Review Article

Natriuretic peptides: Diagnostic and therapeutic use

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ABSTRACT

Natriuretic peptides (NPs) are hormones which are mainly secreted from heart and have important natriuretic and kaliuretic properties. There are four different groups NPs identified till date [atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and dendroaspis natriuretic peptide, a D-type natriuretic peptide (DNP)], each with its own characteristic functions. The N-terminal part of the prohormone of BNP, NT-proBNP, is secreted alongside BNP and has been documented to have important diagnostic value in heart failure. NPs or their fragments have been subjected to scientific observation for their diagnostic value and this has yielded important epidemiological data for interpretation. However, little progress has been made in harnessing the therapeutic potential of these cardiac hormones.

Key words: Atrial natriuretic peptide, B-type natriuretic peptide, heart failure, natriuretic peptides, NT-proBNP

Introduction

Secretory granules were first identified in the atria of guinea pig in 1956.[1] However, it is de Bold, who is credited with the discovery and isolation, in 1979, of atrial natriuretic peptide (ANP), a polypeptide hormone secreted by heart muscle cells. This established the heart as an endocrine gland.[2,3] The family of natriuretic peptides (NPs) comprises at least eight structurally related amino acid peptides stored as three different prohormones: 126 amino acid atrial natriuretic peptide (ANP) prohormone, 108 amino acid B-type natriuretic peptide (BNP) prohormone, and 126 amino acid C-type natriuretic peptide (CNP) prohormone.[4] [Figure 1]. The function of dendroaspis natriuretic peptide, a D-type natriuretic peptide (DNP), the most recent addition to the family of NP, first isolated from the venom of the green mamba, in humans still remains unclear.[5]

The ANP prohormone is synthesized mainly within the atrial myocytes and in a variety of other tissues.[6] The prohormone consists of 126 amino acids which give rise to several peptides with blood pressure lowering properties, natriuretic properties, diuretic properties and/or kaliuretic properties.[7] These peptide hormones, numbered by their amino acid sequences beginning at the N-terminal end of the ANP prohormone, consist of the first 30 amino acids of the prohormone (i.e. proANP 1–30; long-acting NP), amino acids 31–67 (i.e. proANP 31–67; vessel dilator), amino acids 79–98 (proANP 79–98; kaliuretic peptide) and amino acids 99–126 (ANP).[7] The ANP prohormone processing is different within the kidney, resulting in an additional four amino acids being added to the N-terminus of ANP (i.e. proANP 95–126; urodilatin).[8] This was initially purified from human urine and is presumed to be the only one synthesized within the kidney. Urodilatin is not present in the circulation and appears to be a unique intrarenal NP with unexplored physiological significance.[9]

BNP was originally discovered in porcine brain, where it was thought to be a neurotransmitter,[10] hence its original name, brain natriuretic peptide. Subsequently, it was shown to be 10-fold more abundant in the heart than in the brain,[11] hence the current term, B-type natriuretic peptide. There appears to be little storage of BNP in the ventricle, which incidentally is the main source. ProBNP is processed within the human heart to form BNP (consisting of 32 amino acids) with amino acids 77–108 of its 108 amino acid

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.86978

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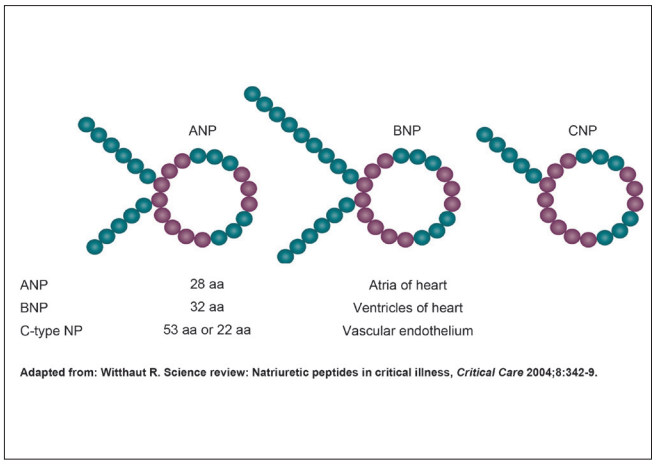

Figure 1: Structure of natriuretic peptides

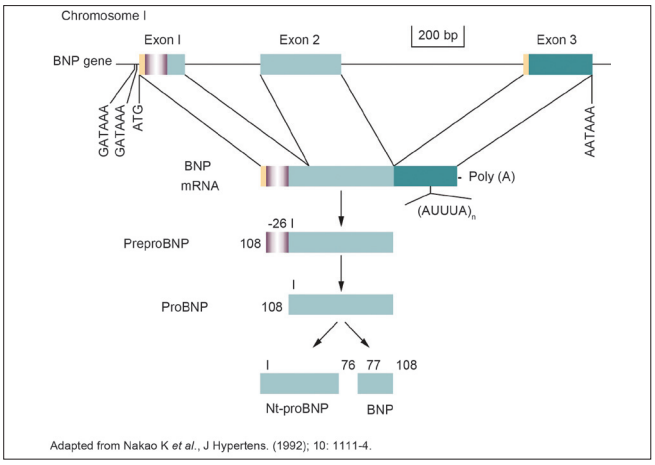

Figure 2: B-type natriuretic peptide transcription and translation

prohormone, and an N-terminal proBNP peptide (amino acids 1–76; NT-proBNP), both of which circulate in humans[12] [Figure 2]. BNP is produced by direct synthesis in response to the degree of ventricular stretch, and also upregulated in failing ventricular myocardium. The messenger RNA for proBNP is unstable, so there is active regulation of BNP levels according to ventricular wall tension. Hence, it acts as a reliable biomarker of ventricular dilatation.[9]

CNP was originally also found in the brain[13] and subsequently was suggested to be present also within the heart.[14] CNP has also been detected in human coronary arteries[15] and in the peripheral circulation in endothelial cells of human veins and arteries at various sites.[16] Two CNP molecules, of 22 and 53 amino acids in length, have been identified within the circulation.[13,14] The 22 amino acid form predominates in plasma and is more potent than the 53 amino acid form.[11] CNP lacks a significant natriuretic function[17] and serves as a regulator of vascular tone[18,19] and growth in a paracrine or autocrine fashion.[20,21]

Functions of Circulating Natriuretic Peptide

Apart from blood pressure lowering properties, natriuretic, diuretic and/or kaliuretic properties of the NP originating from the ANP prohormone[7] and from BNP, inhibition of the renin–angiotensin system, sympathetic outflow, and vascular smooth muscle and endothelial cell proliferation have been attributed to NP.[22] Furthermore, a link of ANP to the immune system has been suggested,[23] and a receptor-mediated modulation of macrophage function[24] and priming of polymorphonuclear neutrophils[25] has been observed. Whether NT-proBNP has biological effects on its own is currently unknown. The function of CNP seems to be the regulation of regional blood flow. The net effects of actions of NPs are a decrease in cardiac preload and afterload.

BNP is eliminated by binding to the NP clearance receptor (NPR-C) or degradation by neutral endopeptidase on endothelial cells, smooth muscle cells, cardiac myocytes, renal epithelium, and fibroblasts. NT-proBNP is cleared mainly by the kidney.[26] BNP has a relatively shorter half-life of about 20 minutes; the half-life of NT-proBNP is about 60–90 minutes and would be expected to be longer in the setting of renal dysfunction. Obese patients (especially those who have body mass index greater than 30) tend to have lower BNP levels than others. Neutral endopeptidases that are secreted by adipose tissue may be related to increased BNP clearance in obese patients.[27]

Receptors of Natriuretic Peptide

Most biological effects of ANP and BNP are mediated by a guanylate cyclase coupled cell surface receptor, the A-receptor (NPR-A).[28] Long-acting NP and vessel dilator have distinct receptors separate from the ANP receptors.[29] The natriuretic effects of the long-acting NP and the vessel dilator have a different mechanism of action from ANP in that they inhibit renal Na^+–K^+-ATPase secondary to their ability to enhance the synthesis of prostaglandin E2, which ANP does not do.[30] CNP is a specific ligand for the B-receptor (NPR-B), another guanylate cyclase coupled NP receptor.[31] The third NP receptor, the so-called NP clearance receptor (NPR-C), binds ANP, BNP and CNP. Apart from a major role in the clearance of NP from the whole body,[31] an increasing number of reports describe that several effects of ANP are mediated via the NPR-C receptor.[32] Stimulation of the NPR-C seems to be related to a G-protein coupled inhibition of adenylate

cyclase.[33] Apart from binding to the NPRs, NPs are also cleared through proteolysis by peptidases, the most closely studied being neutral endopeptidase 24.11. Renal excretion is currently regarded as the main clearance mechanism for NT-proBNP.[33]

Natriuretic Peptides: Diagnostic Use

Natriuretic peptide and left ventricular dysfunction

Increased plasma levels of circulating NP have been described in patients with congestive heart failure and are directly proportional to the severity of congestive heart failure as classified by the New York Heart Association criteria. This rise is seen consistently and has been reported for long-acting NP, BNP and NT-proBNP.[34,35] N-terminal proANP and BNP have been reported to be more sensitive indicators of systolic left ventricular (LV) dysfunction.[36,37] N-terminal proANP has been reported to identify patients with asymptomatic LV dysfunction, with a sensitivity and specificity of more than 90%.[37] For vessel dilator as the only peptide (including ANP, BNP, NT-proBNP, etc.), 100% sensitivity and 100% specificity have been reported in differentiating persons with mild congestive heart failure from healthy individuals.[38] N-terminal proANP has also been reported to be an independent predictor of the development of congestive heart failure and cardiovascular mortality.[39] BNP and NT-proBNP have been shown to be useful markers for prognosis in patients with asymptomatic LV dysfunction and different degrees of congestive heart failure.[40,41] The major site of synthesis and release of BNP, the cardiac ventricles, and BNP's rapid upregulation by gene expression followed by a remarkably augmented plasma concentration exceeding that of ANP in severe cases[42] not only make this peptide useful in estimating the severity of disease in patients with LV dysfunction,[34] but may also help guide the treatment of systolic LV impairment in the future.[43]

In the urgent care setting, it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea. Physical signs, routine laboratory tests, electrocardiograms and chest films are not diagnostically consistent in differentiating heart failure from other diseases, such as pulmonary disease. Rapid testing of BNP and NT-proBNP has been reported to differentiate pulmonary etiologies from cardiac etiologies of dyspnea.[44] However, some types of pulmonary disease, such as cor pulmonale, pulmonary embolism and lung cancer, are also associated with elevated NP levels.[45]

Measurement of NT-proBNP by enzyme-linked immunosorbent assay (ELISA) method compared with a clinical diagnosis was evaluated by receiver operator characteristic (ROC) curve analysis in different populations in primary care [Table 1].[46] The area under the curve (AUC) was consistently greater than 0.85, and confirmed the excellent negative predictive value of the test. This result has been confirmed subsequently in a study in 672 subjects in primary care in Copenhagen where again the AUC was 0.94. The role of BNP as an outcome predictor was explored in a Framingham offspring cohort study.[47] Here, a BNP in the upper tertile was one of the most powerful predictors of cardiovascular events, death and heart failure. A number of observational studies have examined the role of BNP measurement in monitoring treatment in congestive cardiac failure (CCF). The responses to the beta-blocker carvedilol[48] and to the angiotensin 2 antagonist valsartan have been shown to be predicated by BNP levels.[49]

Clinical Trials of Natriuretic Peptide as a Guide for Heart Failure Management

Over the last decade, several randomized-controlled trials (RCTs) have investigated the NP-guided approach in HF patients. Of these, Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score (STARBRITE)[50] and Signal-HF[51] failed to show any benefit of the NP-guided approach, while NT-proBNP–guided management of chronic heart failure, based on an individual target value (PRIMA)[52] showed a significant decrease in mortality and hospitalization in patients who remained on target NP levels. In addition, the Christchurch, New Zealand,[53] Systolic Heart Failure Treatment supported by the BNP (STARS-BNP)[54] and BNP-Guided Care

Table 1: NT-proBNP for diagnosis of cardiac failure in primary care

Cohort sampled	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
General population age >45 (n = 307)	0.92 (0.82–1)	100 (65–100)	70 (65–75)	7 (3–14)	100 (99–100)
Patients with existing diagnosis of heart failure (n = 103)	0.8 (0.72–0.88)	100 (92–100)	18 (10–29)	39 (28–49)	100 (78–100)
Patients taking diuretics (n = 87)	0.87 (0.76–0.99)	93 (66–100)	40 (28–52)	23 (13–36)	97 (83–100)
Patients at high risk of heart failure (n = 133)	0.84 (0.76–0.93)	100 (72–100)	44 (35–54)	12 (5–21)	100 (96–100)

Adapted from Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Br Med J. 2002; 324:1498–1503.

in Addition to Multidisciplinary Care[55] trials showed a decrease in hospitalizations as well as mortality in the NP-guided group compared with usual clinical care. The Placebo-Controlled Randomized Study of the Selective A(1) Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) was terminated early after 1 year due to a significant drop in hospitalizations and cardiovascular-related deaths in the NP-guided group.[56]

Very recently, two large-scale trials, an NT-proBNP–assisted treatment to lessen serial cardiac readmission and death (BATTLESCARRED)[57] and Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF),[58] showed better outcomes with NP-guided uptitration of medications only in patients aged under 75 years. There are two studies still recruiting patients: The Improvement of Patients With Chronic Heart Failure Using NT-proBNP (EX-IMPROVE-CHF), which is double-blinded aiming to recruit 400 patients, and an NT-proBNP stratified follow-up in outpatient heart failure clinics (NORTHSTAR),[59] which will involve 1250 patients.

Meta-analysis of these trials would have been heterogeneous owing to differences in study populations, cut-off NP targets and inclusion levels, interventions, duration of follow-ups, monitoring algorithms, difficulties with double blinding and different end points. Nevertheless, two groups of investigators, one from Duke (NC, USA)[60] and the other from Australia,[61] performed a meta-analysis of NP-guided therapy trials. The former included all major trials except the Signal-HF (six trials with total n = 1627), while the latter meta-analysis added two more small trials (eight trials with total n = 1726). Neither included the BNP-Guided Care in Addition to Multidisciplinary Care trial,[35] as this was more recently published. Both meta-analyses concluded that NP-guided therapy could reduce all-cause mortality in patients with chronic HF, particularly in those aged less than 75 years. Investigators acknowledged the need for additional well-powered studies with a larger number of patients to provide robust evidence of the benefit of NP-guided therapy.

Natriuretic Peptide as a Cardiac Risk Factor

Serial measurements of NT-proBNP in community-dwelling elderly people had been shown to provide additional prognostic information to that from traditional risk factors. NT-proBNP levels independently predict heart failure and cardiovascular death in older adults. NT-proBNP levels frequently change over time, and these fluctuations reflect dynamic changes in cardiovascular risk.[62]

Recent studies have also convincingly documented that both BNP and NT-proBNP are powerful, independent prognostic indicators in patients with stable coronary artery disease. The associations are strongest for the end points of death and heart failure, whereas the association with cardiac ischemic events is weaker or nonexistent, after adjustment for confounding factors. Importantly, BNP and NT-proBNP appear to provide incremental prognostic information to conventional risk factors, including markers of ventricular function and ischemia. Data documenting that BNP or NT-proBNP measurements can be used to guide treatment decisions in patients with stable coronary artery disease, however, is still lacking.[63]

NT-proBNP has also been documented to be an important biomarker for risk prediction in patients with ongoing non–ST-segment elevation acute coronary syndrome and after clinical stabilization. The C-reactive protein (CRP) exhibits increasing predictive value at later measurements. However, only NT-proBNP provided incremental prognostic value and was an independent risk predictor, and might therefore be considered as a complement for early follow-up controls after non–ST-segment elevation acute coronary syndrome.[64]

Cardiac interventions like balloon angioplasty can also increase the BNP, as the release of BNP may be triggered by tissue hypoxia. In a recent study from India, it was documented that BNP levels rose following percutaneous coronary angioplasty not only in patients with acute coronary syndrome but also in patients with chronic stable angina.[65]

NT-proBNP has also been found to be a powerful independent predictor of adverse cardiovascular outcomes following noncardiac surgery. In another study from India, elevated pre-operative BNP or NT-proBNP measurement is documented to be a powerful, independent predictor of cardiovascular events in the first 30 days after noncardiac surgery.[66]

NT-proBNP levels are elevated in patients with rheumatic mitral stenosis and decrease after a successful percutaneous transvenous mitral commissurotomy(PTMC). In yet another Indian study it was shown that NT-pro-BNP levels fall significantly after a successful PTMC, and a significant decrease in levels is a good marker of success of PTMC.[67]

Natriuretic Peptide in Noncardiac Diseases

Natriuretic peptide in pulmonary disease

Cardiac and pulmonary causes of dyspnea often masquerade each other. Sometimes, physical signs, routine laboratory tests, electrocardiograms and chest films are not diagnostically consistent in differentiating heart failure from other diseases, such as pulmonary disease.[68] Rapid testing of BNP and NT-proBNP has been reported to differentiate pulmonary etiologies from cardiac etiologies of dyspnea.[69,70] Some types of pulmonary disease, such as cor pulmonale, pulmonary embolism and lung cancer, however, are also associated with elevated NP levels, but generally not to the same extent as those in patients with acute LV dysfunction. BNP levels in the intermediate range (100–500 pg/ml) have been reported to be attributable to causes other than congestive heart failure.[71]

Increased plasma levels of NP (i.e. ANP,[72] N-terminal proANP[73] and BNP[74]) have also been found in patients with acute respiratory distress syndrome (ARDS). Acute cor pulmonale as a consequence of increased pulmonary vascular resistance occurs in up to 60% of patients with ARDS submitted to conventional mechanical ventilation.[75] An increase of pulmonary vascular resistance observed in ARDS may lead to right ventricular overload and decreased right ventricular output in the presence of impaired right ventricular contractility.[76] BNP levels secreted by the right ventricular myocardium are said not to exceed 300–600 pg/ml.[69] However, there might be a considerable overlap of patients with increased BNP due to ARDS and patients with primary symptomatic congestive heart failure, where BNP levels have to reach more than 500 pg/ml to ensure the diagnosis with a probability greater than 95%.[77] However, in contrast, a BNP cutoff value of 100 pg/ml measured at admission of patients presenting in the emergency department has been reported to have a strong negative predictive value for congestive heart failure in acute dyspneic patients.[35]

Pleural effusions arising from heart failure are usually discriminated from other causes based on clinical criteria in association with biochemical analysis, particularly the discrimination of transudates versus exudates, most commonly using Light's criteria. The sensitivity of Light's criteria for identifying exudative pleural effusions is very high (98%).[78] However, the criteria fare poorly in its ability to exclude transudative effusions.[79] As a result, heart failure associated with pleural effusions can be misclassified as exudates using Light's criteria, particularly after diuretics have been used. Pleural fluid NT-pro-BNP is a very useful biomarker for diagnosing pleural effusions of cardiac origin. A meta-analysis has shown that the pooled sensitivity and specificity of all studies combined was 94% [95% confidence interval (CI): 90–97] and 94% (95% CI: 89–97), respectively. The pooled positive likelihood ratio was 15.2 (95% CI: 8.1–28.7) and the pooled negative likelihood ratio was 0.06 (95% CI: 0.03–0.11). The area under the ROC curve was 0.98 (95% CI: 0.96–0.99) and the diagnostic odds ratio was 246 (95% CI: 81–745).[80]

Natriuretic peptide in renal disease

Renal function clearly influences the diagnostic performance of NT-proBNP; Goei *et al*. showed that NT-proBNP had more favorable discriminative value in patients with glomerular filtration rate (GFR) more than 90 ml/min/1.73 m^2 and lost its prognostic value in patients with GFR less than 30 ml/min/1.73 m^2.[81] Unlike NT-proBNP, BNP levels are relatively independent of GFR. BNP may, therefore, be the more appropriate biomarker to screen for cardiac dysfunction in patients with renal failure.[82] BNP levels could be a valuable tool for risk stratification of hemodialysis patients by confining echocardiographic studies to only patients with BNP levels above the established cutoff values.[83]

Natriuretic peptide in cirrhosis of liver

In patients with cirrhosis of the liver, elevated proBNP and BNP levels reflect increased cardiac ventricular generation of NPs and thus indicate the presence of cardiac dysfunction. Hyperdynamic systemic circulation could also be contributed to elevated NP levels in patients with cirrhosis of liver. In a study evaluating 52 non-alcoholic cirrhotic patients, BNP levels were significantly higher in cirrhotic patients, and BNP levels significantly correlated with Child score, interventricular septal thickness, and LV posterior wall thickness.[84] In another study of 51 cirrhotic patients, hemodynamic investigation revealed that circulating proBNP and BNP levels were related to the severity of liver decompensation (Child score, serum albumin, coagulation factors, and hepatic venous pressure gradient) and to markers of cardiac dysfunction (QT interval, heart rate, plasma volume).[85]

Natriuretic peptide in hyperthyroidism

Serum NT-proBNP levels are affected by thyroid functions and seem to be a direct stimulatory effect of thyroid hormones.[86] In a comparison between 67 patients with clinical hyperthyroidism and normal subjects, elevated BNP levels were mainly found in hyperthyroid patients who had clinical and echocardiographic evidence of LV dysfunction [increased left atrial (LA) diameter and decreased left ventricular ejection fraction (LVEF)], but not in those with normal LV function and normal subjects.[87] Multiple

linear regression analysis demonstrated that free T4 and free T3 were independently associated with a high serum NT-proBNP, whereas cardiac output and resting pulse rate were not. Both NT-proBNP and BNP levels were higher in 21 patients with hyperthyroidism than in hypothyroid patients and normal controls, and treatment of thyroid dysfunctions could result in normalization of NT-proBNP levels in both hypothyroid and hyperthyroid groups.[88]

Natriuretic peptide in subarachnoid hemorrhage

Patients with subarachnoid hemorrhage (SAH) show an increased urine output and urinary excretion of sodium as well as higher BNP levels than the controls.[89] In a study involving 50 patients with traumatic SAH, early rise in BNP levels were associated with myocardial necrosis, pulmonary edema, and LV dysfunction. BNP levels may be elevated in patients with head injuries without echocardiographic evidence of HF.[90] In the absence of evidence for activation of NPs within the brain, prompt and consistent increase in both ANP and BNP strongly supports the view that the heart is the source of increased release of NPs after acute SAH.[91] In a study involving 30 patients with severe isolated head injury, BNP levels were elevated shortly after head injury and progressively rose for 7–8 days after the event in patients with diffused SAH as compared to patients with mild or no SAH.; Similar elevation was noted in patients with elevated intracranial pressure (ICP) as compared to patients without elevated ICP who had a better outcome.[92]

Natriuretic peptide in carbon monoxide poisoning

The levels of NT-proBNP and carbon monoxide (CO) Hb were increased in patients with CO poisoning. In a study involving 15 patients with CO poisoning, there was a positive correlation between the levels of COHb and NTproBNP. Thus, determining plasma NT-proBNP levels may contribute to the early diagnosis of cardiotoxicity in patients with CO poisoning.[93]

Natriuretic Peptides: Therapeutic Uses

Natriuretic peptides or congeners as therapeutic agents

It is conceptually viable that NPs *per se* or their agonists and antagonists would be a welcome addition to the armamentarium of the clinicians for the treatment of cardiac failure because of the obvious salutary effects of NPs on the cardiovascular system.

Increased levels of BNP in patients with congestive heart failure suggest a plausible beneficial effect of it in this condition. Hence, nesiritide, a recombinant human brain NP, has been tried as an infusion in patients with congestive heart failure, which resulted in beneficial hemodynamic effects, including arterial and venous dilatation, enhanced sodium excretion, and suppression of the renin–angiotensin–aldosterone and sympathetic nervous systems. However, pooled analysis from three trials showed that compared with non-inotrope–based control therapy, Nesiritide may be associated with an increased risk of death after treatment for acutely decompensated heart failure. Death within 30 days tended to occur more often among patients randomized to nesiritide therapy [35 (7.2%) of 485 vs. 15 (4.0%) of 377 patients; risk ratio from meta-analysis, 1.74; 95% CI, 0.97–3.12; $P = 0.059$; and hazard ratio after adjusting for study, 1.80; 95% CI, 0.98–3.31; $P = 0.057$].[94] Moreover, it has been noted that usage of nesiritide worsens of renal failure, though it is not clearly understood whether it occurs due to the hemodynamic effect or renal injury. The prognostic importance of worsening renal function demands a reevaluation of nesiritide as a useful adjunct in the treatment of heart failure.[95]

Nesiritide use has been limited in India. However, the successful first usage has been documented in a recent publication.[96]

Omapatrilat, an orally active vasopeptidase inhibitor, is a molecule with potent, long-acting and selective inhibitory activities against neutral endopeptidase and angiotensin converting enzyme (ACE). As a result, this dual inhibitor, omapatrilat increases multiple endogenous vasodilatory peptides including ANP, BNP, bradykinin and adrenomedullin, while it simultaneously inhibits the generation of the vasoconstrictive peptide, angiotensin II. Merely inhibiting the neutral endopeptidase does not really lead to decrease in blood pressure, as unopposed angiotensin II annihilates the effect of increased level of NPs. Omapatrilat's effect on ACE inhibitions adds to the antihypertensive effects and is currently under review by Food and Drug Administration (FDA) for usage as a new group of antihypertensives.[97,98]

Summary

NT-proBNP measurement is a powerful diagnostic and prognostic tool for detection of ventricular dysfunction. It is an ideal test for detection of cardiac failure in primary care, allowing cardiac failure to be definitively ruled out as a cause of dyspnea. Elevated NP levels have shown predictive value in various diseases that have direct or indirect influences on the heart functions in many non-heart failure circumstances, even in the absence of depressed cardiac function. It should be noted that NPs should never be interpreted without a thorough clinical history. Potential clinical applications of NP are expanding. Reports are emerging regarding its role for screening of the presence of secondary cardiac dysfunction, monitoring

the therapeutic responses, risk stratifications, or providing prognostic values in many settings. It should form part of the repertoire of all laboratories. Newer vistas of treatment are being designed based on this important physiological pathway.

Acknowledgments

The contribution of Mr. Pradip Mondal, Department of Endocrinology, IPGME & R and SSKM Hospital, Kolkata, gratefully acknowledged.

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Cite this article as: Pandit K, Mukhopadhyay P, Ghosh S, Chowdhury S. Natriuretic peptides: Diagnostic and therapeutic use. Indian J Endocr Metab 2011;15:345-53.

Source of Support: Nil, **Conflict of Interest:** None declared.