Brain natriuretic peptide (BNP): A diagnostic marker in congestive heart failure-induced acute dyspnea

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INTRODUCTION

Heart failure (HF) is a clinical syndrome that occurs in patients who because of an inherited or acquired abnormality of cardiac structure and/or function develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy.[1] Acute dyspnea is a common clinical finding with which the patient is admitted in the emergency department. A rapid and accurate investigation of acute dyspnea is vital since treatment of dyspnea can differ markedly depending on the initial clinical impression. However, the rapid and accurate differentiation of heart failure from other causes of dyspnea remains a clinical challenge. After evaluating patient's symptoms, conducting a physical examination, and performing electrocardiography (ECG) and chest radiography, the clinician is often left with considerable diagnostic uncertainty, which results in misdiagnosis and delays the initiation of appropriate therapy. Distinguishing between cardiac and non-cardiac causes of dyspnea is often challenging. Therefore, an assay with high sensitivity and high negative predictive value would be useful both in detecting dyspnea due to heart failure and in ruling out the diagnosis in patients with confounding co-morbid conditions.[2] A definitive congestive heart failure (CHF) diagnosis is often based on right heart catheterization or indirect measurement of ejection fraction by means of radionuclide scanning or echocardiography. Lack of immediate availability and high cost make these studies prohibitive as emergency department screening tests. As a result, an emergency diagnosis of CHF is often based on history and physical examination findings along with results of ancillary tests, such as chest radiography and ECG.[3] Therefore, a blood test that could rapidly and accurately confirm or exclude the diagnosis of CHF in the urgent care setting would be a valuable clinical tool.

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NATRIURETIC PEPTIDES

Heart is an endocrine organ which secretes natriuretic peptides (Table 1).[4,5] The natriuretic peptide family consists of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and three other structurally similar peptides: C-type natriuretic peptide (CNP) mostly of central nervous system and endothelial origin, urodilatin from the kidney and dendroaspis natriuretic peptide (DNP), which is of unknown significance.[6] Since, these peptides are secreted in response to haemodynamic stress, they are promising markers of myocardial dysfunction and heart failure.

The main source of BNP is the ventricles of the heart, although it can also be demonstrated in the atria of the failing heart. BNP is synthesized in bursts and is released predominantly in response to stretching of the ventricular wall and volume overload. The biologic actions of BNP include vasodilatation, diuresis, natriuresis and inhibiting or antagonizing the actions of the renin-angiotensin-aldosterone system, the sympathetic nervous system, arginine vasopressin and endothelin.[7] Elevation of plasma

Table 1: Natriuretic Peptides

Name	Structure	Synthesis	Action
Atrial Natriuretic Peptides	28 amino acid peptide	Myocytes of cardiac atria	Increase in sodium excretion, increase glomerular blood flow, increase in GFR, inhibits sodium reabsorption, inhibits aldosterone secretion, decrease rennin release, lower blood pressure.
Urodilatin	32 amino acid peptide	Intercalated cells in cortical collecting duct.	Decrease sodium reabsorption.
Brain Natriuretic Peptide (BNP)	32 amino acid peptide.	Myocytes in cardiac ventricle.	Sodium excretion.
Guanylin	15 amino acid peptide.	Goblet cells in colon.	Sodium excretion.
Uroguanylin	16 amino acid peptide.	Enterochromaffin cell in duodenum	Sodium excretion.
C-type natriuretic peptide	53-amino-acid peptide	Brain and is found in high concentrations in chondrocytes.	CNP is to stimulate long bone growth.

BNP is one of the characteristics of patients with or at risk of diastolic heart failure among subjects with preserved left ventricular systolic function.[8] Hence, the present study was undertaken to study the levels of BNP and to assess its diagnostic accuracy in CHF.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry in collaboration with the Department of Internal Medicine of Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala (Haryana). 100 patients who were admitted in the ED with complaint of acute dyspnea from May 2011 to April 2012 were included in the study.

INCLUSION CRITERIA: Acute shortness of breath or dyspnea was defined as an abnormally uncomfortable awareness of breathing of less than 7 days duration. Those patients primarily presenting with acute shortness of breath (NYHA class III-IV) constituted the study group.

EXCLUSION CRITERIA: Patients with history of renal disease (serum creatinine >2.8 mg/dl), cirrhosis with ascitis, thyroid dysfunction, trauma chest wall, acute bronchial asthma, pneumonia, acute myocardial infarction, unstable angina and on chronic use of β-blockers, diuretics and digoxin, angiotensin-converting enzyme inhibitors.

CATEGORIZATION OF PATIENTS: Those patients fulfilling the Framingham's criteria[9] (Table 2) were classified as having dyspnoea due to congestive heart failure (CHF) and those not meeting the criteria, as dyspnea not due to CHF.

SERUM BNP ASSAY: After taking informed and written consent, 10 ml of blood sample was withdrawn from a peripheral vein by a plastic disposable syringe and collected in an air tight lavender top EDTA (ethylene-diamino-tetra-acetic acid) plastic tube. The sample was centrifuged and BNP was assayed by chemiluminescence method.[10]

Table 2: Framingham criteria

Major criteria	Minor criteria
• Paroxysmal nocturnal dyspnea.	• Bilateral ankle oedema.
• Neck-vein distention.	• Nocturnal cough.
• Rales.	• Dyspnea on ordinary exertion.
• Radiographic cardiomegaly.	• Hepatomegaly.
• Acute pulmonary oedema.	• Pleural effusion.
• S3 gallop.	• Decreased vital capacity by 1/3 from maximum value recorded.
• Central venous pressure ≥16 cm of H_2O.	• Tachycardia (≥120 beats/min)
• Circulation time ≥25 secs.	
• Hepatojugular reflux.	
• Pulmonary oedema, visceral congestion, or cardiomegaly at autopsy.	
• Weight loss ≥4.5 kg in 5 days in response to treatment of congestive heart failure.	

STATISTICAL ANALYSIS: The data obtained was compiled and analyzed using Epi- info version 6.0. Diagnostic accuracy of BNP was evaluated by calculating sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals.

RESULTS

The study sample comprised of 100 patients (55 males and 45 females), out of which 60 were diagnosed as having CHF and 40 as no CHF where final diagnosis was supported by echocardiography. Serum BNP was more than 100 pg/ml in 54 patients with CHF and 8 patients without CHF and it was less than 100 pg/ml in 6 patients with CHF and 32 patients without CHF (Table 3). Higher mean BNP levels were observed with advancing age particularly in patients with CHF with highest mean BNP levels of 770.02 pg/ml in age group of more than 75 years in males and 706 pg/ml in age group of 66–75 years in females. However, lower BNP levels were observed in patients without CHF with lowest mean BNP levels of 51.05 pg/ml in age group of 56–65 years in males, whereas 63.06 pg/ml in age group of 15–25 years in females (Table 4, Figures 1, 2). It was also observed that out of 60 patients diagnosed to have CHF, majority had BNP levels more than 400 pg/ml (Table 5).

DISCUSSION

In the present study, 100 patients of different age groups were studied whose predominant symptom was dyspnea of acute onset (<7 days). Out of 100 patients, 55% were males and 45% were females. Patients of dyspnea were clinically evaluated which included complete history and examination, ECG and X-ray chest. Subsequently, patients were divided into two groups namely CHF group and No CHF group. Out of 100 patients, 47 were diagnosed to have CHF and 53 were not having CHF. Cut off of <100 pg/ml BNP levels was taken to exclude heart failure. It was observed that according to BNP levels alone 62 patients had heart failure (BNP levels of >100 pg/ml) and 38 patients had dyspnea not due to heart failure (BNP levels < 100 pg/ml.). In this study, the final diagnosis of CHF was made in 60 patients and 40 patients were included in No- CHF group (those

Table 3: Diagnosis of CHF

Final diagnosis of CHF based on echocardiography	Based on serum BNP level		Based on clinical evaluation	
	>100 pg/ml	<100 pg/ml	CHF present	CHF absent
CHF present	54	06	42	18
CHF absent	08	32	05	35

Table 4: Serum BNP levels in patients with or without CHF in both sexes with respective to their age groups

Age (years)	Males	Females	Total	Mean serum BNP in (pg/ml) in patients with CHF		Mean serum BNP (pg/ml) in patients without CHF	
				Males	Females	Males	Females
15–25	5	3	8	140	134	57.6	63.06
26–35	4	8	12	243	206.5	59.2	70.58
36–45	9	7	16	408.4	366.5	53.06	125.6
46–55	10	8	18	550.17	343	200	109.12
56–65	8	7	15	404.35	480.75	51.05	102
66–75	6	6	12	394.32	706	63.9	65.2
>75	13	6	19	770.02	628	78	84
Total	55	45	100				

Table 5: Serum BNP levels in patients with or without final diagnosis of CHF

BNP levels (in pg/ml)	With CHF	No CHF	Total
<100	6	32	38
100–199	1	3	4
200–299	5	3	8
300–399	10	1	11
400– 699	20	0	20
>700	18	1	19
Total	60	40	100

Table 6: Diagnostic accuracy of serum BNP levels versus clinical evaluation

Diagnostic accuracy	Serum BNP levels (pg/ml)	Clinical assessment
Sensitivity	90% (78.83–95.86)	70 (56.62–80.79)
Specificity	80% (63.86– 90.38)	87.5 (72.39–95.30)
Positive predictive value	87.09% (75.59–93.38)	89.36 (76.10–96.01)
Negative predictive value	84.21% (68.07–93.41)	66.03 (51.64–78.11)

patients who had non cardiac dyspnea). It was observed that clinical examination has a sensitivity of 70%, specificity of 87.5%, positive predictive value of 89.36%, negative predictive value of 66.03% for diagnosing CHF where as BNP levels has a sensitivity of 90%, specificity of 80%, positive predictive value of 87.09, negative predictive value of 84.21 for diagnosing CHF (Table 6). It was also observed that out of 100 patients 9 patients which included 7 males and 2 females had normal systolic functions (LVEF > 50%) but were included in the final diagnosis of diastolic heart failure by the cardiologist based on diastolic filling abnormalities on echocardiography. All these 9 patients had BNP levels >100 pg/ml (mean BNP 523.9 pg/ml). Out of these 9 patients, 3 patients had initial clinical diagnosis of heart failure. Similarly, in a study conducted by Lubien E et al[11] it was found that BNP can reliably detect diastolic heart failure in presence of normal left ventricular systolic function. Therefore, BNP assay can reinforce the diagnosis of diastolic heart failure in such patients. Furthermore, it was seen that 18 patients had BNP levels of more than 700 pg/ml at the time of admission. These patients had severe heart failure and majority had markedly reduced ejection fraction. Out of these, 8 died within 7 days of hospital stay which indicates the correlation of BNP levels with severity of CHF and also its prognostic significance. Martin and Ricou[12] also reported that raised BNP has a prognostic value to predict mortality after CHF.

CONCLUSION

There is strong and convincing evidence that BNP is a reliable and useful biomarker in acute dyspnea due to CHF and has a diagnostic as well as prognostic value. Used in conjunction with other clinical information, rapid measurement of BNP may reduce the total treatment cost of patients. Due to its prognostic implication it is recommended that BNP should be measured in all the patients with clinical signs of CHF even if the diagnosis is apparent. A careful history and examination of the patient and a systematic search for complicating factors is necessary for the appropriate analysis and the correct use of these biomarkers.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

ETHICAL CONSIDERATION

The protocol for this study was approved by the Institutional Ethical Committee. All work was performed according to the international guidelines for human experimentation and biomedical research.[13] Approval was obtained from the subjects by taking the informed consent.

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