The Role of B-Type and Other Natriuretic Peptides in Health and Disease

Ashok Krishnaswami, MD, FACC

Abstract

Natriuretic peptide (NP) physiology is a complex field. NPs also are known to be highly phylogenetically preserved. NPs can be thought of as counterregulatory hormones antagonizing the effects of the renin-angiotensin-aldosterone and sympathetic systems. These peptides are primarily responsible for maintaining salt and water homeostasis, but they also have vasodilatory properties. It was originally thought that B-type NP (BNP) and *N*-terminal-pro-BNP are secreted in a 1:1 ratio. However, recent data has shed further light into this area. Commercial assays for NPs will need to keep up with these changes. Currently, BNP levels within Kaiser Permanente are obtained by multiple providers in a variety of clinical scenarios in order to help them manage their patients. Therefore, a basic understanding of the physiology of NPs and the methodology of assays are needed to appropriately interpret an NP test result within the corresponding clinical scenario.

Introduction

B-type natriuretic peptide (BNP) is a cardiac biomarker that has become increasingly useful in numerous clinical settings. It was first discovered by de Bold and colleagues[1] in 1981. The application of the physiology of the natriuretic peptides (NPs) has led to numerous clinical trials that have attempted to assess the indications for the diagnostic and therapeutic use of BNP. A rudimentary search for *NPs* and *BNP* on PubMed resulted in 17,020 and 3372 articles, respectively.

The mechanisms of action of NPs under normal conditions and in pathologic states are extremely complex. In daily clinical practice, physicians address only a small area within the spectrum of natriuretic physiology. Physicians and other clinicians experience a good deal of confusion and frustration in interpreting BNP values within specific clinical scenarios. To gather sufficient knowledge for interpreting a BNP value, one must have a basic understanding of the spectrum of NP physiology and pathology.

This review article aims to provide an overview of the structure and function of NPs in general and, when applicable, BNP specifically. The assays currently available for BNP and *N*-terminal pro-BNP are discussed in relation to their use at Kaiser Permanente (KP) Northern California. Some of the accepted as well as the newer applications of BNP or other NPs are also discussed.

Structure of B-Type Natriuretic Peptide

Cardiac NPs are just one among many families of NPs. The cardiac NPs (also called atrial NPs from their original description of synthesis location) are produced from three different genes and are stored as prohormones. These are the 126–amino acid atrial natriuretic peptide (ANP), 22-amino acid C-natriuretic peptide (CNP), dendroapsis natriuretic peptide (DNP) and V-type natriuretic peptide (VNP). The 108-amino acid BNP is not stored as a prohormone. Other NPs include guanylin, uroguanylin, adrenomedullin, and urodilantin (renal NP). The BNP molecule consists of 32 amino acids attached by a cystine bridge with an *N*-terminal and a *C*-terminal. An understanding of the structure of the molecule is important because assay measurements are based on the recognition of certain areas within the molecule (Figure 1). All of the NPs, with the exception of adrenomedullin, share important structural elements that are required in receptor mediated cell signaling. There is a common 17–amino acid ring structure that shares a high degree of homology among the family members. The differences between members of the family are within the *N*- and *C*-terminal portions, and it is thought that this difference may play a role in the function of the particular peptide.[2, 3]

Ashok Krishnaswami, MD, FACC, is a Staff Cardiologist and Local Research Chair in the Department of Cardiology at the San Jose Medical Center, CA.
E-mail: ashok.krishnaswami@kp.org.

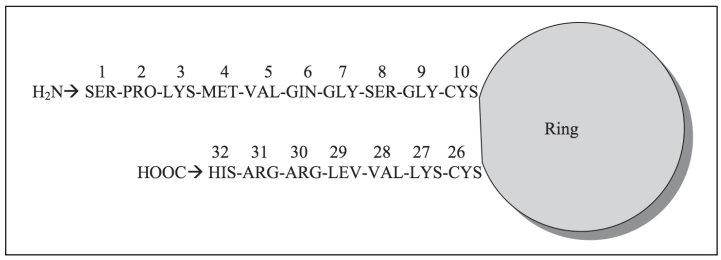

Figure 1. Schematic structure of B-type natriuretic peptide beginning at the *N*-terminal end and ending at the *C*-terminal, with amino acids 11 through 25 comprising the ring.

Biosynthesis and Secretion of B-Type Natriuretic Peptide

BNP is released as a 134–amino acid precursor, pre–pro-BNP. Original thought was that further breakdown resulted in the active 32–amino acid BNP and the inactive 76–amino acid *N*-terminal pro-BNP. However, this simplistic scenario has undergone a paradigm shift (Figure 2). Recent studies using Western blot analysis have characterized both low- and high-molecular-weight forms of BNP. Once BNP is in the circulation, numerous BNP fragments are noted, with each having various biologic activities.[4]

Release of BNP occurs in a secretory fashion constitutively (continuous transcription and translation of its gene that is determined by left ventricular pressure and volume overload) and in a pulsatile fashion through coronary sinuses (in response to left ventricular [LV] wall stretch, volume overload, and tissue hypoxia, along with multiple neurohumoral factors).[2,3,5] Regulation of BNP synthesis and secretion occurs at the gene level. BNP is not stored in secretory granules.[6] ANP, however, is stored in secretory granules. It responds to atrial stretch by secreting previously synthesized ANP and also increasing ANP gene transcription, which results in messenger RNA abundance. Because of the difference in constitutive versus pulsatile secretion, it is thought that BNP may provide a better index of LV mass and load and that ANP gives better information on volume status in normal renal function.[2] The genes for ANP and BNP are located in close proximity on chromosome 1.

Location, Stimulus for Release and Systemic Effects of Natriuretic Peptides

ANP and BNP are predominantly located in the cardiac atria and ventricle respectively. BNP is found in atrial and ventricular tissue. Due to the larger mass of the ventricle, there is an increased concentration produced from the ventricles. Both ANP and BNP decrease plasma volume and blood pressure in response to an increased tension of the respective cardiac chamber. CNP is found in the heart, brain, kidney and vasculature. The primary effect of CNP is venodilatation. CNP lacks significant natriuretic and diuretic action when infused into humans.

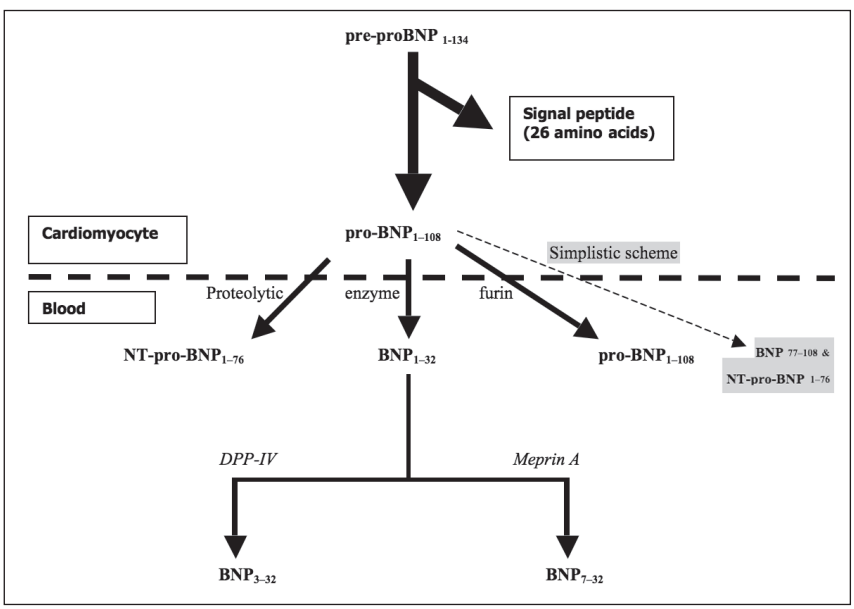

Figure 2. Simplistic scheme (in gray highlight). Prior model regarding B-type natriuretic peptide (BNP) release was that only two products of pro-BNP were released: BNP (active) and *N*-terminal-pro-BNP ([NT-pro-BNP] inactive). The current paradigm of natriuretic peptide (NP) synthesis and release consists of a variety of peptides released into bloodstream, each with varying biologic activity. NP location and release has not been fully elucidated.

BNP = B-type natriuretic peptide; NT-pro-BNP = *N*-terminal-pro-BNP; DPP-IV = dipeptidyl peptidase–IV.

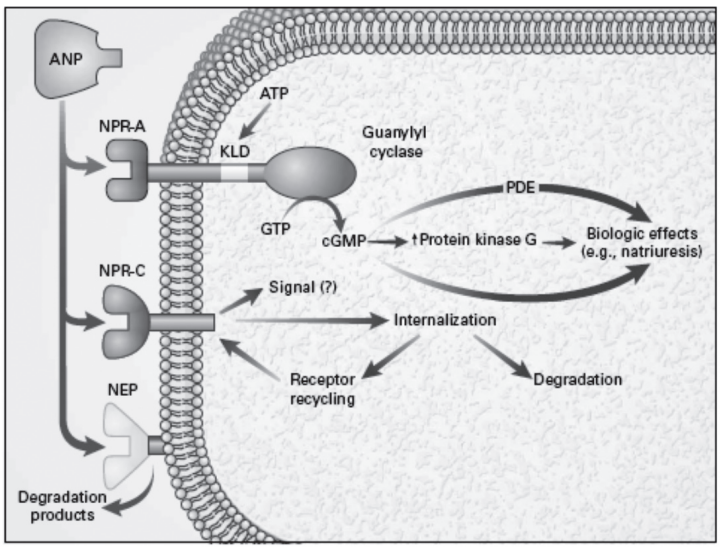

Figure 3. Action of atrial natriuretic peptide (ANP) at target cells. Binding of ANP to natriuretic peptide receptor A (NPR-A) and, in an ATP-dependent fashion, stimulating the intrinsic guanylyl cyclase activity of the receptor. Cyclic guanosine monophosphate (cGMP) exerts its biologic effects. ANP binds to natriuretic peptide receptor C (NPR-C), after which it is internalized and degraded. The C-receptor may also have independent signaling functions. Finally, ANP may be degraded by the extracellular neutral endopeptidases (NEPs) in the kidney and vasculature.

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CNP also possesses more potent antiproliferative and collagen-suppressing properties in cardiac fibroblasts as compared with ANP or BNP. DNP, which was discovered in 1992, acts as a potent natriuretic and diuretic. It also possesses cardiac unloading actions but at the cost of significant hypotension. The stimulus for release of DNP is not fully understood. Guanylin and uroguanylin which are presumed to arise from the gastrointestinal mucosa are thought to regulate salt and water transport (see Table 1).[2] Incorporating part of CNP and BNP, the novel chimeric peptide CD-NP was recently synthesized. The properties of CD-NP appear to be attractive in patients with the cardiorenal syndrome.[7]

Location and Ligand Specificity of Natriuretic Peptide Receptors

The mechanisms of action of the NPs are mediated by high-affinity NP receptors (NPR)-A and NPR-B.[2,6,8] All receptors share a relatively common molecular configuration, consisting of an extracellular binding site, a transmembrane sequence, and an intracellular domain (Figure 3). The actions of each of the NPs are determined by the binding specificity of the receptor to the ligand. This is important to know as systemic effects may be varied based on the specificity of the ligand to its receptor and the tissue distribution of the receptor.

The tissue distribution of NPR-A is within the kidney, adrenal, endocardial, brain, lung, and aorta. The ligand specificity of the receptor is highest to ANP and least to CNP with specificity of BNP between the other two. NPR-B is located

Table 1. Natriuretic peptide origin, stimulus for release and biologic effect[a]

Natriuretic peptide	Location(s) of peptide	Stimulus	Effect
ANP	Cardiac atria	Increased atrial stretch and tension	Decreased plasma volume and blood pressure
BNP	Cardiac ventricle	Increased ventricular wall tension	Decreased plasma volume and blood pressure
CNP	Heart, brain, kidney, vasculature	Shear stress	Vasodilatation, possibly acts as system neurotransmitter
D-type natriuretic peptide	Unknown	Unknown	Vasodilatation
Guanylin Uroguanylin	Gastrointestinal mucosa	Unknown	Regulates salt and water transport
Adrenomedullin	Adrenal medulla, cardiac ventricles, lungs, and kidneys	Unknown	Reduction in plasma volume, blood pressure, vasodilatation

ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CNP = C-natriuretic peptide.

[a] Adapted from: Joffy S, Rosner MH. Natriuretic peptides in ESRD. Am J Kidney Dis 2005 Jul;46(1):1-10.[2] Reprinted from the American Journal of Kidney Diseases, Vol 46, Joffy S, Rosner MH, Natriuretic peptides in ESRD, 1-10, Copyright Elsevier, 2005.[2]

Table 2. Ligand specificity, second messenger and tissue distribution of natriuretic peptide receptors[a]

Receptor	Ligand Specificity	Tissue Distribution
NPR-A	ANP>BNP>>CNP	Kidney, adrenal, endocardium, brain, lung, aorta
NPR-B	CNP>>ANP>BNP	Kidney, adrenal, cerebellum, pituitary, lung
NPR-C	CNP>ANP, BNP	Widely distributed

NPR = natriuretic peptide receptors; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CNP = C-natriuretic peptide.

[a] Adapted from: Joffy S, Rosner MH. Natriuretic peptides in ESRD. Am J Kidney Dis 2005 Jul;46(1):1-10.[2] This article was published in the American Journal of Kidney Diseases, Vol 46, Joffy S, Rosner MH, Natriuretic peptides in ESRD, 1-10, Copyright Elsevier, 2005.[2]

within the kidney, adrenal, cerebellum, pituitary, and lung. The ligand specificity is highest to CNP and less to ANP and BNP. NPR-C has a wide tissue distribution with CNP having the highest ligand specificity. A simple method of remembering ligand specificity to an individual receptor could be ABC for NPR-A and CAB for NPR-B and C. The second messenger for both NPR-A and NPR-B is cyclic-GMP (see Table 2).[2] One example of receptor specificity is the lack of a renal natriuretic effect of CNP even after direct injection into the renal artery. This may be due to a lack of binding by NPR-A located in the inner medullary collecting duct of the kidney.[2]

Clearance of Natriuretic Peptide Receptors

Clearance of the NPs is by NPR-C. The NPs bind to the receptor and then are internalized and enzymatically degraded. Subsequently, the receptor returns to the cell surface. This process occurs primarily in the kidneys. Approximately 30% of the time the degradation is by neutral endopeptidases that are present within vascular and renal tubular cells.[7] Both BNP and NT-pro-BNP have been found in urine. The exact mechanism of clearance of NT-pro-BNP is not known. It appears to be cleared not by active clearance mechanisms but instead by organ beds with increased blood flow (muscle, liver, renal, etc). Renal extraction ratios for both BNP and NT-pro-BNP are 15% to 20% respectively.[9]

What Is a Normal Level of B-Type Natriuretic Peptide?

A normal BNP level is thought to be less than half the chronologic age of the patient.[10] BNP levels vary in health and are slightly higher in women than in men. The exact reason is unclear, but it is speculated that ventricular stiffening is more pronounced in females at all ages. BNP levels are 40% lower in obese individuals than those of normal body weight, either because of impaired production or increased peripheral clearance.

Abnormal Levels of B-Type Natriuretic Peptide and Conditions That Cause Increased B-Type Natriuretic Peptide Levels

It is thought that in the context of patients presenting with dyspnea and a BNP level <100 pg/mL, the diagnosis of heart failure is highly unlikely (~2%). A diagnosis of heart failure is highly likely with a BNP value >500 pg/mL (~95%). A value between 100 and 500 pg/mL renders a diagnosis of heart failure as probable (~90%). There are many conditions that cause an increased BNP level, such as advancing age. Women have higher slightly higher levels than men. Cirrhosis of the liver is associated with BNP levels three times higher than normal. Renal failure, further described later in this article, is associated with increased BNP levels. Primary pulmonary hypertension, pulmonary embolism, primary hyperaldosteronism, and Cushing syndrome are associated with increasing BNP levels. Other cardiac conditions besides congestive heart failure (CHF) associated with increased BNP levels are cardiac inflammatory processes: myocarditis, cardiac transplant rejection, Kawasaki disease, and LV hypertrophy.[8,10]

Natriuretic Peptide Assays

According to Panteghini and Clerico, "Several methods for cardiac natriuretic hormone determination have been proposed measuring similar or identical peptides, showing, however, different analytical performance, reference values, clinical results and possibly diagnostic accuracy. In addition, there is no general agreement about the cardiac natriuretic hormone terminology used by different researchers and manufacturers; this may increase confusion and cause misleading interpretation."[11] There appears to be an attempt to try to rectify this confusion. A report recently published by the Committee on Standardization of Markers of Car-

... ANP and BNP decrease plasma volume and blood pressure in response to an increased tension of the respective cardiac chamber.

diac Damage of the International Federation of Clinical Chemistry and Laboratory Medicine, meant primarily for manufacturers but helpful for all who use BNP or NT-pro-BNP assays, addressed the variety of factors that contributed to inconsistencies. Analytic factors that were addressed by this committee included the type of antigen used for calibration, assay specificity and imprecision, and interferences by factors such as hemoglobin and bilirubin or by heterophilic antibodies. Preanalytic factors that were addressed included sample type (serum, plasma, whole blood, and type of specimen collection tubes) and sample stability at different temperatures of storage.

First-generation commercial assays for ANP and BNP—those available before 1990—were competitive immunoassays. These were radioimmunoassay (RIA) and enzyme immunoassay (EIA) methods. Both of these methods required a preliminary purification chromatographic step because of their poor sensitivity and specificity, which subsequently decreased assay precision and practicability. Second-generation immunoassays that became available during the 1990s were noncompetitive immunoassays (immunoradiometric assays, or IRMAs). These did not require a purification step, but the long turnaround time did not allow their use in time-sensitive scenarios.

Noncompetitive IRMA methods have been set up to overcome the problems with the earlier BNP assays. This method uses a two-site sandwich method, employing two specific monoclonal antibodies or antisera against two remote epitopes on the ANP or BNP molecule. These can be based on a solid-phase or liquid-phase system as the means for separation. The advantages of IRMAs versus RIAs are that

- IRMAs use radiolabeled antibody, which is more stable than radiolabeled ANP or BNP
- IRMAs do not require the purification step because of their increased sensitivity and are not affected by specific or nonspecific interferences
- IRMAs use lower plasma volumes.

One of the drawbacks of the IRMA method is that it uses two monoclonal antibodies that are specific for the intact ANP or BNP molecule. However, it is possible that the intact pro-BNP or pro-ANP molecule will also contain the biologically active component, resulting in measurement of both these components. The second drawback is the result of falsely low levels of BNP, despite the clinical scenario, that would

Table 3. Assays for BNP and NT-pro-BNP

Marker	Company	Available at Kaiser Permanente–Northern California	Cost/test[a]	Initial technology	Current fully automated assays Calibrator material, capture antibody, detection antibody
BNP	Abbott AsSYM	Was run by regional laboratory	$36.00	Microparticle enzyme immunoassay	BNP_{1-32} synthetic peptide (Peptide Institute), Abbott (amino acids 5-13), Shionogi (C-terminus)
BNP	Bayer ADVIA Centaur ACS : 180	Initially run by Quest	$96.00	Direct chemiluminescent sandwich immunoassay	BNP_{1-32} synthetic peptide (Phoenix Pharmaceutical), Scios (ring), Shionogi (C-terminus)
BNP Triage BNP	Biosite, Inc	No		Single-use fluorescence immunoassay device (point-of-care testing)	
BNP	Biosite, Inc Beckman Access	May be available at all local laboratories in near future	$12.00	Two-site chemiluminescent immunoenzymatic assay	$BNP_{1–32}$recombinant peptide (Scios), Scios (ring), Biosite (*N*-terminus)
NT-pro-BNP Elecsys	Roche Diagnostics	May be available		Electrochemiluminescent immunoassay	NT-pro-$BNP_{1–76}$ synthetic Peptide, (Roche), Roche (*N*-terminus), Roche (amino acids 39–50)

BNP = B-type natriuretic peptide; NT-pro-BNP = *N*-terminal-pro-BNP.

[a] Cost/test is the approximate cost of the test.

suggest otherwise (eg, CHF, renal insufficiency). This phenomenon is known as the hook effect, which occurs during RIA, when the antibody-binding sites become saturated and the binding curve is no longer proportional to the actual level of BNP. The hook effect can be resolved by using a monoclonal antibody coated onto the solid phase showing high binding capacity.

Subsequently newer generation immunoassays, including point-of-care testing, use noncompetitive sandwich immunoassays. These do not use radioactive materials as labels for the antigen/antibody reaction. Instead they use monoclonal antibodies, polyclonal antibodies or a combination for BNP binding. One antibody binds to the ring structure and the other to either the *C*- or *N*-terminal end of BNP. These methods have allowed their use as a point of care method/emergency situations (see Table 3).

Uses of B-Type Natriuretic Peptide

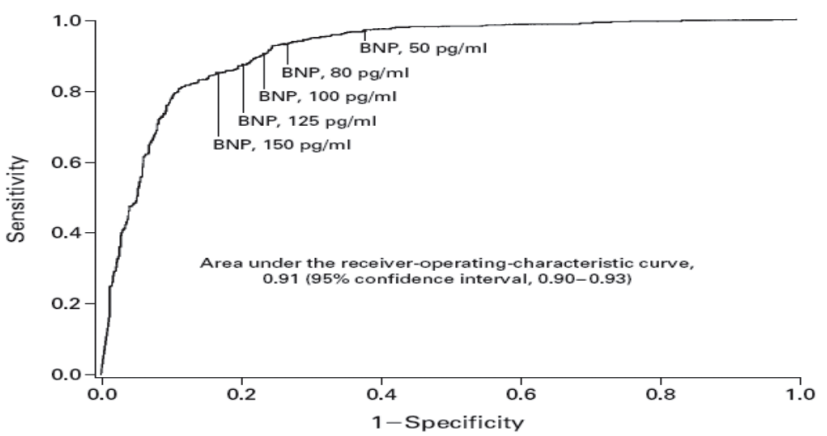
There have been numerous studies using BNP in various settings. Silver and colleagues[10] suggested a hub-and-spoke model of applications using BNP testing. BNP is the center hub, with the spokes being screening, diagnosis, prognosis, therapy, and treatment monitoring.

Screening

There are currently no data to support the use of BNP as a screening tool.[10] Therefore, the decision to order a BNP test should be based on cardiac risk factors and symptoms.

In the Emergency Department

Three clinical trials have assessed the value of BNP as an additive tool to the history, physical examination, and chest radiograph. One of the initial pilot studies, originating from the group in San Diego, CA, provided preliminary data for the subsequent large, seven-center study. The Breathing Not Properly study[12] enrolled 1586 patients who were being evaluated in an Emergency Department (ED) for shortness of breath. It showed that BNP used in conjunction with other clinical information was useful in differentiating the etiology shortness of breath. Patients with a diagnosis of acute CHF had a median BNP level of 675 ± 460 pg/mL (n = 744), whereas those patients without CHF had a BNP level of 110 ± 225 pg/mL (n = 770), and the 72 patients who had LV dysfunction at baseline but no acute exacerbation had a BNP level of 346 ± 390 pg/mL. It is apparent by the data that there was overlap between patients in each group. Receiver-operating characteristic (ROC) curves are meant to judge where to draw the line between normal and abnormal to obtain the maximum sensitivity and specificity. In the Breathing Not Properly study, the recommended cutoff was 100 pg/mL on the basis of the ROC curve, but some believe that a better cutoff in view of the study's data might be 150 pg/mL, on the basis of a sensitivity of 85%, specificity of 83%, positive predictive value of 83%, and negative predictive value of 85%, with an accuracy of 84% (Figure 4).



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Figure 4. Receiver-operating characteristic curve for various cutoff levels of B-type natriuretic peptide (BNP) in differentiating between dyspnea due to congestive heart failure and dyspnea due to other causes.

BNP = B-type natriuretic peptide.

Reprinted from Maisel AS, Krishnaswamy P, Nowak RM, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002 Jul 18;347(3)161–7.[12]

The second study, the REDHOT [13] trial, also originated from the San Diego group. This trial recruited 464 patients from ten sites and assessed the relationships between BNP levels within a diagnostic range, clinical decision making, and outcomes. It showed that there was a difference between perceived severity of CHF by ED physicians and the severity as determined by BNP. The presumption was that if ED physicians had access to BNP data at the time of the patient presentation, an improvement of the triage of patients would have resulted.

The third study, by a Swiss group, was called the BASEL[14] study and was a prospective, randomized, controlled clinical trial that enrolled 452 patients presenting to the ED with acute dyspnea. Of those, 225 patients were assigned to a strategy that measured BNP with a rapid bedside assay and 277 were randomized to a standard treatment (not using BNP). The median number of days to discharge and total cost of treatment were the primary endpoints. The time to treatment was 63 minutes in the BNP group and 90 minutes in the control group (p = 0.03). The number of days in the BNP group was 8.0 days and 11.0 days in the control group. The median total treatment cost was $5410 in the BNP group and $7264 in the control group.

BNP values reflect LV function, mass, and load more than volume status.[2]

A substudy from the original Breathing Not Properly study suggested that BNP should be taken into context with the presenting clinical scenario.[15] The diagnostic accuracy of clinical judgment was 74.0%, the accuracy when BNP was >100 pg/mL was 81.2%, and a combination of BNP data and clinical judgment yielded a diagnostic accuracy of 81.5%.

The results of these studies suggest that:

- BNP can be used as a triage tool in the ED in patients presenting with dyspnea to help with ascertaining the diagnosis
- Increased diagnostic accuracy will be attained when the combination of BNP data and good clinical judgment
- There may be some cost-effectiveness to this strategy.

Management of Congestive Heart Failure

Studies using BNP to guide the effectiveness of therapy in patients with heart failure have been reported. For example, the Val-HeFT and RALES trials suggested that valsartan and spironolactone lowered BNP levels in patients with heart failure. The STARS-BNP[16] study, evaluated patients with New York Heart Association (NYHA) class II to III CHF whose ejection fraction was <45% and who were in stable condition and treated by optimal medical therapy. Patients were randomized to a BNP group and a clinical group for assessment of whether BNP-guided therapy (target BNP <100 pg/mL) would affect outcome in this population. The BNP group had an increased number of changes in medications (the highest changes were in diuretics and β-blockers) and an increased event-free survival period between the two groups at 450 days. The mean BNP levels in the BNP group had a statistically significant decrease at three months when compared with baseline BNP (from 352 ± 260 pg/mL to 284 ± 180 pg/mL). It is to be noted that the target BNP of <100 pg/mL was reached in only 16% of patients at baseline and in 33% of patients by a follow-up examination at three months, suggesting that lowering BNP to a predefined level may be impractical. The inability to lower BNP may be a reflection of basal constitutive secretion due to factors already mentioned. A recent study suggested that patients with nonischemic dilated cardiomyopathy, admitted for decompensated heart failure with elevated BNP levels >190 pg/ml, six-months after admission had a worse prognosis.[17]

B-Type Natriuretic Peptide in Renal Insufficiency

Renal insufficiency is a spectrum of disease that can be characterized on the basis of glomerular filtration rate as chronic kidney disease (CKD) stages 1 through 5. Most physicians have noted in their daily practice that BNP levels appear to be higher in patients with CKD. One of the primary trials to evaluate BNP in the setting of CKD was the Breathing Not Properly study. This study established that BNP levels in patients with CKD should not be interpreted without the corresponding clinical scenario. It also suggested that the cutoff points for BNP in patients with CKD and CHF should be higher. The cutoff point of 200 pg/mL with a glomerular filtration rate of <60 mL/min was thought to be a balancing point for diagnostic utility. This will still maintain a high diagnostic sensitivity with an area under the ROC of >0.807.[10]

The individual contributions of CHF and renal failure to the total level of BNP are unknown. These two diseases are known to be highly salt- and water-retentive states. In CHF, there is

an increased production of NPs to overcome this retentive state. With the advent of progressive renal failure, there is increased production but also decreased degradation and hyporesponsiveness of NPs because of postulated reasons such as renal hypoperfusion and activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Cardiac transplantation is not known to decrease BNP values for multiple reasons that include advanced age, decreased renal function, and the presence of hypertension.[2] BNP levels >250 pg/mL in chronic cardiac transplant survivors was closely related to allograft failure and development of coronary artery disease and had an increased likelihood of death.[18] Successful renal transplantation, however, lowers elevated levels of NPs.[19]

In patients who have CKD stage 5 (receiving renal replacement therapy by hemodialysis [HD]), the exact role of the NPs are unclear. The natriuretic effect is minimal, but the strength of other effects, such as antifibrotic or antiproliferative, is unknown. There does not appear to be any known endogenous clearance of these peptides. A sevenfold elevation of BNP and a fourfold elevation of ANP were noted before HD in patients with CKD stage 5 when compared with study control subjects. HD decreased ANP levels by 36% and BNP levels by 9%. Final concentrations of both were still significantly higher than in study control subjects. Another study showed that ANP and BNP levels were the highest in patients receiving HD when compared with patients with CKD not receiving HD or with cardiac transplant patients. Levels of BNP as compared with levels of ANP decreased less after HD (16% vs 43%).[19]

The determination of dry weight has been suggested as a use of ANP or BNP. Numerous studies have sought to define the exact role of ANP or BNP in the determination of dry weight. Confounding variables such as concomitant valvular disease and arteriovenous fistulas (increase ANP and BNP levels) influence levels of NPs in this determination. To summarize, ANP levels before dialysis have a good correlation with volume overload but levels after dialysis are not reliable for dry weight determination. BNP values reflect LV function, mass, and load more than volume status.[2]

Prognosis

A discussion of the use of BNP in assessing prognosis is beyond the scope of this article, but some examples of its use in prognosis are mentioned here. In the Val-HeFT[9] trial, outpatients with the highest quartile of BNP levels (>238 pg/mL) had the highest mortality. Its use in acute coronary syndrome has not been shown to predict ischemia but has been shown to be a powerful tool for obtaining prognostic information. The OPUS-TIMI 16 trial[20] showed that the combination of troponin+ (troponin >0.04 ng/mL) and BNP+ (BNP >485 pg/mL) had a relative risk of >12 and a mortality rate approaching 45%. One of the most intriguing and provocative uses of BNP is in trying to determine the risk of sudden cardiac death in patients with CHF. Berger and colleagues[21] sought to determine the risk of sudden cardiac death by using BNP values in approximately 450 patients with mild to moderate CHF (ejection fraction <30%) classified as NYHA class I or class II. He found that BNP levels >130 pg/mL separated patients into high versus low rates of sudden death. Only 1% (1 of 110) of patients with BNP levels <130 pg/mL died suddenly, compared with 19% (43 of 227) with BNP levels of >130 pg/mL. Further work is needed before we can use BNP as a guide to defibrillator placement in those patients with CHF.

Clinical Utility of Natriuretic Peptides in Aortic Stenosis and Mitral Regurgitation

An emerging use of NPs, specifically BNP, NT-BNP, NT-pro-BNP, and ANP, have been directed toward the determination of functional class, assessing the relation of NP levels with invasive and noninvasive measurement, timing of surgery, and prognosis for patients with aortic stenosis (AS)[22-31] or mitral regurgitation (MR).[32-28] There is also an attempt to correlate NP levels with the underlying ultrastructural changes that the left ventricle faces with either pressure or volume overload in patients with AS or MR. The use of NPs may become part of mainstream clinical management in this subgroup of patients in the future. However, with the wide variations in the assays used and the cohort selected by the initial studies, generalized applicability in its use is currently not recommended.

Gerber and colleagues[22] selected three NPs in one of the first articles that examined the use of NPs in the assessment of patients with AS. They were BNP, N-terminal BNP and ANP. The study cohort was 74 patients with isolated AS. All three NP levels correlated with NYHA functional class and aortic valve area. BNP, ANP and N-terminal BNP levels

increased with increasing NYHA functional class. The median BNP level (expressed in pmol/L) in NYHA class I was 8 (range, 6–14), in NYHA class II was 25 (range, 13–35) and NYHA class III/IV was 40 (range, 18–66). When divided into asymptomatic and symptomatic groups, all the NP levels measured increased in the symptomatic group. N-terminal BNP of 60 pmol/L and a BNP value of 14 pmol/L were the cutoffs for maximum sensitivity and specificity for the presence of symptoms. Gerber et al[23] also assessed NT-pro-BNP in 29 initially asymptomatic patients with aortic stenosis and suggested the NT-pro-BNP above normal limits suggested the future development of symptoms. Lim and coworkers[24] showed that a BNP cutoff value of 66 pg/mL was able to detect the presence of symptoms with a sensitivity of 84%, specificity of 82%, and accuracy of 84%. Angina was not associated with elevated BNP levels. A Kaplan-Meier survival curve suggested a BNP value >97 pg/mL as an indicator of survival at a follow-up point of 308 days (range, 11–472 days). Berger-Klein and colleagues[25] suggested a benefit of serial measurement of NPs (BNP, *N*-terminal BNP, *N*-terminal ANP) in patients with aortic stenosis AS to determine timing of conversion from an asymptomatic to symptomatic status. Prognostic information was also available, and suggested BNP levels >130 pg/mL in this subgroup of patients with AS had worse outcomes. Preoperative *N*-terminal BNP levels were significant predictors of postoperative symptomatic status also. Nessmith and colleagues[26] monitored patients who did not undergo aortic valve replacement. BNP values <296 pg/mL, between 296 and 819 pg/mL, and >819 pg/mL resulted in one-year mortality rates of 6%, 34%, and 60%, respectively, and BNP value of 190 pg/mL discriminated between the presence and absence of symptoms. Kupari and colleagues[27] studied 49 patients undergoing cardiac catheterization for isolated AS. Blood samples were obtained from the aortic root and coronary sinus for *N*-terminal BNP. An increase in the transcardiac plasma *N*-terminal BNP in patients with diastolic heart failure (threefold increase) and systolic heart failure (sixfold increase) from that of study control subjects and patients with AS without heart failure suggest a spectrum of stages that patients with AS go through, and NPs may aid in identifying these stages. A recent article regarding the TOPAS study[28] suggested that NPs (BNP) in the TOPAS study can be used to differentiate the truly severe from the pseudo severe stenosis in low gradient AS, and its use here has prognostic ability in determining survival from aortic valve replacement.

NPs have also been used in patients with MR to correlate functional status,[29] severity of valvular regurgitation, and prognosis. There has been again a variety of NPs that have been used, with varying assays for the detection of these peptides, different methods for determining MR, and differences in the patient cohort making the assessment difficult of where this clinical tool will fit in the clinical care of these patients. Sutton and coworkers[30] assessed the use of ANP, BNP, and *N*-terminal-BNP in 49 patients with isolated MR and preserved LV systolic function. Symptomatic patients had higher levels of all three NPs and had an increased severity of MR. In the symptomatic patients with MR, BNP was 16.9 pmol/L (range, 13.3–21.4 pmol/L), compared with 7.1 pmol/L (range, 6.0–8.4 pmol/L) for the asymptomatic patients. Mayer and coworkers[31] attempted to assess how BNP values can be interpreted in patients presenting with the clinical diagnosis of heart failure using the Framingham criteria in those with and in those without associated MR. They noted a median BNP value of 826 pg/mL (range, 410–1300 pg/mL) and a mean ejection fraction of 37% ± 17%. Patients with increased BNP levels had associated increased LV end-diastolic, end-systolic dimensions, lower LV ejection fraction, and increasing MR severity ($p = 0.024$). In patients in whom diastolic heart failure had been diagnosed, all subgroups had higher BNP values, with restrictive filling pattern having the highest BNP levels (925 ± 52 pg/mL).

The Mayo group[32] made some key observations that enabled progression of this field of study. First, they noted as before that when stratified by NYHA functional class, BNP levels increase significantly with symptom severity and with severity of MR. It should be noted, however, that within each class of symptoms there was a wide range of BNP levels with large overlap between classes. Second, using indexed and nonindexed volumes (left atrial volume, LV end-diastolic volume index, LV end-systolic volume index), they showed a significant correlation between volumes and BNP levels. Third, they also noted the use of BNP had prognostic value. A BNP level of >31 pg/mL versus <31 pg/mL predicted survival (at five years, 42% ± 10% versus 16% ± 7%; $p = 0.03$). Using volumetric analysis, they believed that BNP

reflected the hemodynamic, atrial, and ventricular burden placed by the presence of MR. A subsequent study by the same group noted that functional MR had greater BNP activation than organic MR did. Organic MR was defined as being present if the MR was due to intrinsic valvular disease with at least a moderate degree of regurgitation (regurgitant fraction >40%). Functional MR was associated with a low ejection fraction (<50%) and structurally normal cardiac valves. Two studies reported in 2007 suggested that the ratio of BNP to ANP may be useful in determining the severity of MR[33] and that the use of plasma BNP may correlate well with the myocardial performance index,[34] which has been shown to be a useful parameter in assessing patients with MR.

Brief Overview of *N*-Terminal-pro-B-Type Natriuretic Peptide

A complete review of NT-pro-BNP is beyond the scope of this article, but a brief overview of the concepts and current theories regarding the subject follows. The June 2005 issue of the *Journal of Cardiac Failure*[35] and the February 4, 2008, supplement to the *American Journal of Cardiology*[36] devoted their entire issue to NT-pro-BNP. It appears that there is no significant evidence to suggest that either BNP or NT-pro-BNP is superior to the other. The differences between the two are based on the principles outlined earlier. Some points that must be considered in choosing which assay (BNP or NT-pro-BNP or other yet undetermined assays) should be used by KP:

What is the clinical scenario in which the assay is going to be primarily used—as a screening tool, for diagnosing shortness of breath, as a follow-up diagnostic tool after heart failure? It is assumed that different clinical scenarios will give rise to different output of individual NPs. Knowledge of the scenario and the assay are important.

With the new paradigm of NP synthesis and release and knowledge of varying biologic activities, we must ask what specific peptide are we trying to measure? Will we be measuring a biologically active or an inactive peptide?

With the constant change in knowledge of the biology of NPs, how will KP laboratories adapt?

Summary

The NPs are extremely complex families of peptides that have numerous responsibilities. Among them are the maintenance of sodium and water homeostasis and vasomotor tone. The pathways for regulating these functions are located in a variety of end organs. Resistance to the effects of cardiac natriuretic hormones can also occur due to prereceptor, receptor, and postreceptor factors.[4] Assays have been developed to capture NP levels at a certain point of time within the natural history of a disease. These assays also help us to understand the physiology and pathology of NPs. However, with an insufficient knowledge of the fate of the NPs and their end products, as well as of cross-reactivity of the assays between active and nonactive components, the stage is set for inappropriate interpretation of the NP that has been assayed.

BNP and the other NPs have shown promising results in a variety of clinical scenarios. When using BNP, the clinician should be sure to understand the clinical context in which it is measured and to ask what the current BNP value reflects. The physician in the ED may ask whether the presenting patient's symptoms are indeed heart failure or are instead pulmonary based. The cardiologist may want to know whether BNP reflects ultrastructural LV changes in patients with AS or MR. The electrophysiologist may want to further risk-stratify patients presenting for empiric placement of an implantable cardioverter defibrillator to assess their risk of sudden cardiac death. BNP appears to be a finicky diagnostic tool. However, that finicky nature may be better withstood, if there is an understanding of the NP physiology and also an understanding of the lack of standardizations in assays currently available. With the large number of laboratories within KP Northern California, a variety of assays have been used with possible resultant confusion. These will have to be eventually standardized in the future. As assays continue to be further developed, we must be cognizant of the changing landscape and make adjustments as needed, to ensure adequate representation of the clinical scenario by the NP we are seeking to determine. ❖

Disclosure Statement

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Health And Sickness

Health and sickness, like strength and weakness, are not simple, sharply divided conditions, but very complex, highly involved and relative conditions, with no sharp borderlines. No one is absolutely or completely healthy, and no one is absolutely sick; everyone is in such a condition only more or less.

— The Value of Health to a City, *Max von Pettenkofer, 1818-1901, Bavarian chemist and hygienist*