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BRAIN TYPE NATRIURETIC PEPTIDE (BNP) -A MARKER OF NEW MILLENNIUM IN DIAGNOSIS OF CONGESTIVE HEART FAILURE

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ABSTRACT

The burden of disease in patients with congestive heart failure is high. The future of BNP looks promising as it may be a better diagnostic tool for the diagnosis of CHF in developing countries in new millennium. Natriuretic peptide hormones, a family of vasoactive peptides with many favourable physiological properties, have emerged as important contenders for development of diagnostic tools and therapeutic agents in cardiovascular disease. Measurement of B-type natriuretic peptide has become as an easy-to-perform bedside test. The clinical and diagnostic significance of the measurement of plasma Nt-proBNP in the diseases of the cardiovascular system with particular emphasis on the assessment of patients with heart failure and their effects on predicting survival rate. The plasma levels of Nt-proBrain Natriuretic peptide responds more vigorously after myocardial infarction than those of other natriuretic peptides. This article is an attempt to give a short overview on the utility of BNP-blood levels for the diagnosis and treatment of heart failure

KEY WORDS

Congestive heart failure, B-Type Natriuretic peptide, Amino terminal pro brain natriuretic peptide, Left ventricular ejection fraction, Myocardial Infarction.

NATRIURETIC PEPTIDES AS CARDIAC BIOMARKER

In recent years, researchers have developed new tools to diagnose heart failure. There may be different causes of heart failure some of them are mentioned in Table 1. Measurement of plasma Brain Natriuretic Peptide concentration is a very efficient and cost effective mass screening technique for identifying patients with various cardiac abnormalities regardless of aetiology and degree of left ventricular systolic dysfunction that can potentially develop into obvious heart failure and carry a high risk of a cardiovascular event. B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide cardiac neurohormone secreted from membrane granules in the cardiac ventricles especially the left ventricle, as a response to ventricular volume expansion and pressure overload (1). Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are of myocardial cell origin and C-type natriuretic peptide (CNP) is of endothelial origin (2). BNP was originally named brain natriuretic peptide (3), and it was first detected in porcine brain. BNP levels are elevated in patients with various clinical conditions (Table 2). The levels correlate with severity of symptoms and with prognosis. It helps

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Table-1 : Causes of Heart Failure

COMMON :
• Coronary artery disease
• Hypertension
• Idiopathic
LESS COMMON :
• Diabetes mellitus
• Valvular disease
• Viral myocarditis
• Peripartum cardiomyopathy
• Tachyarrhythmia
• HIV infection etc.

Table-2 : Conditions associated with increased BNP levels :

- Heart failure
- Myocardial infarction
- Left ventricular hypertrophy in hypertension
- Cardiac inflammation eg. Myocarditis, cardiac allograft rejection
- Arrhythmogenic right ventricle with decreased ejection fraction
- Kwasaki disease
- Primary pulmonary hypertension
- Renal failure
- Ascitic cirrhosis
- Endocrine disease
- Geriatric age

to detect the presence of heart failure, determine its severity, and estimate prognosis. BNP has the potential to considerably improve the management of patients with congestive heart failure (CHF) and may become a routinely assessed serum parameter in clinical medicine (4). BNP is considerably less costly, as cost-effectiveness is highly desirable in the developing countries. Originally, the FDA approved the use of BNP or NT-proBNP (Amino terminal pro brain natriuretic peptide) for the evaluation of dyspnoea to assist in differentiating a cardiac cause for dyspnoea (e.g, congestive heart failure) from a non-cardiac origin for dyspnoea (chronic obstructive pulmonary disease).

Recently, NT-proBNP was approved by the FDA for the use in assessing the prognosis of patients with congestive heart failure and acute coronary syndromes, whereas BNP assay is also approved for risk stratification in acute coronary syndrome (5). Table 3 shows the comparison between all forms of natriuretic peptide for the laboratory testing.

Table-3 : Comparison of Different Natriuretic Peptides

	ANP	BNP	NT-proBNP
Half-life	3-5 minutes	20 minutes	60-120 minutes
Regulation	Granule stores	Transcription	Transcription
Pre-analytic	Exercise, posture	Minimal	Minimal
Stability	EDTA WB unstable	24 hr EDTA at 2-8 ^{0}C	72 hr EDTA at 2-8 ^{0}C

NATRIURETIC PEPTIDE BINDING AND CLEARANCE

There are three natriuretic peptide receptors i.e., NPR-A, NPR-B and NPR-C. Binding of natriuretic peptides to the A and B receptors on the surface of target cells leads to generation of the second messenger cyclic guanosine monophosphate, which mediates most of the biological effects of the natriuretic peptides (6). ANP and BNP bind preferentially to NPR-A and CNP to NPR-B. NPR-C is a clearance receptor for ANP and BNP. Lower affinity of NPR-C for BNP contributes to a longer plasma half-life of BNP compared with ANP in human beings. Commonly, natriuretic peptides relax vascular smooth muscle, causing arterial and venous dialation and leading to reduced blood pressure and ventricular preload. BNP and ANP also have important central and peripheral sympatho-inhibitory effects. Both hormones block cardiac sympathetic nervous system activity, even when cardiac filling pressures fall. These hormones also inhibit the rennin-angiotensin-aldosterone axis: BNP has direct lusitropic (relaxing) properties in the myocardium, and might have antiproliferative and antifibrotic effects in vascular tissues (7).

EFFECTS OF TREATMENT ON BNP CONCENTRATIONS

In patients with decompensated heart failure who are treated aggressively with diuretics and vasodilators, BNP concentrations fall rapidly together with intra cardiac filling pressure (8). ACE inhibitors angiotensin-II receptor antagonists (valsatan) and candesaritan (9) and an aldosterone antagonist (spironolactone) also lead to modest reductions in Brain Natriuretic Peptide concentrations (10).

Beyond its diagnostic and prognostic value, BNP can also help physicians to make clinical decisions about patients with heart failure, although much work remains in this emerging field. The premise of this approach is that decisions to start pharmacological treatments, or to use a more invasive strategy such as cardiac transplant, which might be based not only on symptoms and physical examination findings, but also on the concentrations of BNP. Various provocative pilot studies have prospectively assessed use of BNP to guide selection and intensity of pharmacotherapies (11). BNP could ultimately prove useful in helping doctors to select the appropriate drugs and drugs doses and of the need for more invasive, non-pharmacological strategies such as implantable defibrillators, ventricular assist devices, or cardiac transplantation.

In heart failure, as much as 75% of the total immunoreactive plasma BNP is of the high molecular mass form (12). The total immunoreactive plasma level of BNP is still an index of augmented synthesis and secretion. Apart from the secretion, peptide elimination is also important. BNP has a relatively short half-life with in the circulation than other peptides; the affinity of BNP for the clearance receptor is less. Brain natriuretic peptides are hydrolysed by neutral endopeptidases (13). In the pathophysical conditions, the raised levels of the brain

natriuretic peptides lead to intravascular volume overload, increased central venous pressures, tachycardia and reduced renal functions (14).

Plasma BNP increases with the age, values being about two fold higher in older subjects and possibly much higher (three to five folds) in the elderly patients than in the middle-aged people (15). Plasma BNP levels are not significantly influenced by the posture during blood collection but are higher (≈two folds) after several days of a high sodium diet. The presence of markedly elevated plasma natriuretic peptides suggests both atrial and ventricular overload as seen from plasma peptide measurements in patients with mitral stenosis or dilated cardiomyopathy (16). In mitral stenosis, the plasma levels of ANP are higher than BNP while in dilated cardiomyopathy associated with both atrial and ventricular overload, there are marked increase in the BNP and ANP levels.

MYOCARDIAL INFARCTION AND ISCHAEMIC DAMAGE

Plasma Brain Natriuretic Peptide (BNP) and ANP are raised after acute myocardial infarction even in the absence of ventricular failure and of raised atrial pressures; Investigation of the time course and BNP and ANP after acute myocardial; infarction has demonstrated a biphasic response. Both plasma levels of ANP and BNP were raised on the first day after infarction and, while ANP levels subsequently declined, BNP levels remained elevated during subsequent follow-up (17). Moreover BNP levels were associated inversely with left ventricular ejection fraction (LVEF), positively with infarct size, (assessed from myosin light chain I) and more importantly those with a distinct biphasic response had more severe heart failure. The marked increase in those without previous heart failure suggests that the raised levels may be due to myocardial necrosis and/or increased mechanical stress on cardiac tissue (18,19). Although it remains to be seen whether natriuretic peptides will substitute for established biochemical markers of infarct sizes (e.g. creatinine kinase and myosin light chain I), measurement of natriuretic peptides after myocardial infarction may provide potentially important prognostic information (20).

PROGNOSTIC SIGNIFICANCE

Several exciting uses for these tests have been identified in the last few years. These tests have been used effectively to assess prognosis after MI. BNP and NT-proBNP are better predictors of adverse events than LVEF(21) as predictors of death or heart failure. Plasma BNP is significant powerful independent predictor of cardiovascular mortality in Congestive Heart Failure (22). The three natriuretic peptides are powerful predictor of cardiovascular mortality but plasma BNP provides additional information independent of LVEF. A Global Utilization of Strategies to Open Occluded arteries IV sub-study has revealed that the use of Nt-pro brain natriuretic peptide (Nt-proBNP) appears to add critical prognostic insight to the assessment of patients with acute coronary syndrome (23). Prognosis is worse for those with higher BNP plasma levels a four folds increase of mortality in patients with BNP values twice above the normal (24). Patients with Nt-proBrain Natriuretic Peptide>1654ng/L had 27 times greater risk of dying than patients with Nt-proBrain Natriuretic Peptide <122 ng/L (25,26). Table 4 shows the BNP levels in health and different disease state.

Table-4 : BNP Levels in health and disease

BNP level (pg/ml)	Clinical Condition
< 100	Normal
< 500	Goal at hospital discharge
= 700	Decompensated congested heart failure
≈ 3,000	During nesiritide infusion

THERAPEUTIC ASSESSMENT

Increase of BNP plasma concentration can be achieved either with intravenous administration of the peptide or with inhibition of the endopeptidases i.e. partially responsible for its removal from circulation. Intravenous administration of synthetic human BNP nesiritide in heart failure patient causes dilation of the arteries and veins without causing any change to the heart rhythm, thus leading to increased cardiac output due to increased stroke volume (27). An average dose of nesiritide 0.030 mg/kg/min reduces pulmonary wedge pressure from 28 to 18 mmHg and increases cardiac index from 1.9 to 2.3 L/min/m^2 .The most important side effect of hypotension, which is nonetheless dose-related (administration of 0.030 mg/kg/min decreases systolic pressure about 10 mmHg). In July 2001 the FDA approved the administration of BNP in the treatment of heart failure.

CONCLUSION

Measurement of circulating endogenous BNP has proven to be sensitive and specific test for heart failure by various research workers (Table-5) and it can easily be used in emergency department. BNP facilitates natriuresis and diuresis while enhancing GFR, produces vasorelaxation, supresses neurohormonal activation of angiotensin II, aldosterone and endothelin -I, and regulates fluid and electrolyte homeostasis,

Table-5 : BNP levels in some Cardio Vascular Diseases

No	Diseases type	BNP levels	Reference
1	Essential hypertension	*	Buckley et al (29)
2	Tachycardia	**	Kohno M et al (30)
3	Heart failure	***	Yandle T et al (31)
4	Isolated diastolic dysfunction	***	Lang et al (32)
5	Mitral stenosis	***	Matsumo et al (33)
6	Aortic Stenosis	***	Ikeda t et al (34)
7	Dialeted cardiomyopthy	****	Thurpaf DJ et al (35)
8	Hypertrophic cardiomyopathy		
	a. Non obstructive	***	Hasegawa et al (36)
	b. Obstructive	** * *	
9	Myocardial infarction		
	a. At admission	***	Morita et al (37)
	b. During recovery	****	
10	Chronic renal failure		
	i. Dialysis -independent	**	Buckley M,et al (38)
	ii. Dialysis dependent	***	Lang C et al (39)

* Low ** Medium ***High **** Very High

contributing to volume and blood pressure regulation. Besides acute and chronic heart failure, BNP levels are elevated in cardiac ischemia, arrhythmias, pulmonary disorders and indirectly chronic kidney disease; thus, patients with elevated BNP levels should be evaluated for the presence of these other conditions. Patients with CHF despite poly-pharmacotherapy have a tremendous morbidity and mortality exceeding that of most solid organ cancers. Improvement of care and outcome in these patients is definitely needed. BNP testing may be a significant first step. BNP levels are predictive of clinical outcomes and therefore might be useful in making decisions with regard to treatment of congestive heart failure. The determination of BNP or NT-proBNP is one of the modern success stories in laboratory medicine. Many studies have documented the unquestionable clinical value of these tests for the diagnosis and assessment of CHF, in addition to their application to several other cardiovascular disease and entities. Future observation will clarify analytical and diagnostic difference between the BNP and NT-proBNP and the application of these tests to other diseases. Laboratories not currently offering BNP or NT-proBNP measurement should consider adding them to their clinical armamentarium.

FUTURE RESEARCH

Data from randomised clinical trails are eagerly awaited and it is absolutely necessary to correlate the role of BNP in different clinical settings i.e. incidence of heart failure- related death, hospital admission. Still more clinical trails are needed to establish the role of BNP in the diagnosis of CHF, LVD and acute MI more effectively in Indians. In an elderly population, measurements of BNP may add valuable prognostic information and may be used to predict mortality in the total population as well as in patients with known cardiovascular disorders. In subjects without any known cardiovascular disorder, BNP was a strong and independent predictor of total mortality.

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