Reviews

B-Type Natriuretic Peptide Measurement in Heart Failure

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Summary

Serum testing for the hormone B-type natriuretic peptide (BNP) may have clinical utility in congestive heart failure (CHF). This hormone is secreted predominantly by the left ventricular myocardium in patients with CHF. Measurement of serum BNP may improve diagnosis of CHF and may also help guide therapy in patients with CHF. The literature regarding the clinical utility of BNP measurement in CHF is reviewed.

Key words: natriuretic, heart failure, B-type natriuretic peptide, diagnosis, prognosis

Introduction

The syndrome of chronic heart failure (CHF) frequently presents with symptoms and physical signs that suffer from poor diagnostic and prognostic reliability (Table I).^{1–6} Emerging data on serum measurement of B-type natriuretic peptide (BNP), a hormone secreted mainly by the left ventricular (LV) myocardium in CHF, show promise that it may be an important aid to physicians in identifying patients with heart failure and defining outcomes. Levels of BNP may be used as a surrogate marker of decreased ventricular function and increased ventricular filling pressures^{7, 8} and compare favorably with other surrogate markers of CHF prognosis, such as plasma renin activity and serum norepinephrine.^{9–11} Levels also corre-

late with exercise capacity and peak oxygen consumption.¹² Initial studies revealed that BNP levels improve clinicians' ability to diagnose CHF in the emergency room and are important predictors of death or readmission following hospital discharge for CHF.^{13, 14} Other studies have shown improved outcomes in patients with CHF managed by BNP-guided therapy compared with those managed by history and physical examination.¹⁵ This paper reviews the basic physiology of BNP in the natural history of CHF, details the existing literature, and explains the various clinical settings in which BNP measurement may be used.

Physiology of B-Type Natriuretic Peptide

In 1956, Henry and Pearce inflated a balloon in a dog's left atrium and noted an increase in urine flow.¹⁶ This experiment first led to the hypothesis that the heart has endocrine function and that the natriuresis seen was caused by a yet to be identified hormone secreted by the atrium. In 1984, this hormone was identified as atrial natriuretic factor, later renamed A-type natriuretic peptide (ANP). This was soon joined by several other hormones of similar structure and function (Fig. 1).¹⁷ Of these, BNP (formerly known as brain natriuretic peptide because it was originally isolated from porcine brain) has recently received much attention. The continual release of BNP by the left ventricle in response to pressure and volume overload, in combination with its short plasma half-life of 12 to 22 min, makes it an attractive marker for aiding diagnosis and determining prognosis in CHF.^{18–22}

Because BNP levels are stable both in vivo and in drawn blood tubes, levels can be measured accurately with fewer logistical problems than other biochemical markers of CHF, such as norepinephrine or plasma renin activity.^{23–27}

B-type natriuretic peptide is synthesized in the myocardium as a pro-hormone, pro-BNP.²⁸ Cleavage of pro-BNP to the active hormone occurs in the blood, releasing an inactive byproduct, N-terminal BNP (N-BNP). Like BNP, N-BNP circulates in the plasma, and levels are predictive of LV function and prognosis.^{15, 29} In patients with more severe heart failure, N-BNP levels are higher than BNP levels.²⁸ For this reason, some investigators believe that N-BNP may be a more discerning marker for CHF than active BNP.^{15, 28, 29}

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TABLE I Descriptive power of physical examination and simple diagnostic tests for detection of decreased ejection fraction and increased wedge pressure

	Sensitivity (%)	Specificity (%)
Detection of ejection fraction <50%		
Rales, n = 14,507 (1)	11	73
Third heart sound, n = 14,507 (2)	9	97
Chest x-ray, n = 14,507 (2)	20	89
Electrocardiogram, n = 14,507 (2)	49	88
Physician assessment, n = 2,322 (3)	91	62
Detection of wedge pressure > 16		
Jugular venous distension, n = 52 (4)	55–81	74–80
Chest x-ray, n = 52 (5)	54	84
Physician assessment, n = 764 (3)	62	76

Numbers in parentheses are references.

The natriuretic peptides exert their effects via peptide receptors in kidney, heart, adrenal gland, and vascular endothelium.^{30,31} Binding of natriuretic peptides to their receptors activates G-proteins leading to the production of the second messenger cyclic guanosine monophosphate (c-GMP), which mediates most of the actions of these hormones.^{17,32} Since ANP and BNP both bind to the same receptor, they have similar actions. The effects of these two hormones are largely counterregulatory to the neurohormonal activation seen in CHF (Table II). They downregulate the renin-angiotensin-aldosterone system, causing decreased renin secretion from the renal juxta-glomerular apparatus.³³ They impair angiotensin

TABLE II Actions of B-type natriuretic peptide on the kidney, adrenal gland, and heart

B-type natriuretic peptide actions

Kidney

Inhibits renin production from the juxta-glomerular apparatus

Inhibits sodium reabsorption in the collecting duct

Afferent arteriolar vasodilation

Efferent arteriolar vasoconstriction

Adrenal gland

Inhibits aldosterone release

Heart

Decreased sympathetic nerve activity

II-mediated aldosterone release from the adrenal gland and decrease sympathetic nerve activity in the heart and kidney.^{34,35} Both ANP and BNP also improve renal blood flow via afferent arteriolar vasodilation and efferent arteriolar vasoconstriction.^{36,37} There is also a direct effect on the collecting duct, leading to increased sodium excretion.³⁸ C-type natriuretic peptide acts primarily through a different receptor and plays a little known role in CHF.³⁹ The natriuretic peptides are excreted via the kidney, degraded by tissue endopeptidases, and cleared from the circulation via clearance receptors, leading to their relatively short plasma half-lives.^{17,21,40}

Studies have consistently found that BNP synthesis is more abundant in LV myocardium in CHF, with ANP synthesis primarily in the atria.^{18–20} This may account for the fact that BNP levels correlate better with LV dysfunction and LV failure than ANP levels.^{41,42} Although there seems to be attenuation of the

FIG. 1 The biochemical structures of three known natriuretic peptides. ANP = A-type natriuretic peptide, CNP = C-type natriuretic peptide. Reprinted from Ref. No. 17 with permission.

TABLE III Conditions associated with increased serum levels of B-type natriuretic peptide

Causes of elevated B-type natriuretic peptide levels
Myocardial stretch
Systolic heart failure
Diastolic heart failure
Volume overload
Independent of left ventricular myocardial stretch
Ischemia
Arrhythmia
Hypertrophy
Pregnancy
Pulmonary embolus
Renal failure
Increased intracranial pressure
Older age
Female sex

natriuretic peptides' potency in late-stage CHF, exogenously administered human BNP in pharmacologic doses raises measured BNP levels three- to six-fold in CHF and has been shown to be effective in lowering filling pressures and relieving dyspnea.^{41, 43–46} The therapeutic utility of BNP has been reviewed elsewhere.^{47–49}

Levels of BNP may be elevated in diseases that are not purely related to LV myocardial stretch (Table III). Elevations in serum BNP have been described in arrhythmia, ischemia, hypertrophy, pregnancy, pulmonary emboli, pulmonary hypertension, renal failure, and raised intracranial pressures.^{50–56} Levels also increase with age and tend to be higher in females.^{57, 58}

Diagnosis of Chronic Heart Failure

The ability of BNP measurement to suggest CHF as the cause of dyspnea in the acute care setting was recently studied by Maisel *et al.* in the Breathing Not Properly trial.⁵⁹ This trial enrolled 1,586 consecutive patients presenting with shortness of breath in the emergency rooms of seven centers worldwide. Over one-third had a history of myocardial infarction and CHF, and over 40% had a history of obstructive pulmonary disease. The assay was compared with the consensus of two cardiologists blinded to the BNP results. These cardiologists were provided with all medical records, including chest x-rays, echocardiograms, data on hospital course, and catheterization reports. As found in earlier pilot studies, BNP levels were markedly elevated in CHF (675 ± 450 pg/ml), moderately elevated in those with a history of LV dysfunction and dyspnea of noncardiac etiology (346 ± 113 pg/ml), and mildly elevated in patients with dyspnea unrelated to CHF (110 ± 204 pg/ml). While these groups as a whole had significantly different BNP levels, there was a substantial amount of overlap, with many patients in all groups having moderately elevated

BNP levels. The study did show that a low BNP (< 50 pg/ml) had a 96% negative predictive value and that BNP level was the strongest predictor of CHF on multivariate analysis, adding considerable independent diagnostic information to that gained from history, physical examination, chest x-ray, and even emergency physician assessment.

Logeart *et al.* examined the predictive value of serum BNP in emergency room patients with acute dyspnea compared with hemodynamic evaluation by echocardiography.⁶⁰ They found that BNP levels had a positive predictive value of 94% for CHF when levels were > 300 pg/ml, with a negative predictive value of 93% when levels were < 80 pg/ml; BNP levels between 80 and 300 pg/ml had poor predictive value. Intermediate levels were found in almost 40% of patients studied. Further, BNP levels were not markedly elevated in rapid onset "flash" pulmonary edema and were quite high in patients with severe pulmonary embolic disease. They concluded that BNP measurement can be useful if interpreted within a diagnostic algorithm (Fig. 2).

Prognosis

The prognostic implications of elevated BNP levels in CHF have been studied thoroughly.^{14, 42, 61–65} Harrison *et al.* reported on a cohort of 325 emergency room patients with dyspnea, showing that an initial BNP level > 480 pg/ml had a high discriminatory power to predict all-cause 6-month mortality.⁶⁶ Koglin *et al.* also examined the relation of BNP levels with survival and showed that levels correlated strongly with heart failure survival scores (a well-validated prediction model for CHF survival).⁶⁷ They also showed that changes in BNP level were related to limitations in physical activity. These studies

Fig. 2 Algorithm for using B-type natriuretic peptide (BNP) measurement in the evaluation of acute dyspnea. ECG = electrocardiogram, CHF = chronic heart failure. Adapted from Ref. No. 60.

support earlier findings of Tsutamoto *et al.*, who showed that patients who died during the first year after hospitalization for CHF had markedly higher BNP levels, and that the ability of BNP to predict adverse outcomes compared favorably with known prognostic indicators such as norepinephrine level, wedge pressure, and LV function.⁴¹

The utility of serial BNP measurement for defining prognosis was tested by Cheng *et al.*¹⁴ They followed 72 patients admitted with CHF with serial measurements of BNP and looked at a primary endpoint of death or 30-day readmission. There was a mean New York Heart Association (NYHA) class of 3.6 on admission, and 42% were placed on intravenous inotropic therapy. The authors found that patients who died or were readmitted had BNP levels which rose, whereas patients who did not had BNP levels which fell or remained unchanged. Changes in BNP levels over time closely correlated with changes in wedge pressure.⁸ The authors concluded that BNP levels were accurate in predicting which patients would suffer adverse outcomes after discharge. They also showed that BNP level compared favorably with NYHA class, a known predictor of outcomes in CHF. The authors did not include the outcomes of individual patients in the study, and it is possible that some individuals who displayed marked decreases in BNP did not subsequently fare well.

The Role of B-Type Natriuretic Peptide Measurement in Chronic Heart Failure

Measurement of BNP can be used to screen for ventricular dysfunction in asymptomatic patients at risk for CHF.^{7, 68, 69} It is known from the Studies Of Left Ventricular Dysfunction (SOLVD) prevention study that individuals with asymptomatic LV systolic dysfunction had a 16% mortality during 3 years of follow-up in the placebo arm, and that adding an angiotensin-converting enzyme (ACE) inhibitor had a significant impact on reducing events.⁷⁰ The prevalence of asymptomatic systolic dysfunction in the community has been reported to be almost 5%.⁷¹ Debate still exists, however, over the cost effectiveness of using BNP as a screening tool in unselected populations.

Measurement of BNP can also be used to help confirm or refute a diagnosis of CHF in patients with vague symptoms and difficult to interpret physical signs. The effectiveness of BNP measurement in the assessment of emergency room patients with CHF complaints has already been discussed.^{13, 59, 72} The application of these results to the outpatient setting and on hospital wards has yet to be established.

Serial BNP measurement can be performed to assess response to therapy in those with known CHF. As described above, BNP levels predict cardiac events in patients hospitalized with decompensated CHF. Elevated or increasing BNP levels during hospitalization serve as a warning that a patient may not yet be ready for hospital discharge. Similarly, serial BNP can be used to monitor therapeutic response in the office setting. Troughton *et al.* published data on the utility of N-BNP in clinic patients with CHF.¹⁵ Sixty-nine patients with a history

TABLE IV Known clinical uses for measuring serum B-type natriuretic peptide levels

Clinical uses for B-type natriuretic peptide measurement
Screening for asymptomatic left ventricular dysfunction
Increasing accuracy of heart failure diagnosis in patients with vague symptoms and difficult to interpret physical signs
Predicting prognosis in patients with known heart failure
Assessing response to treatment in patients with heart failure

of CHF and ejection fraction under 40% were assigned to have CHF medications titrated solely by clinical assessment or solely by N-BNP level. In addition to their regular physicians, all patients were followed by a study investigator blinded to treatment assignment, who regularly assessed whether the patients met one of the study's primary endpoints of death, hospitalization for CHF, or decompensation. A 50% relative reduction in cardiac events at a median follow-up of 9 months was shown. Patients in the N-BNP group received significantly higher doses of ACE inhibitors, diuretics, and aldosterone antagonists. The conclusion from this study may be that the physicians were not aggressive enough in titrating medications which have been shown to have dose-related benefits. However, BNP levels may help guide physicians to know when more aggressive medical therapy is warranted.

Conclusion

Serum levels of the hormone BNP are elevated in patients with increased myocardial wall tension and therefore have important clinical implications. Measurement of BNP may be used to screen populations for asymptomatic ventricular dysfunction and to aid diagnosis of CHF in patients with confusing presentations (Table IV). The levels of BNP are related to wedge pressure and predict CHF outcomes. Serial measurement of BNP can also be used to assess response to medical therapy in patients with known CHF.

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