although levels may not exceed diagnostic cutpoints, they do decrease with treatment of the hyperthyroid state.[31] Elevated NP levels have also been reported in the setting of high-output cardiac failure caused by an oversized arteriovenous fistula in a hemodialysis patient.[32]

Caveats: Low Levels of NPs

Several scenarios can account for low levels of NPs, even below diagnostic cutpoints, despite the clear presence of HF. Keeping in mind certain caveats may help resolve clinical dilemmas that seem discrepant with NP values.

Obesity. A known risk factor for cardiac disease, obesity has recently been implicated as a more direct risk factor for development of HF because of the increased plasma volume and increased cardiopulmonary volume in obese patients.[33-35] It is important to recognize that as a large subgroup of patients with HF, obese patients typically have much lower NP levels than nonobese patients. Caution must be taken when interpreting NP results in obese patients, as the NP levels themselves may not accurately reflect the fluid status and/or severity of HF in these patients.

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Several studies have demonstrated an inverse relationship between body mass index and BNP levels in patients with HF. Mehra and colleagues[33] found that BNP levels were significantly lower in obese versus nonobese patients. In patients less than 65 years of age, those who were obese were found to have BNP levels 40% lower than those who were not. Additional findings from the Breathing Not Properly study showed that 50% of nonobese patients presenting to the ED with HF had BNP values above 1000 pg/mL, whereas only 8% to 24% of obese patients presenting with HF had BNP values greater than 1000 pg/mL.[34] This pattern is likely caused by the fact that NP receptors in adipose tissue cause more rapid degradation of BNP in obese patients.[35]

Flash pulmonary edema. In patients presenting with a very rapid onset of HF symptoms of 1 hour or less, NP levels may seem inappropriately low. This is likely due to the time required for NP up-regulation and expression in response to ventricular wall stress. BNP, unlike atrial NP, has only minimal storage in secretory granules; rather, it is primarily synthesized and secreted in bursts.[36] When a patient presents early in the early stages of flash pulmonary edema, there may be insufficient time for gene expression to take place between the initial trigger (ie, wall stretch) and subsequent measurement of NP levels. Occasionally one will see an NP elevation the following day, even though the patient has been successfully treated.

HF due to causes upstream from the left ventricle. When HF is attributable to causes upstream from the left ventricle, such as acute mitral regurgitation or mitral stenosis, NP levels can be low or normal despite severe HF. This is because LV function may not be compromised in these patients, especially in the acute setting. Similarly, patients with constrictive pericarditis or cardiac tamponade may have symptoms of HF and elevated filling pressures, but tend to have low NP levels due to lack of ventricular stretch.[37]

Using NPs in the management of HF. *Inpatient management.* Therapy for decompensated HF is aimed at the reduction of filling pressures

needed to produce adequate cardiac output; however, patient symptomatology may not accurately reflect underlying hemodynamics, and thus is likely responsible for the high readmission rate. Clinicians must be able to determine the severity of heart disease in hospitalized patients and distinguish between those patients who can be discharged early and those who need more aggressive therapy. Gold standard measurements of filling pressures include either pulmonary catheter-guided pressure measurements or, less optimally, estimates based on Doppler echocardiography. However, the routine performance of these procedures is not practical in most patients. As such, much attention has been focused on finding biomarkers that can estimate LV end-diastolic pressure for the tailoring of HF therapy.

Because BNP is released mainly in response to LV stretch from volume overload, levels would be expected to closely correlate with pulmonary capillary wedge pressure (PCWP) measurements.[38] Indeed, in a study by Kazanegra and colleagues,[39] patients admitted for decompensated HF had BNP levels and hemodynamic measurements taken every 2 hours for the first 24 hours and every 4 hours for the next 24 to 48 hours. PCWP showed a decrease from 33 to 25 mm Hg over the first 24 hours, whereas BNP levels decreased in parallel from 1472 to 670 pg/mL. In addition, there was a correlation between rate of change of BNP levels and rate of change of wedge pressure. It should be emphasized that although high filling pressure in the left ventricle is the strongest stimulus for increased BNP levels, it is not the only culprit of elevated BNP in hospitalized patients, and as such, failure of the BNP to fall is not an absolute indicator of treatment failure.

The NP level of a patient who is admitted with decompensated HF is composed of 2 components: that of a baseline, optivolemic (dry) NP level and that occurring from acute pressure or volume overload (the wet) NP level. At the point of decompensation, a patient's BNP level is the sum of the baseline NP level plus what volume overload adds. In the decompensated HF patient, a state of BNP insufficiency may exist.[40] Evidence for a state of deficiency comes from molecular analysis of BNP in subjects with acute HF, which reveals 2 distinct circulating forms of BNP: a high molecular weight form, thought to be the biologically inactive pro-BNP, and a low molecular weight form, the 32-amino acid active BNP.[41] Abnormal processing of pro-BNP into less active forms may also factor into the state of relative BNP insufficiency.[42]

NP measurements during hospitalization should probably be obtained at the very least on admission and discharge. NP levels taken 24 hours after the initiation of treatment have proven to be useful in determining whether the patient is in need of more aggressive treatment. BNP levels should not be drawn during infusion of nesiritide or for 2 hours after the infusion is stopped, because the result will include exogenous as well as endogenous BNP. NT-pro-BNP levels can be drawn during infusion of nesiritide.

Patients whose BNP levels do not fall with treatment may suffer from higher rates of subsequent adverse events.[43] Logeart and coworkers[44] found that patients discharged with BNP levels above 350 pg/mL were at much higher risk of adverse events than those with lower BNP levels. Additionally, patients with discharge BNP levels greater than 700 pg/mL had a 31% prevalence of death or HF readmission after 1 month. This prevalence increased to 93% after 6 months. Thus all efforts should be made to "decongest" the patient prior to hospital discharge.

Outpatient monitoring. Treatment of patients after a HF hospitalization may turn out to be just as valuable as management during the hospital stay. Several studies have investigated the potential role of BNP as a means to guide titration of outpatient treatment. Troughton and colleagues[45] conducted a randomized clinical pilot study comparing NT-pro-BNP–guided treatment titration with clinically guided treatment in 69 HF outpatients. In this study, NT-pro-BNP–guided treatment was associated with a significant reduction in the composite endpoint of admission, cardiovascular death, or worsening HF.

The Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial[46] was a European multicenter trial designed to test the hypothesis that using BNP to guide treatment of outpatients with systolic dysfunction could reduce mortality and HF admission rates. Patients were randomized to have their treatment guided by BNP levels or to receive standard treatment. Those who were to receive BNP-guided treatment were asked to use medication to drive the BNP levels as low as they could, preferably to below 100 pg/mL. For purposes of this study, events included HF admission, death, or emergency transplantation. The patients who received BNP-guided treatment were significantly more likely (84.3%) to have event-free survival than those who received standard treatment (73.3%). Only 1.8% of patients in the BNP group were readmitted 2 or more times for HF, whereas 9.0% of patients in the control group were readmitted 2 or more times during the study. Not all patients in the BNP-guided group were optimized to BNP levels of under 100 pg/mL by

the end of the titration phase of the study. There were significantly more HF-related hospitalizations ($P < .001$) and deaths ($P < .05$) in the control group than the BNP group. The STARS-BNP investigators concluded that using BNP to guide therapy of HF patients is an effective strategy for reducing both morbidity and mortality. The above trials were small in nature but certainly suggest the need for larger trials. These trials are currently underway.

It appears that angiotensin-converting enzyme inhibitors (lisinopril, 20 mg/d), angiotensin receptor blocker agents, spironolactone (25 mg/d), and perhaps β-blockers (carvedilol, 25 mg twice daily over long periods of time) drive NP levels down, although it is unclear whether this is a true marker of clinical improvement.[47-51] In the Valsartan Heart Failure Trial (Val-HeFT),[51] changes in BNP over time induced by pharmacologic therapy were shown for the first time to correlate with morbidity and mortality. Compared with baseline, patients with the greatest decrease in BNP and norepinephrine (NE) from baseline had the lowest morbidity and mortality, whereas those with the greatest increase in BNP and NE were at highest risk.

The "holy grail" for BNP testing might be its usefulness as a surrogate for adjusting cardiac medications. Unlike hypertension, diabetes, and lipid disorders, there is no surrogate marker that is inexpensive, accurate, and reliable. In this area of personalized medicine it is possible that BNP will help personalize therapy for HF; in other words, guideline doses of medications may be altered based in part on BNP levels. More work is needed in this area.

Conclusions

NPs have become increasingly important markers for evaluation of the dyspneic patient and treatment of CHF. Although NPs are primarily used as a tool for diagnosing or ruling out acute CHF in the dyspneic patient, recent work suggests a much broader application for NPs, including but not limited to diagnosis of HF, prognosis in HF, management of acute HF, prognosis in coronary artery disease and ACS, diagnosis of pulmonary embolism, and titration of outpatient therapy. NPs are not stand-alone tests and there is a learning curve associated with their use. Further research is likely to help elucidate and refine our understanding and clinical use of the NP levels. ■

Dr. Maisel is a speaker/consultant/investigator for Biosite Inc.; a speaker/investigator for Scios Inc.; an investigator for Bayer, Roche, and Abbott.

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Main Points

- Natriuretic peptides (NPs) are not only a useful adjunct for diagnosing and monitoring patients with heart failure, but studies now suggest that they provide independent prognostic information for patients with acute and chronic heart failure (HF) as well as acute coronary syndromes (ACS).
- Higher NP levels are associated with more severe underlying coronary artery disease, more extensive ischemic areas, and more affected left or right ventricular function. All these reasons, and the fact that the NP levels may be indicators of comorbidities such as diabetes, hypertension, left ventricular hypertrophy, repetitive symptomatic or silent ischemia, and renal dysfunction, could provide a potential pathophysiologic explanation of the observed prognostic significance of NPs in ACS.
- The NP level of a patient who is admitted with decompensated HF is composed of 2 components: that of a baseline, optivolemic (dry) NP level and that occurring from acute pressure or volume overload (the wet) NP level.
- Using B-type natriuretic peptide to guide therapy of HF patients may be an effective strategy for reducing both morbidity and mortality.

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