CLINICAL REVIEW

B-type Natriuretic Peptide: A Review of Its Diagnostic, Prognostic, and Therapeutic Monitoring Value in Heart Failure for Primary Care Physicians

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Background: **Congestive heart failure is misdiagnosed clinically 50% to 75% of the time. B-type natriuretic peptide (BNP) concentrations have shown to be useful in the diagnosis of heart failure in addition to having prognostic and therapeutic monitoring value. Studies were evaluated for validity and potential value of BNP measurements for managing patients with heart failure.**

Methods: **A literature review using MEDLINE (1966 to present), CINAHL (1980 to present) and Evidence-Based Medicine Reviews was performed with the following key words: "cardiac neurohormone," "B-type natriuretic peptide," "congestive heart failure," and combination of the key terms.**

Results and Conclusions: **A BNP level of 80 pg/mL is useful in diagnosing heart failure in symptomatic patients without a history of heart failure. BNP is not specific for any disease state, however, especially in patients with a history of heart failure or left ventricular dysfunction. BNP levels are potentially more useful when a baseline concentration is known for a patient, because BNP levels are proportional to the severity of heart failure. The role of BNP as a prognostic marker and for therapeutic monitoring is closely related. Whereas larger studies are needed to support further recommendations, a goal to maintain a BNP concentration of less than 100 pg/mL has shown to correlate with functional improvement in patients with heart failure and has tended to decrease clinical endpoints, such as cardiovascular death. Consequently, using BNP concentrations to monitor patients with heart failure and manage their medical therapy accordingly might improve overall morbidity and mortality. (J Am Board Fam Pract 2003;16:327–33.)**

There are approximately 500,000 new cases of heart failure in the United States each year, with a current census of nearly 5 million Americans with congestive heart failure.[1] The Centers for Medicare and Medicaid Services has selected heart failure as one of the diseases most worthy of cost-effective management.[2] Heart failure accounts for approximately 3% of the health care budget and is the leading cause of hospitalization for patients older than 65 years.[3]

Primary care physicians manage and treat congestive heart failure in a substantial number of patients and are frequently the first to diagnose heart failure. Many diagnostic and therapeutic advances have been developed in the past 20 years, decreasing the morbidity and mortality of heart failure. Recently, there has been great interest in the use of cardiac neurohormone levels, especially B-type natriuretic peptide (BNP), for the management of left ventricular dysfunction, whether for diagnostic, prognostic, or therapeutic monitoring purposes.

B-type natriuretic peptide is a cardiac neurohormone secreted from the ventricles in response to volume expansion and pressure overload.[4] Natriuretic peptides, in general, have a natriuretic and vasodilatory effect and suppress the renin-angiotensin-aldosterone system.[5] BNP is a 32 amino acid polypeptide containing a 17 amino acid ring structure common to all natriuretic peptides.[6] The BNP gene contains the destabilizing sequence "tatttat," suggesting the turnover of BNP messenger RNA is high and that BNP is synthesized in bursts directly proportional to ventricular expansion and pressure overload.[7] It has been found to be a highly sensitive and specific marker for left ventricular dysfunction.[8]

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Table 1. Comparing the Validity of Studies Using B-Type Natriuretic Peptide (BNP) to Diagnose Heart Failure.

1. Was there an independent, blind comparison with a reference standard of diagnosis?	
Cowie et al, 1995–1996[13]	May be assumed while blindness was not explicitly stated
Dao et al, 1999[11]	Yes
Maisel et al, 1999–2000[12]	Yes
Morrison et al, 1999–2000[15]	Yes
2. Was the diagnostic test (BNP level) evaluated in a appropriate spectrum of patients (ie, NYHA class I–IV)?	
Cowie et al, 1995–1996[13]	Yes
Dao et al, 1999[11]	Yes
Maisel et al, 1999–2000[12]	Yes
Morrison et al, 1999–2000[15]	Yes
3. Was the reference standard applied (ie, echocardiogram) regardless of the diagnostic test result?	
Cowie et al, 1995–1996[13]	Yes
Dao et al, 1999[11]	Yes
Maisel et al, 1999–2000[12]	Yes
Morrison et al, 1999–2000[15]	Yes
4. Was the test validated in a second independent group of patients?	
Cowie et al, 1995–1996[13]	No
Dao et al, 1999[11]	No
Maisel et al, 1999–2000[12]	Yes*
Morrison et al, 1999–2000[15]	No

Adapted from *Evidence-Based Medicine: How to Practice and Teach EBM*, by Sacket DL et al, 2nd edition; Churchill Livingston, 2000.
*The study by Dao et al may be considered as a second group by some authors.

The purpose of this review is to evaluate the potential use of BNP levels for primary care physicians in both outpatient care and urgent care settings for the management of congestive heart failure, including its role as a diagnostic, prognostic, and therapeutic monitoring tool.

Methods

A literature review was performed using Ovid, accessing the following databases: MEDLINE (1966 to present), CINAHL (1986 to present), and Evidence Based Medicine Reviews (including Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, ACP Journal, and Database of Abstracts of Reviews of Effectiveness). Key search terms included, "cardiac neurohormone," "B-type natriuretic peptide," "congestive heart failure," "heart failure," "diagnosis," "prognosis," "treatment," and combination of the key terms. The articles were preferentially selected using the following criteria:

1. They reported randomized, blinded, controlled studies and well-designed cohort studies.
2. They included a standard reference, such as echocardiography, to diagnose heart failure.
3. Diagnostic tests were evaluated in a spectrum of patients with heart failure, ie, New York Heart Association heart failure class I, II, III, and IV. Outcome data were available, such as: sensitivity, specificity, or receiver-operating curve data.

Results

B-Type Natriuretic Peptide and the Diagnosis of Heart Failure

The diagnosis of heart failure is difficult and commonly misdiagnosed. The symptoms are nonspecific, and clinical signs, although specific, are not sensitive.[9] A study by Hlatky et al[10] showed that even experienced physicians disagree on the diagnosis in individual cases, especially mild heart failure. Only 25 to 50 percent of patients with a primary care diagnosis of heart failure had evidence of this disease after further cardiac assessment.[9] Several studies have found strong evidence that BNP is both sensitive and specific for heart failure.[11–13] In a single center study by Yamamoto et al,[14] BNP was found to be the single best marker of left ventricular systolic dysfunction, left ventricular diastolic dysfunction, and left ventricular hypertrophy compared with two other cardiac neurohormones, C-atrial natriuretic peptide and N-atrial natriuretic peptide. The validity and quality of each study is listed in Table 1, and the findings of the following studies are in Table 2.

Three well-designed studies found a BNP level of 80 pg/mL to have sensitivities ranging from 93% to 98% in diagnosing heart failure in symptomatic patients, and negative predictive values ranging from 92% to 98%, demonstrating BNP ability to

Table 2. List of Findings in Studies Using B-Type Natriuretic Peptide to Diagnose Heart Failure.

	N	BNP value pg/mL	Sensitivity %	Specificity %	+LR	PPV %	NPV %	AUC
Cowie et al, 1995–1996[13]	122	76	97	84	6.1	70	98	0.96
Dao et al, 1999[11]	250	80	98	92	12.3	90	98	0.98
Maisel et al, 1999–2000[12]	1586	80	93	74	3.6	77	92	0.91
Morrison et al, 1999–2000[15]	321	94	86	98	43.0	98	83	0.97

N = study population; BNP = B-type natriuretic peptide; +LR = positive likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve for receiver-operator curves.

rule out congestive heart failure.[11–13] Morrison et al[15] found a BNP level of 94 pg/mL to have a sensitivity of 86% to differentiate dyspnea caused by heart failure from pulmonary causes. A community-based prospective cohort in the Framingham Heart Study, however, attempted to determine the usefulness of BNP levels in screening for left ventricular hypertrophy and systolic dysfunction in asymptomatic patients.[16] The authors found that adding BNP to other clinical variables, such as age and hypertension, minimally contributed to diagnosing elevated left ventricular mass and systolic dysfunction, thus the usefulness of BNP measurements as a mass screening tool remains uncertain. Nonetheless, among patients who complain of symptoms such as dyspnea, a BNP determination was more accurate at diagnosing heart failure than a medical history of congestive heart failure, radiologic findings, and signs and symptoms of congestive heart failure.[11] In addition, BNP levels were found to be proportional to the New York Heart Association class as shown in Table 3.[12]

Whereas BNP has been found to be useful in diagnosing symptomatic heart failure, certain results should be interpreted with caution. For example, the mean BNP concentration in patients with congestive heart failure was markedly different in two of the studies: 1076 ± 138 pg/dL in the study by Dao et al[11] compared with 675 ± 450 pg/dL in the study by Maisel et al.[12] More importantly, patients with left ventricular dysfunction, but not congestive heart failure, were found to have BNP levels of 141 ± 31 pg/dL by Dao et al compared with 348 ± 390 pg/mL by Maisel et al, both considerably higher than the BNP cutoff (80 pg/mL) used to suggest congestive heart failure. This finding shows that moderate elevations of BNP are sensitive for left ventricular dysfunction but not necessarily specific for any disease state. Elevated levels can be attributable to other causes, such as myocardial infarction, ventricular hypertrophy, cardiomyopathy, tuberculosis, lung cancer, pulmonary embolism, renal failure, and chronic obstructive pulmonary disease.[15,17]

Table 3. B-Type Natriuretic Peptide (BNP) Levels Among Patients in Each New York Heart Association (NYHA) Classification.

NYHA Classification Level	Mean BNP Level pg/mL ± SD
I	244 ± 286
II	389 ± 374
III	640 ± 447
IV	817 ± 435

SD = standard deviation.

B-Type Natriuretic Peptide: Prognostic in Heart Failure?

Congestive heart failure constitutes one of the major causes of morbidity and mortality in the United States. Among the many lifestyle modifications and pharmacotherapy available to control symptoms of heart failure, heart transplantation is another important option for patients with refractory heart failure. Although primary care physicians refer patients to specialists to determine whether the patient is a candidate for heart transplantation, knowledge of the patient's prognosis guides physicians' therapy and aggressiveness while patients wait on transplant lists.

Many patients hospitalized with acute exacerbations of heart failure are cared for by primary care physicians after discharge. Although some patients avoid rehospitalization within the next 6 months, others are prone to multiple hospital admissions. Recently, BNP determinations have shown the potential to be a good prognostic marker for morbid-

Table 4. Comparing the Validity of Studies Evaluating the Prognostic Value of B-Type Natriuretic Peptide (BNP) in Heart Failure.

1. Was a defined, representative sample of patients assembled at a common point in the course of the disease?†	
Harrison et al, 1999–2000[18]	No, patients admitted to an emergency center with an dyspnea (acute) were recruited for the study
Koglin et al, 1999[19]	Yes, all patients had chronic heart failure and were included after optimization of medical therapy
2. Was follow-up sufficiently long and complete?	
Harrison et al, 1999–2000[18]	Borderline, follow-up was at 6 months.
Koglin et al, 1999[19]	Yes, the mean follow-up period was 398 days.
3. Were objective outcome criteria applied in a blind fashion?	
Harrison et al, 1999–2000[18]	Yes
Koglin et al, 1999[19]	Yes

Adapted from *Evidence-Based Medicine: How to Practice and Teach EBM* by Sacket DL et al, 2nd edition; Churchhill Livingston, 2000.
†Range of the severity of heart failure was accepted for the prognostic interpretation of a laboratory test, such as BNP.

ity and mortality in patients with heart failure, including predicting future cardiac event in patients with acute exacerbations.[18,19] The validity and quality of the following studies are presented in Table 4.

One prospective study found that an initial BNP concentration of 480 pg/mL had a sensitivity of 68%, specificity of 88%, and an accuracy of 85% of predicting a congestive heart failure endpoint (death, hospital admissions, and repeated emergency department visits) after a 6-month follow-up period after hospital discharge.[18] Patients with BNP levels greater than 480 pg/mL had a 51%, 6-month cumulative probability of a heart failure event (35% of these patients had death from heart failure as their event), whereas BNP levels of less than 250 pg/mL had a much better prognosis, with only a 2.5% cumulative probability of a heart failure event. The authors reported that increased BNP levels were associated with progressively worse prognosis.

Another well-designed study compared BNP levels with the patient's heart failure survival score (HFSS), a recognized and accepted tool in determining a patient's prognosis.[19] Patients were classified into three different prognostic groups based on the HFSS score: low risk, medium risk, or high risk. There were significant differences in each group. The mean BNP concentration for the low-risk group was 95.7 ± 11.2 pg/mL, for the medium-risk group was 244.4 ± 33.4 pg/mL, and for the high-risk group was 419.9 ± 55.5 pg/mL. More importantly, the authors were able to show that higher BNP levels were associated with a change in cardiovascular functional class with time. The initial BNP level in patients who improved during the ensuing 12 months had a BNP concentration of 42.4 ± 8.6 pg/mL, those who remained stable had a BNP level of 102.2 ± 16.1 pg/mL, and those who deteriorated during the ensuing 12 months had a BNP level of 256.9 ± 28.5 pg/mL.

B-Type Natriuretic Peptide and Therapeutic Monitoring of Heart Failure

Primary care physicians have the task of managing patients with congestive heart failure. An important aspect of patient management is the ability to monitor the therapeutic efficacy of the patient's pharmacological regimen. BNP levels have been found to follow ventricular function in response to medical management.[20,21]

One study evaluated left ventricular volume and mass, including neurohormone levels, in patients with mild to moderate nonischemic congestive heart failure before and after 4 months of treatment with spironolactone or placebo.[20] Patients who received a fixed 25-mg dose of spironolactone had a change in their mean BNP concentration from 200 ± 66 pg/mL at baseline to 89.7 ± 27 pg/mL at 4 months ($P < .01$), whereas the control group showed no significant change.

Another study managed to show that BNP-guided treatment of heart failure reduced total cardiovascular events and delayed time to first event compared with intensive clinically guided treatment.[21] The BNP concentration decreased 79 pmol/L in the BNP-guided group compared with 3 pmol/L in the clinically-guided group. More importantly, the primary combined clinical endpoint (cardiovascular death, hospital admission, and outpatient heart failure) was significantly reduced in the BNP-guided group ($P < .02$). This significance increased when covariates were accounted for (baseline left ventricular ejection fraction, baseline BNP, and medication dosages, New York Heart Association heart failure class, and systolic blood pressure) in the regression model ($P < .001$). The authors suggested that BNP-guided treatment represents a preventive strategy targeting more intensive pharmacotherapy and follow-up for patients with elevated circulating BNP levels who are at high risk of cardiovascular events.

Although both studies describe an important use of BNP, the small study sizes should raise caution when applying these findings to clinical practice.

Discussion

Although major advances in the pathophysiology, diagnosis, and treatment of congestive heart failure have occurred in recent years, the syndrome still remains a clinical challenge. A team of physicians and allied health colleagues manages most patients with congestive heart failure. Primary care physicians remain one of the key components in the multidisciplinary approach of managing congestive heart failure. Although a thorough history and physical examination remain the basis in the management of these patients, other modalities that can assist in the diagnosis, risk stratification, and therapeutic monitoring might be highly beneficial, especially when resources are limited, such as echocardiography. BNP is becoming a well-accepted adjunct in the management of congestive heart failure.

We created initial recommendations for the clinical use of BNP, which are summarized in Table 5. For diagnostic purposes, we found that BNP determinations are useful in a limited number of clinical scenarios. As Vasan et al have recently reported, BNP has a limited role for mass screening for left ventricular hypertrophy and systolic dysfunction in asymptomatic patients.[16] In symptomatic patients with no history of left ventricular dysfunction or heart failure, a BNP level of more than 80 pg/mL is both sensitive and specific for an acute exacerbation of heart failure. BNP determinations lose sensitivity and specificity, however, in patients with acute symptoms who have a history of left ventricular dysfunction or heart failure.

Because BNP levels have shown to be proportional to cardiovascular functional class,[12] the elevated BNP level might represent only an individual patient's baseline rather than any disease state, such as an acute exacerbation. For patients who have BNP levels regularly monitored, however, such as diabetic patients who have glycosylated hemoglobins monitored, a BNP result above baseline can add to the clinical decision-making process. Nonetheless, the higher the level above the baseline, the more predictive BNP becomes, because moderate increases might represent only a progressive decrease in functional status or laboratory error.

Physicians may also interpret BNP levels based on the patient's functional status as determined by history, although caution is advised. As displayed in Table 3, those with New York Heart Association class III heart failure would have an approximate BNP level of 640 ± 447 pg/mL. Unfortunately, the wide standard deviation limits the practical use of BNP measurements. Additionally, Masiel et al[12] recommended increasing from 80 pg/mL to 100 pg/mL the BNP level used to diagnose heart failure in symptomatic patients. We found, however, that doing so would only increase the positive likelihood ratio from 3.57 to 3.75, while potentially increasing the number of false-positive results. We were therefore not compelled to increase the BNP level to 100 pg/mL.

The prognostic use, as well as the therapeutic monitoring value, of BNP measurements looks promising. For patients who are hospitalized with congestive heart failure, we recommend measuring BNP in patients with known or unknown BNP baselines. BNP levels greater than 500 pg/mL have a grave prognosis compared with levels less than 100 pg/mL. Because higher levels are proportional to worsening prognosis, physicians might be more aggressive with the patient management. Koglin et al showed that patients with BNP levels of 100 pg/mL or lower either improved or remained stable,[19] so that 100 pg/mL might be a potential goal for outpatient therapy and hospitalized patients with newly diagnosed congestive heart failure. It could be presumed this goal is less applicable for those patients with advanced or irreversible heart failure with baseline BNP levels well above 100 pg/mL. To monitor therapy by serial BNP levels only, however, requires observing a downward trend to show therapeutic efficacy. Additionally, using a BNP level of 200 pg/mL as an indicator to intensify or modify treatment has been found to reduce clinical endpoints, such as cardiovascular death, hospital admission, and outpatient heart failure. Whether attaining a BNP level of 100 pg/mL further decreases clinical endpoints needs to be determined by large randomized control trials.

Finally, a limited number of articles addressed other causes of elevated BNP levels. As mentioned

Table 5. Recommended Clinical Use of B-Type Natriuretic Peptide (BNP) and Congestive Heart Failure.

Clinical Scenario	BNP Level	Recommendation
*Diagnostic uses of BNP**		
Screening asymptomatic patients for left ventricular dysfunction and heart failure	Not available	No evidence supports use of BNP for mass screening
Acute symptoms without a history of left ventricular dysfunction or CHF	>80 pg/mL	Suggestive of an acute exacerbation of CHF
Acute symptoms with history of left ventricular dysfunction	>80 pg/mL–<200 pg/mL	Limited diagnostic value
Without known BNP baseline	>200 pg/mL	Limited diagnostic value but possible acute exacerbation of CHF
		Correlate with New York Heart Association classification (Table 3)
With known BNP baseline		Increase of BNP >2–3 times baseline suggests acute exacerbation of CHF. Mild to moderate increases can suggest natural progression of CHF or other causes
Prognostic utility or therapeutic monitoring value of BNP		
Hospitalized patient		
Without known BNP baseline	Consider observing a downward trend of BNP before discharge	
With known BNP baseline	Consider observing a downward trend of BNP before discharge or attempt to bring BNP level back to patient's baseline	
Outpatient		
Left ventricular dysfunction CHF, well controlled	Goal: <100 pg/mL	Consider aggressive management based on BNP level. Adjust therapy when BNP >200 pg/mL. Consider monitoring effects of therapy by BNP levels.
Left ventricular dysfunction, CHF poorly controlled or deteriorating	Maintain baseline BNP	Monitor effects of therapy by BNP levels. Limited diagnostic value otherwise
Conditions affecting BNP levels	*Cause*	
Cardiovascular	Myocardial infarction Cardiomyopathy Ventricular hypertrophy	
Pulmonary	Pulmonary embolism COPD Lung cancer	
Infectious	Tuberculosis	
Renal	Renal failure	

CHF—congestive heart failure, COPD—chronic obstructive pulmonary disease.
*Include thorough history and physical examination. Consider other causes of elevated BNP based on clinical signs and symptoms (dyspnea, chest pain, peripheral edema, paroxysmal nocturnal dyspnea, dyspnea with exertion, dry cough, etc).

earlier, various disease states, such as tuberculosis, lung cancer, and acute pulmonary embolism, need to be ruled out,[15] reinforcing the importance of a thorough history and meticulous physical examination so that the physician can create a complete medical picture.

Conclusion

Although further studies are needed to modify our initial clinical guidelines for using BNP as an indicator of congestive heart failure, BNP currently has a role once physicians understand its strengths and weaknesses. No laboratory test should be a replacement of a thorough history and physical examination, including referring patients to specialists.

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