Cardiac Natriuretic Peptides: A Proteomic Window to Cardiac Function and Clinical Management

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Congestive heart failure (CHF) is a leading cause of adult hospitalization in the United States, and despite advancements in treatment, the disease remains a major clinical challenge. The chief symptom of CHF is dyspnea, but in the urgent-care setting, it is often difficult to distinguish between cardiac and pulmonary causes of this symptom. B-type natriuretic peptide (BNP) is mainly synthesized, stored, and released in the ventricular myocardium and is strongly induced during ventricular-wall tension or stretch. It can be measured rapidly at the point of care and can be used to differentiate cardiac from pulmonary etiologies of dyspnea. In addition to its diagnostic utility, it also has prognostic value and may help guide the treatment of patients with CHF. Thus, it is likely that future algorithms incorporating BNP levels and other clinical indicators will become available to guide critical-care physicians in making management decisions for their CHF patients.

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Key words: Congestive heart failure • B-type natriuretic peptide • Dyspnea • Left-ventricular dysfunction

Congestive heart failure (CHF) is the fourth leading cause of adult hospitalizations in the United States and the most frequent cause of hospitalization in patients over the age of 65, representing a chronic disease epidemic.[1-5] Advances in our understanding of the pathophysiology of CHF

have led to treatments affording symptomatic improvement and longer life. However, the disease remains a major clinical challenge.[4] Considerable effort is made in diagnosing of CHF using conventional means.[5] This paper will review the rationale for B-type natriuretic peptide (BNP) as a diagnostic test and management tool in CHF patients.

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP), also called brain natriuretic peptide, was originally cloned in extracts of porcine brain.[6] Its name is a misnomer because the protein is mainly synthesized, stored, and released in the ventricular myocardium.[6] While atrial natriuretic peptide (ANP) is contained in storage granules in the atria and ventricles, and even minor stimuli such as exercise may trigger its significant release into the bloodstream, only small amounts of BNP are colocalized in atrial granules.[7] Instead, the stimuli for BNP secretion are changes in left-ventricular (LV)-wall stretch and volume overload. This fact suggests that BNP may be a "distress hormone," more specific to ventricular disorders than are other members of the natriuretic peptide family.[7]

Biochemistry and Molecular Biology

Human pro-BNP consists of 108 amino acids (Figure 1). Processing of pro-BNP produces a mature, biologically active BNP, which consists of 32 amino acids and an amino-terminal BNP. Both polypeptides, pro-BNP and mature BNP, circulate in plasma. BNP contains a 17-amino-acid ring with a cysteine-cysteine disulfide cross-link, which is present in all natriuretic peptides.[8-11] Eleven amino acids in the ring are homologous among all members of the natriuretic peptide family. BNP DNA has a 3', untranslated region that

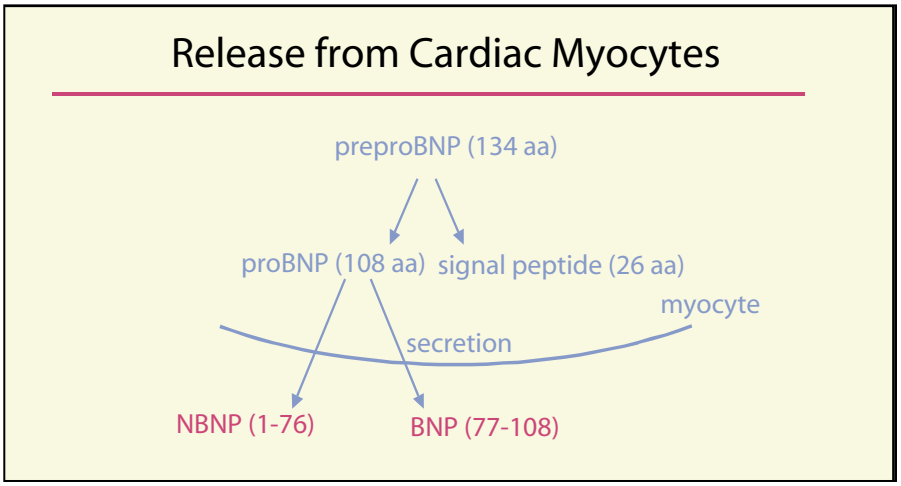


Figure 1. *The generation of B-type natriuretic peptide (BNP) and N-terminal pro-BNP from its precursor molecule. aa, amino acids.*

is rich in adenosine-thiamine sequence. This sequence destabilizes the mRNA molecule and causes it to have a short half-life.[8-11] This TAT-TAT sequence is absent in ANP DNA.

BNP expression in myocytes is induced with rapid kinetics of the primary response gene.[10] The rapid induction of transcription can be achieved by molecules that increase mRNA half-life. BNP mRNA is inducible via ventricular-wall tension or stretch.[10,12] As a result, changes in BNP expression may represent a response to myocardial ischemia, necrosis, damage, and local mechanical stress on ventricular myocytes, even when global hemodynamic parameters remain unchanged.

Mechanism of Action

The natriuretic peptides incite their action through binding to high-affinity receptors, mainly on endothelial cells, vascular smooth-muscle cells, and other target cells. Three distinct natriuretic peptide receptors (NPRs) have been identified in mammalian tissues and are known as NPR A, B, and C.[11] NPR A and B are structurally similar, with a 44% homology in the ligand-binding domain. A single, membrane-spanning portion bridges the intracellular and extracellular segments of these receptors. Both types of receptors use a cyclic guanine monophosphate signaling cascade. NPR B is mostly found in the brain, whereas NPR A is more commonly located in large blood vessels.[13] Both receptor types are also found in the adrenal glands and kidneys. NPR A binds preferentially to ANP, but also binds to BNP. On the other hand, C-type natriuretic peptide is the natural ligand for B receptors.[13]

BNP is removed from plasma through two distinct mechanisms: endocytosis and enzymatic degradation by endopeptidases.[14] NPR C binds to all members of the natriuretic peptide family with equal affinity. When a ligand-receptor complex forms, it undergoes receptor-mediated endocytosis. The C-type receptors are recycled to the cellular membrane, and the various natriuretic peptides are degraded to building blocks. The second mechanism to remove natriuretic peptides from plasma involves zinc-containing endopeptidases. These enzymes are present in renal tubules and vascular endothelial cells. They chew and

degrade natriuretic peptides, among other proteins.

Physiological Effects of BNP

BNP is a potent natriuretic, diuretic, and vasorelaxant peptide. It coordinates fluid and electrolyte homeostasis through its activity in the central nervous system and peripheral tissue. BNP promotes vascular relaxation and lowers blood pressure, particularly in states of hypervolemia. It inhibits sympathetic tone, the renin-angiotensin axis, and synthesis of vasoconstrictor molecules such as catecholamines, angiotensin II, aldosterone, and endothelin-1.[15] It improves central hemodynamics, including the cardiac index, in patients with chronic heart failure through suppression of myocyte proliferation, cardiac growth, and compensatory hypertrophy of the heart.[15] Its renal effects include increasing glomerular filtration rate and enhancing sodium excretion. BNP reinforces diuretic effects by suppressing centers for salt appetite and counteracting sympathetic tone via its action in the brainstem.[15]

BNP Levels in the Population

BNP levels rise with age, regardless of whether patients have CHF (Figure 2).[16] Over time, the left ventricle stiffens naturally and stimulates BNP production. Women without CHF tend to have somewhat higher BNP levels than do men of the same age group. Although the reason for this difference is unknown, it is speculated that diastolic dysfunction is more pronounced in women. There are no significant differences in BNP levels between normal patients with hypertension or diabetes and age-matched controls.

The New York Heart Association (NYHA) functional system of classification correlates well with symptoms and mortality in patients with heart failure, but it has many drawbacks. It is a subjective analysis, and many patients, including those with lung disease, arthritis, and peripheral vascular disease, cannot even be classified using NYHA criteria. These problems belie the fact that NYHA class remains the primary means to describe the clinical condition of patients with heart failure and underline the need for more objective surrogates. BNP levels correlate significantly with hemodynamic parameters such as right-atrial pressure, pulmonary capillary wedge pressure (PCWP), and LV end-diastolic pressure. Yasue and associates reported that BNP is secreted mainly from the left ventricle in response to the degree of LV dysfunction.[17] In addition, BNP is strongly induced during ventricular-wall tension or stretch. Because BNP levels correlate with elevated end-diastolic pressure, and end-diastolic pressure is linked closely with dyspnea, the chief symptom of CHF, it is not surprising that BNP levels correlate well with the NYHA classification scheme.

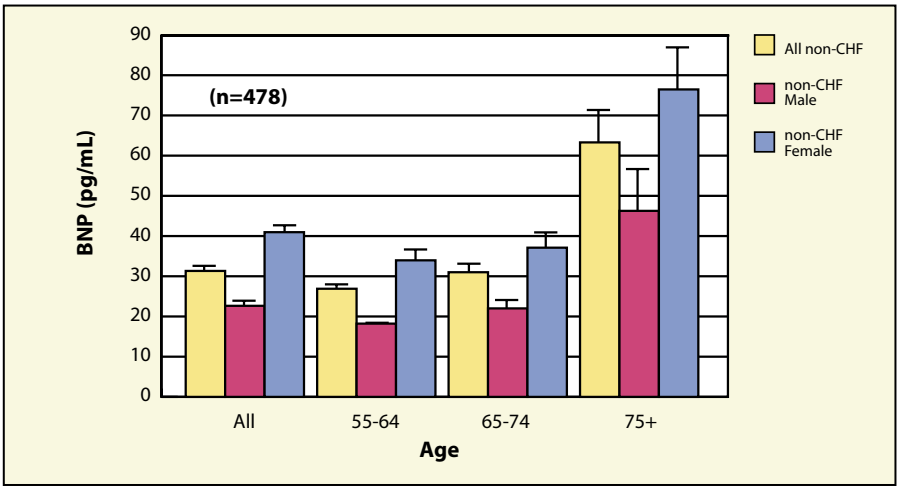
A misdiagnosis could place the patient at risk for both morbidity and mortality, especially if treatment is inappropriate.

The Clinical Challenge—Just-in-Time Evaluation of Dyspnea

In the urgent-care setting, it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea.[18] A misdiagnosis could place the patient at risk for both morbidity and mortality, especially if treatment is inappropriate. Sympathomimetic amines and β-agonists, for instance, can induce angina and arrhythmias in patients with dyspnea related to heart failure and create a confusing scenario in the emergency department (ED).[19]

Table 1 shows the degree of sensitivity and specificity of symptoms as they correspond to measurable predictors of CHF in a group of 250

Figure 2. *Levels of B-type natriuretic peptide (BNP) in patients without congestive heart failure (CHF). Women tend to have higher levels of the neurohormone than do men of the same age.*



patients reporting acute dyspnea in the ED.[20] A helpful history is often not obtainable in the acutely ill patient, and dyspnea can be nonspecific. The symptom may be observed in elderly or obese patients in whom comorbidities such as respiratory disease and physical deconditioning are common.[18] Physical signs, such as elevated jugular venous pressure, a third heart sound, pulmonary rales, and edema, are often absent in patients with CHF. Routine laboratory tests, electrocardiograms (ECGs), and chest films are also not diagnostically consistent.[5] A *dyspnea differentiation index,* comprising peak expiratory flow and partial pressure of arterial oxygen, has been used to diagnose the cause of dyspnea correctly in 72% of patients studied, but its availability is limited.[21] Routine lab values, ECG, and x-rays are also not accurate enough to always make the appropriate diagnosis. All of these factors contribute to clinicians' difficulty in differentiating CHF from other diseases, such as pulmonary disease.

BNP is stable in whole blood, and a portable 15-minute assay, the Triage® BNP Test (Biosite Incorporated, San Diego, CA), has been approved by the US Food and Drug Administration (USFDA). It has an analytical range of 5 to 5000 pg/mL and a coefficient of variation of approximately 15%.[22] Since the assay is designed for point of care, it can be used in clinical settings such as the ED, the intensive care unit, and the primary care or cardiology office. Point-of-care–testing (POCT) immunoassays for cardiac markers can now identify patients with ischemia, infarction, and CHF more quickly than can standard, laboratory-based platforms.[23-24] The rapid BNP immunoassay has all the features of the ideal POCT tool for detecting CHF in patients who present with dyspnea—especially in the critical-care setting. Davis and colleagues measured levels of ANP and BNP in 52 patients presenting with acute dyspnea and compared those values with LV ejection fraction.[25] They found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection-fraction levels or ANP plasma concentrations. Very importantly, elevations in BNP can pick up concomitant diastolic dysfunction, which is common in the elderly population with pulmonary disease.[26-27]

Elevated BNP Levels That Do Not Represent CHF

The range from 100 to 500 pg/mL represents levels of BNP attributable to causes other than CHF.[28] These causes are listed in Table 2. Patients presenting with noncardiac dyspnea may still have underlying LV dysfunction. BNP levels are often greater than 100 in these patients, but if the cause of dyspnea is something other than acute exacerbation, levels are usually under 500 pg/mL.[29] Morrison and colleagues were recently able to show that rapid testing of BNP could help differentiate pulmonary from cardiac etiologies of dyspnea.[29] In a substudy of the Breathing Not Properly study, of 417 subjects with a history of asthma or chronic obstructive pulmonary disease without a history of CHF, 21% (87 patients) were found to have newly discovered CHF, as adjudicated by cardiologists blinded to BNP results.[30] Only 37% of these 87 patients were identified by ED physicians (also blinded to BNP results), whereas a BNP greater than 100 pg/mL identified 93%.

Some types of pulmonary disease, such as cor pulmonale, lung cancer, and pulmonary embolism, are associated with elevated BNP levels, but not generally to the same extent as those in patients with acute LV dysfunction. Thus, clinical judgment

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Table 1
Accuracy of History and Physical Findings in Diagnosing Congestive Heart Failure

Variable	Sensitivity, %	Specificity, %	Accuracy, %
Hx of HF	62	94	80
Dyspnea	56	53	54
Orthopnea	47	88	72
Rales	56	80	70
S3	20	99	66
JVD	39	94	72
Edema	67	68	68

Hx, history; HF, heart failure; JVD, jugular venous distention.

Table 2
Factors That Can Account for High BNP Levels in Patients Presenting with Dyspnea

Age
Renal failure (creatinine clearance < 60 mL/min/1.73 m^2) or on dialysis
Myocardial infarction
Acute coronary syndrome
Lung disease with right-sided failure
Acute pulmonary embolism
Sepsis
Baseline left-ventricular dysfunction

needs to be used in these cases. Patients often present with both pulmonary and cardiac disease, as one often causes the other, again calling for clinical acumen and further tests. Nagaya and associates measured hemodynamics and BNP levels in 44 patients with right-ventricular (RV) overload from pulmonary hypertension.[31] The mean BNP level in this population was 294 pg/mL. BNP level correlated with indices of pulmonary-artery and RV end-diastolic pressures, as well as with long-term changes in hemodynamics. Thus, the positive predictive value of BNP might decrease at values between 80 to 300 pg/mL in patients with possible RV involvement. Finally, a pulmonary embolism large enough to raise pulmonary-artery pressure due to RV strain can raise BNP levels. BNP appears to be highly prognostic in these patients.[32] If all of the above can be ruled out, it is highly likely that BNP levels between 100 and 500 pg/mL represent CHF (Figure 3).

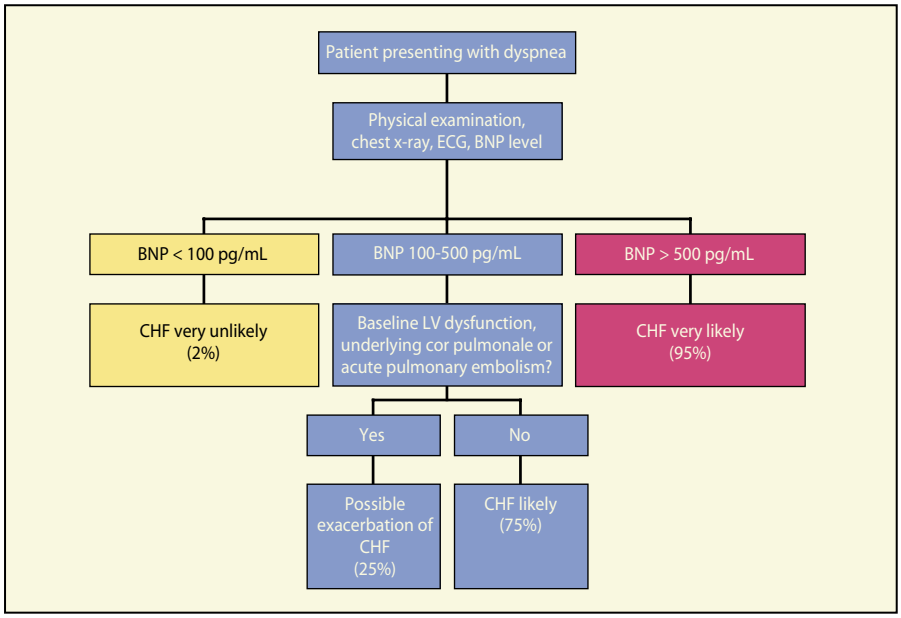
Monitoring Patient Therapy with BNP Levels

Though not yet a USFDA-approved indication, BNP testing may someday be useful in monitoring patients, both in the hospital and in the outpatient clinic. There is certainly precedent for targeted treatment of disease. Treatment of hypertension is targeted to blood pressure, diabetes to blood sugar, and hypercholesterolemia to cholesterol levels. The fact that BNP has a short half-life and easy-to-measure levels and is an indicator of wedge pressure volume, NYHA class, and prognosis suggests its usefulness as a guide for heart-failure therapy.

Hospitalized patients

Cheng and associates followed the course of 72 patients admitted to the hospital with compensated NYHA class III to IV CHF and measured BNP levels daily.[33] Twenty-two patients either died[13] or were readmitted.[8] In these 22 patients, BNP levels increased during hospitalization (mean increase 232 pg/mL, $P < .001$). Patients were treated in standard fashion with diuretics and vasodilators. Outcomes were positive for patients whose NYHA class and BNP levels declined during hospitalization. Patients who were readmitted within 30 days of discharge had had only minimal reductions in their BNP levels during their initial stay, despite improvement in NYHA classification. The BNP levels of patients who ultimately died in the hospital continued to increase, and little change was noted in their symptoms. With appropriate treatment, however, patients whose discharge BNP levels fell below 430 pg/mL had a reasonable likelihood

Figure 3. *A clinically validated diagnosis algorithm used at the San Diego Veteran's Affairs Healthcare System. ECG, electrocardiogram; BNP, B-type natriuretic peptide; CHF, congestive heart failure; LV, left-ventricular.*



of not being readmitted within the following 30 days. These data were supported in a recent study by Bettencourt and colleagues, who found that failure of BNP levels to fall over the course of hospitalization predicted death or rehospitalization, and that discharge levels less than 250 pg/mL predicted event-free survival.[34]

While in a given patient BNP level does not always correlate with wedge pressure, in those admitted to the hospital with CHF and high filling pressures along with a high BNP level, a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP, as long as the patient is maintaining adequate urine output. Kazanegra and associates measured wedge pressure, hemodynamic measurements (PCWP, cardiac output, right-atrial pressure, systemic vascular resistance [SVR]), and BNP levels every 2 to 4 hours for the first 24 hours and every 4 hours for the next 24 to 48 hours in patients admitted for decompensated CHF.[35] PCWP dropped from 33 ± 2 to 25 ± 2 mm Hg over the first 24 hours, while BNP dropped from 1472 ± 156 to 670 ± 109 pg/mL.[35] The percent change in PCWP from baseline correlated significantly with the percent change of BNP from baseline ($r = 0.73$, $P < .05$), with an average BNP decline of 33 ± 5 pg/mL per hour. The correlations between BNP levels and other indices of cardiac function-cardiac output (thermodilution), mixed venous oxygen saturation, and SVR were not significant.

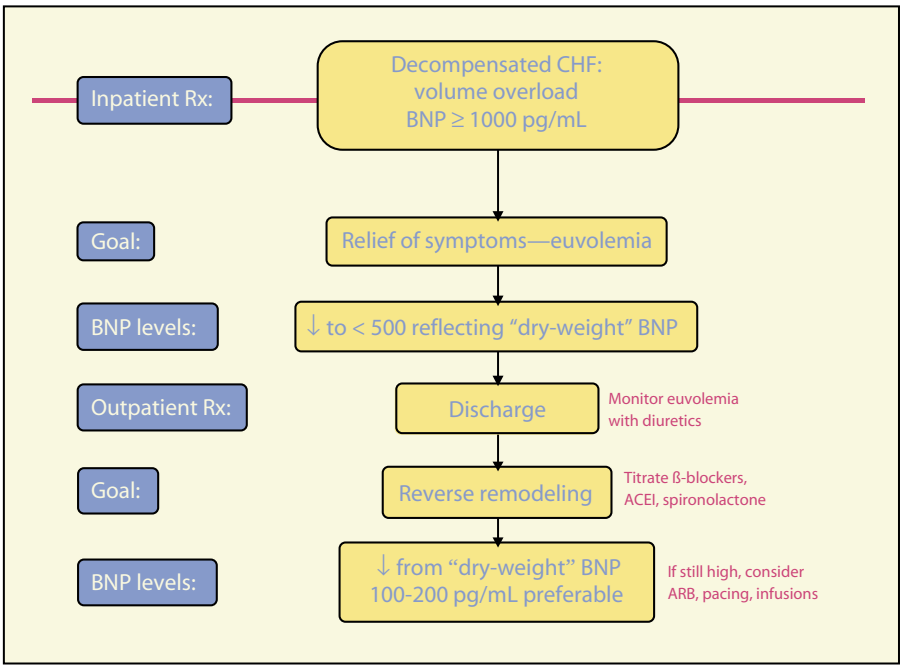


Figure 4. *Treatment algorithm for decompensated and compensated congestive heart failure (CHF) using B-type natriuretic peptide (BNP) levels. Rx, treatment; ACEI angiotensin-converting enzyme inhibitors; ARB, angiotensin II-receptor blocker.*

Wet and Dry BNP Levels

A treatment algorithm based on "wet" and "dry" BNP levels is presented in Figure 4. In patients who are admitted with volume overload, high SVR, and low cardiac output, diuretics and vasodilators are the first line of treatment. Achieving a euvolemic state is extremely important in these patients. Determining a dry-weight BNP level should help ensure that the patient is ready to go home. Table 3 differentiates wet BNP levels from dry BNP levels. Physicians have expressed frustration with the fact that, in some patients, high BNP levels do not fall with treatment. There are several explanations for this problem. First and foremost, the high BNP level may actually be their "dry" BNP level and will not be acutely lowered with diuretics or vasodilators. These patients tend to be NYHA class IV and have a poor prognosis. It is also possible that with parenteral diuretic treatment of a decompensated patient, a prerenal azotemic state is occurring. This situation will likely down-regulate BNP clearance receptors, and BNP levels will rise. In another common scenario, a patient with left and right heart failure, with massive ascites or edema, diureses many liters before BNP levels drop. This situation may occur because, rather than lowering wedge pressure, the urine output is taking place secondary to mobilization of third-space fluid. Continuing diuresis and/or vasodilatation should eventually lower BNP levels. Dry-weight euvolemic state must be evaluated in conjunction with other clinical and labora-

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tory features, listed in Table 4.

Preventing Decompensation in Outpatient Treatment

As stated earlier, the lower the patient's discharge dry-weight BNP level, the lower the risk of rehospitalization. This is because a low BNP level (<200—300 pg/mL) represents an NYHA II patient and one who is likely to have little extra volume. The patient's baseline dry-weight BNP level is likely to be important in monitoring him or her in the first 30 days after discharge. Figure 5 shows a hypothetical plot of dry BNP levels, NYHA class, and what happens when a patient decompensates.[36] At the point of decompensation, a patient's BNP level will be the sum of his or her baseline BNP plus what volume overload adds. Elevations of BNP over baseline soon after hospitalization may trigger the need for more vigorous diuresis, additional vasodilators, or outpatient infusions of nesiritide. Figure 6 illustrates the San Diego Veteran's Affairs Hospital practice.[36] When a patient comes to the ED with symptoms that could represent a decompensated state, a BNP level is drawn. If the level is no different from baseline values, decompensation is unlikely. The extent to which BNP level should be raised from baseline in order to characterize the patient as decompensated is not known. BNP is not a standalone test and should be used in conjunction with other examination features. In the authors' experience, clinical features of decompensation, along with a BNP-level, increase of 50% or more from baseline are often associated with decompensation.

Table 3
Wet versus Dry B-Type Natriuretic Peptide (BNP) Levels: Definition

Wet BNP level	Dry BNP level
• Anything significantly over the patient's dry weight BNP level	• BNP level once euvolemia is reached
• If patient comes to ED, often >500 pg/mL	• Correlated with functional class and prognosis
• Falls rapidly with treatment	• May be 20-2,000 pg/mL- depending on severity of disease
	• Falls slowly with treatment

ED, emergency department.

Measuring BNP levels in the ED might help not only triage patients (in the home, observation unit, hospital ward, or intensive care unit), but might also lead to appropriate treatment. A multicenter trial known as BNP: Rapid Emergency Department Heart failure Outpatient Trial (REDHOT) has been completed and is in the final stages of analysis. The primary objective of this trial is to determine the clinical utility of BNP point-of-care testing as an aid in the management of patients with CHF. Investigators are seeking to determine whether the assay allows physicians to assess effectiveness of therapy and whether it helps them to make more informed decisions related to the admission and discharge of their patients. In the future, an algorithm such as the one illustrated in Figure 7 might be used.

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Table 4
Achieving Dry-Weight (Euvolemic) B-Type Natriuretic Peptide (BNP) Levels

Too Little: Wet—Hypervolemia	Dry Weight Euvolemic (May Take a Long Time) Just Right	Too Much: Over-Shoot
BNP level still dropping	BNP levels off—some patients take longer than others	BNP levels off or continue to decrease, or increases
Signs of congestion	No signs of congestion	No signs of congestion; may be clinically dry
BP may be high or normal	BP normal	Orthostatic or frankly hypotensive
Improving renal function	Steady-state stabilization of renal function	Pre-renal
Warm and wet	Warm and dry	Cold and dry

BP, blood pressure.

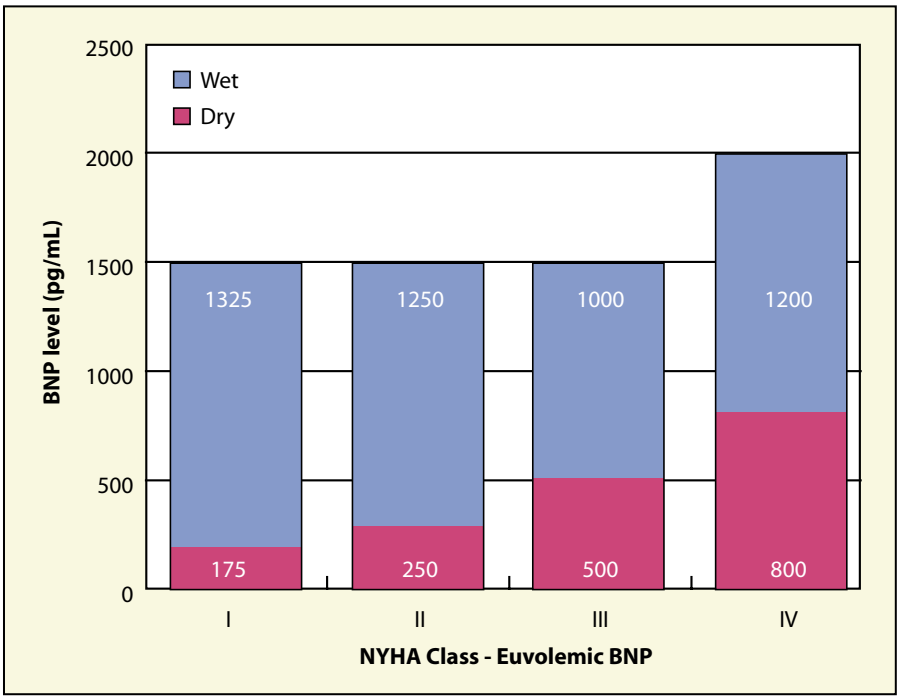


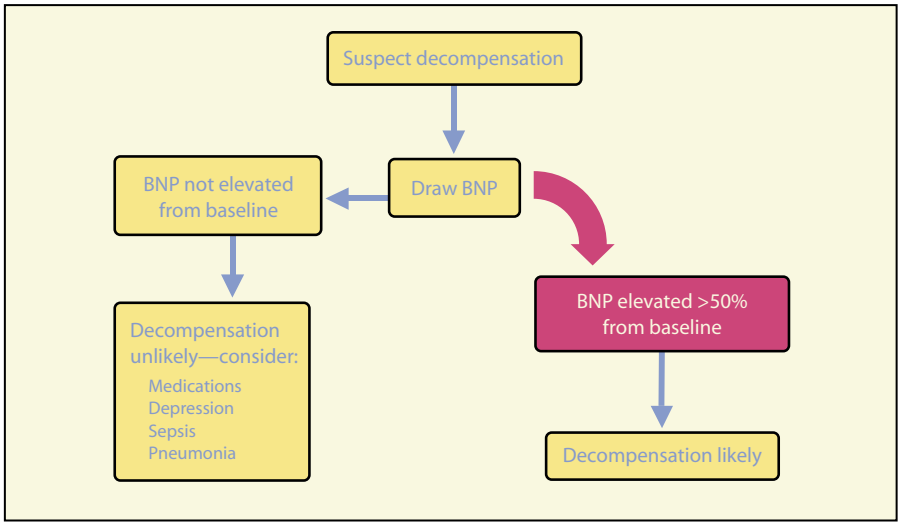
Figure 5. *Hypothetical plot of dry B-type natriuretic peptide (BNP) levels, New York Heart Association (NYHA) class, and what happens when a patient decompensates. In volume-overloaded patients, BNP level = baseline BNP (dry) + change from increased volume (wet).*

Determining Optimal Outpatient BNP Levels

Perhaps the best way to keep patients out of the hospital is by not allowing BNP to rise above discharge levels. This possibility will be tested in the multicenter Rapid Assessment of Bedside BNP In Treatment of heart failure (RABBIT) trial. A more important question may be whether there is an outpatient level of BNP for which we should aim. This number may be the "holy grail" for BNP testing. If an optimal BNP level can be determined, it may become the point of reference in titrating medications for all patients. It is evident that patients with poor ejection fractions but BNP levels under 200 pg/mL have a very good prognosis. A study of 452 ambulatory patients with LV ejection fractions less than 35% found that, in patients with mild to moderate CHF (NYHA class I/II), BNP levels were independent predictors of sudden death, an important cause of mortality in this population.[37] They found that a cutoff BNP level of approximately 130 pg/mL differentiated well between patients with high and low sudden-death rates. Only 1% (1 of 110) of those patients with BNP levels below the cutoff point died suddenly, in comparison with a sudden-death rate of 19% (43 of 227) among those patients with BNP levels above the cutoff point. Using BNP levels to identify a patient population with a higher risk of sudden death can help to tailor treatment and extend survival.

It also appears that angiotensin-converting enzyme (ACE) inhibitors, angiotensin II—receptor blockers, spironolactone, and perhaps β-blockers drive BNP levels down. Our current practice is to aim for BNP levels under 200 pg/mL with standard therapy of ACE inhibitors, β-blockers, and diuretics (Figure 4). Patients with BNP levels between 200 and 500 pg/mL are often NYHA class II to III and may require more diuretics, especially spironolactone. These theories will be tested in the RABBIT and BNP Assisted Treatment To LEssen Serial CARdiac REadmissions and Death (BATTLE-SCARRED) trials. Patients who despite standard medical treatment have advanced symptoms along with high BNP lev-

Figure 6. *B-type natriuretic peptide (BNP) levels help determine whether a patient has decompensated heart failure. Adapted with permission from Maisel.*[36]



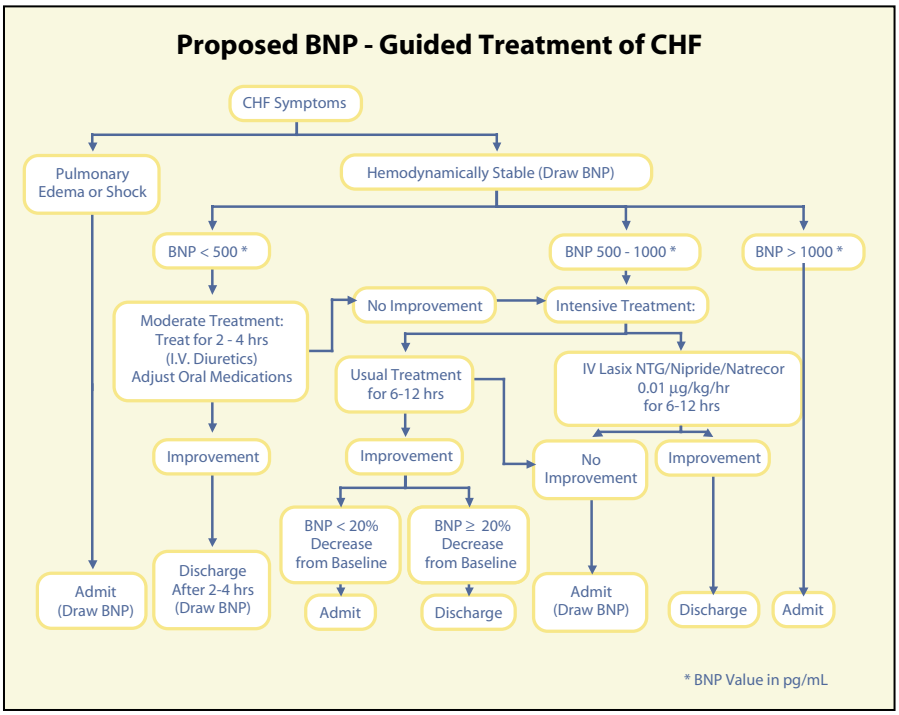


Figure 7. *Potential triage and treatment algorithm for B-type natriuretic peptide (BNP) levels in the emergency department. CHF, congestive heart failure; IV, intravenous; NTG, nitroglycerine.*

els (>400—600 pg/mL) might be candidates for outpatient infusions of inotropes or nesiritide, biventricular pacing (if QRS >120—130 msec), cardiac transplantation, assist device, or even gene therapy.

Conclusion

BNP, which is synthesized in the cardiac ventricles and correlates with LV pressure, amount of dyspnea, and the state of neurohormonal modulation, promises to be of immense help to physicians in their evaluation of patients presenting in the ED with dyspnea. While not a stand-alone test, the BNP assay clearly adds valuable information for the diagnosing ED physician. The cause of high plasma BNP levels needs to be determined; normal or low BNP levels have excellent negative predictive value for CHF and may obviate the need for further, more costly studies. Because BNP levels not only fall rapidly with effective treatment, but have prognostic value as well, it is likely that future algorithms incorporating BNP levels and other clinical indicators will become available to guide critical-care physicians in making management decisions for their CHF patients. ■

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Main Points

- Dyspnea is the chief symptom of congestive heart failure (CHF), but in the critical-care setting, it is often difficult to differentiate cardiac from pulmonary causes of this symptom.
- B-type natriuretic peptide (BNP) levels have been shown to help accurately differentiate CHF from pulmonary conditions, such as asthma and chronic obstructive pulmonary disease, in patients presenting with dyspnea.
- A number of studies have demonstrated the prognostic value of BNP test results; BNP level can help determine the likelihood of outcomes such as decompensation, rehospitalization, or sudden death.
- BNP may also allow physicians to assess the effectiveness of therapy and make more informed decisions regarding treatment of their CHF patients.

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