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Original Article

Biochemistry Section

Brain Natriuretic Peptide Levels in Hypertensive Heart Failure Patients with and without Diabetes Mellitus: A Cross-sectional Study

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ABSTRACT

Introduction: Heart Failure (HF) is a major disorder causing mortality and morbidity in the elderly population. Brain Natriuretic Peptide (BNP) is considered as the gold standard biomarker for diagnosis of HF.

Aim: To find the association of plasma BNP levels with heart failure in hypertensive patients with and without diabetes mellitus.

Materials and Methods: This cross-sectional study consisted of 35 hypertensive heart failure patients who attended the Outpatient General Medicine Department at Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, between March 2020 to December 2020. The patients who belonged to class IV heart failure of the New York heart association were included. Total 35 HF patients were divided into two groups. Group 1 included 10 patients with hypertensive heart failure without diabetes mellitus. Group 2 included 25 patients with hypertensive heart failure with diabetes mellitus. Parameters such as Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), waist to hip ratio, Body Mass Index (BMI), Ejection Fraction (EF), transmitral filling velocities (E/A ratio), Left Ventricular Posterior Wall Thickness (LVPW), Left Ventricular Internal Dimension in diastole (LVIDd) and BNP level, random plasma glucose and HbA1c% were assessed in all the patients. Student's t-test and Mann-Whitney U test were used to statistically analyse the data and p-value ≤ 0.05 was considered statistically significant.

Results: Mean age of patients were 65.80±12.72 years in group 1 and 66.56±11.72 years in group 2. All patients in group 1 and most of the patients in group 2 (15,42%) were males. All the patients were in the obese category (BMI >27 kg/m^2). Serum BNP level was 1365 (243-3680) ng/L in group 1 and 691 (44.7-4261) ng/L in group 2, but this difference was not statistically significant (p-value=0.23). Echocardiography showed significant differences in left ventricular internal dimension in diastole, left ventricular posterior wall thickness and E/A ratio-integrated between hypertensives and hypertensives with diabetes mellitus. Serum BNP had a significant positive correlation with systolic blood pressure (r=0.33, p-value=0.05). There were highly significant differences in random plasma glucose and glycated haemoglobin between the groups.

Conclusion: Plasma BNP levels were associated with systolic blood pressure in heart failure patients with hypertension. The significance of association is the same in hypertensives with diabetes mellitus. Thus, BNP as a biomarker plays a major role in the prediction of heart failure. But BNP could not differentiate whether the heart failure was due to hypertension alone or due to associated metabolic conditions.

Keywords: Diabetic heart failure, Ejection fraction, Left ventricular internal dimension in diastole, Left ventricular posterior wall thickness

INTRODUCTION

Heart Failure (HF) is a major illness and cause of death in the elderly population. Nearly 64.3 million people are living with heart failure worldwide [1]. Heart failure has been defined as global pandemic, since it affects many million individuals. It is estimated that 5.8 million people in the United States have heart failure with approximately 670,000 new cases occurring each year. The current worldwide economic burden of HF can be estimated at 346.17 billion US dollars [2]. Heart failure is increasing in India as well, affecting 8-10 million individuals [3]. In Western countries, heart failure is predominantly a disease of the elderly [4]. But in India it affects younger age group also and have been found that essential hypertension is the commonest cause for HF [5]. Among the various states of India, Punjab, Tamil Nadu and Haryana have the highest number of heart failure cases, the disease burden has increased to 104% since 1990 and it was estimated that there were 17.8% deaths due to HF in 2016 [5].

Diagnosis of HF remains a challenge despite the advancements in medicine. With increasing age of the population, the number of cases with mortality and morbidity due to HF is also high. Biomarkers provide valuable information about the pathophysiology of the disease process [6]. Biomarkers are also effective in various aspects of the disease such as early diagnosis, risk stratification, have high sensitivity and specificity, and assess the disease progression in patients with heart failure [7]. Till date, Brain Natriuretic Peptide (BNP) is considered to be the gold standard biomarker of heart failure. The BNP is a member of the Natriuretic Peptides (NP) family. It is primarily expressed in cardiomyocytes, in both atria and ventricles of the heart; but it is found that the left ventricle is the predominant source of BNP in the body. The BNP dilates blood vessels, decreases vascular resistance, increases stroke volume, increases renal sodium secretion and increases urine production. All these result in a decrease in circulatory blood volume and thus blood pressure. This in turn decreases pressure or stretch on the various chambers of the heart [8].

The progression of heart failure is not the same in all the individuals. It varies according to race, ethnicity, age, presence of co-morbid conditions such as obesity, hypertension, diabetes mellitus, as well as change in phenotypes of heart failure as classified by a imaging study [7]. Hence, diagnosis and management of HF will not be uniform in all the patients. Therefore, a combined approach of history, biomarkers and imaging studies could help to reduce the rate of development

of the disease. Based on the results obtained, appropriate treatment modalities can be initiated in the deserving patients. People with hypertension and diabetes mellitus have the high risk of developing HF in the long run. Both are metabolic disorders with involvement of almost of all organs including heart in the body [7].

Diagnosis of HF was based on clinical manifestations and echocardiography. But with the introduction of natriuretic peptides the management of these patients has become better. Various societies which cater to the management of heart failure and other heart diseases have included brain-type natriuretic peptides in their guidelines [9]. Studies are lacking both at international and national levels with regard to the damage caused by hypertension and diabetes mellitus and its association with phenotypic variations of HF [3,8,10]. Hence, the present study was done to assess the BNP levels in hypertensive heart failure patients with and without diabetes mellitus.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry and General Medicine, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, from March 2020 to December 2020. The study was approved by the Institutional Ethics Committee (IEC-NI/19/FEB/68/09, 10.11.2020). All study participants provided written informed consent before being inducted into the study.

Inclusion criteria: All 35 heart failure patients aged between 30-85 years of both sexes, diagnosed to be in class IV of New York Heart Failure Association (NYHA) [9], had Ejection Fraction (EF) of ≤49% as shown by echocardiography were included in the study.

Exclusion criteria: Patients with acute heart failure, myocardial infarction, valvular heart diseases, and patients on anticancer drugs, pregnancy, thyroid, pulmonary and renal disorders, connective tissue and infectious diseases were excluded from the study.

Sample size calculation: With significance of 95%, power of 80% and odds ratio of 1.9 the sample was calculated to be 270 [10]. Out of which only 35 patients had BNP done at the time of emergency admission. Hence only these 35 patients were included in this manuscript. Other patients were subjected to further investigations. Total 35 HF patients were divided into two groups:

- Group 1 (n=10): Patients with hypertensive heart failure without diabetes mellitus.
- Group 2 (n=25): Patients with hypertensive heart failure with diabetes mellitus.

Study Procedure

The transthoracic 2D doppler echocardiography was performed in Phillips and GE Healthcare echocardiography with patients in the left lateral decubitus position.

Parameters such as SBP, DBP, W/H ratio, BMI, ejection fraction (EF), E/A ratio, LVIDd, LVPW and BNP level, random plasma glucose and HbA1C % were assessed in all the patients.

Ejection Fraction (EF): According to the definition in European and United States (US) guidelines, the normal EF range is 52-72% in men and 54-74% in women, with normal Mean±SD being 62±5% for male and 64±5% for female [11].

E/A ratio: The E/A ratio is the ratio of the early (E) to late (A) ventricular filling velocities. In a healthy heart, the E velocity is greater than the A velocity >1.0 [12]

Left Ventricular Internal Dimension in diastole (LVIDd): The normal range for LVIDd was 3.5-5.6 cm [13].

Left Ventricular Posterior Wall Thickness (LVPW) [14]:

- Normal individuals have LVPW of 42-59 and 39-53 mm in male and female, respectively.
- Mildly dilated HF patients have LV of 60-63 and 54-57 mm in male and female, respectively.
- Moderately dilated LV was found to be 64-68 and 58-61 mm in male and female respectively.
- Severely dilated HF patients, LV is ≥69 mm and ≥62 mm in male and female respectively.

Blood samples: Ten mL was taken for measurement of following:

- Random plasma glucose: Normal value <140 mg/dL,
- Glycated haemoglobin (HbA1c)%: Value of <5.7% was considered normal. In diabetic patients HbA1c was ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2 hr plasma glucose or random glucose ≥200 mg/dL were considered [15].
- Brain Natriuretic Peptide (BNP) levels: The BNP levels were estimated by fluorescence Immunoassay method (Quidel Triage Cat. No. 01531) [16].
  - -Plasma BNP ≤99 pg/mL was considered normal in individuals without HF.
  - -Plasma BNP ≥100 pg/mL was suggestive of HF.
  - -Plasma BNP >5000 pg/mL was considered as very high.

Anthropometric characteristics: Body Mass Index (BMI) in Kg/m^2 and waist-to-hip ratio were measured according to the standard procedures. As per Asia-Pacific guidelines; normal WHR is <0.90 in male and <0.85 in female [17]. Systolic and diastolic blood pressures were measured using standard procedure.

STATISTICAL ANALYSIS

The statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) software version 16.0. The continuous variables were reported as mean±Standard Deviation (SD) or median and Inter Quartile Range (IQR). For the comparisons between the groups, student's t-test or Mann-Whitney U test and Chi-square rank sum test were used. The relationships between BNP and other variables were assessed using Pearson's correlation coefficient. The p-value ≤0.05 was considered statistically significant.

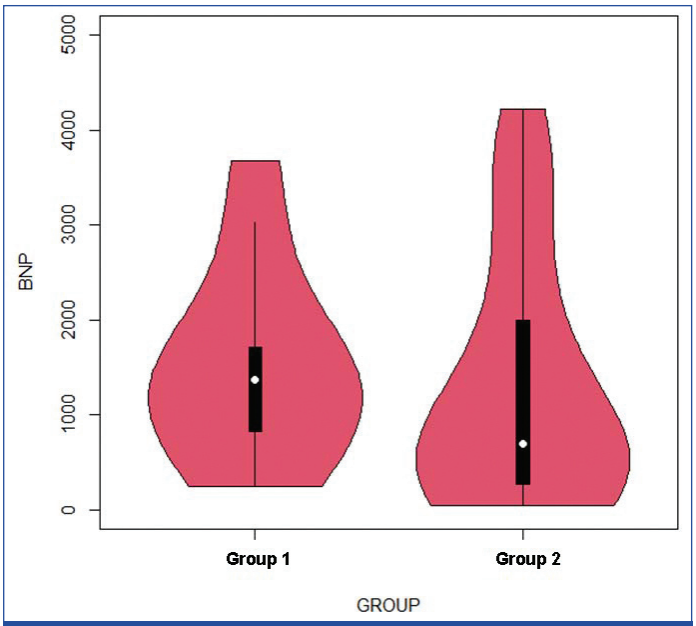
RESULTS

[Table/Fig-1] shows baseline characteristics and echocardiographic measurements of the patients with the mean age of 65.80±12.72 years in group 1 and 66.56±11.72 years in group 2. All patients in group 1 and most of the patients in group 2 (15,42%) were males. The BMI of groups 1 and 2 were 27.89±3.16 and 27.29±2.19 Kg/m^2

Parameters	Group 1 (Mean±SD)	Group 2 (Mean±SD)	p-value
Age (years)	65.80±12.72	66.56±11.72	0.87
Gender			
Male (n, %)	10 (29%)	15 (42%)	0.06
Female (n, %)	0	10 (29%)	
BMI (kg/m^2)	27.89±3.16	27.29±2.19	0.59
WHR	0.94±0.009	0.94±0.01	0.45
SBP (mmHg)	142.0±4.21	147.72±16.73	0.12
DBP (mmHg)	91.0±3.16	92.4±8.79	0.49
EF (%)	32.9±8.7	32.6±8.07	0.92
LVPW (mm)#	9 (8-14)	9 (7-146)	0.006**
LVIDd (mm)	39.9±5.64	53.0±4.83	0.001**
E/A ratio	2.32±1.13	1.22±0.63	0.009**
RPG (mg/dL)#	123 (104-140)	176 (148-242)	0.0041**
HbA1c (%)#	5.6 (5.4-6.0)	9.2 (6.8-10.55)	0.00036**

[Table/Fig-1]: Baseline characteristics and echocardiographic measurements of study participants.
BMI: Body mass index; WHR: Waist hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EF: Ejection fraction; LVPW: Left ventricular posterior wall thickness; LVIDd: Left ventricular internal dimension in diastole; E/A ratio: Transmitral filling velocities-integrated, RPG: Random plasma glucose; HbA1c: Glycated haemoglobin
#Data expressed as median and interquartile range; others are expressed as mean and SD
Student t test, Mann Whitney U test, Chi-square rank sum test were used
**p-value: <0.001 was considered as highly significant

respectively, which were not statistically significant (p-value=0.59). The waist to hip ratios were 0.94±0.009 and 0.94±0.01, respectively, which were not statistically significant (p-value=0.45). Violin plot displays the distribution of BNP among the study group [Table/Fig-2].



[Table/Fig-2]: Violin plot displaying the distribution of BNP among the study group.
BNP: Brain natriuretic peptide; Expressed as median and interquartile range.
In each violin plot, the white spot indicates the median value. The thick broad rectangle indicates interquartile range. The thin line connects the entire range of values in each group. The violin shape (width) indicates the distribution of data in the individual groups (Pink color)

In group 1, BNP level was 1365 (243-3680) ng/L and in group 2 was 691(44.7-4261) ng/L, but this difference was not statistically significant (p-value=0.23). [Table/Fig-3] shows serum BNP had a significant positive correlation with systolic blood pressure among the patients (r=0.33, p-value=0.05).

Parameters	Correlation coefficient (r)	p-value
BMI	0.28	0.10
WHR	0.08	0.65
SBP	0.33	0.05*
DBP	0.22	0.20
EF%	-0.04	0.80
LVPW	-0.01	0.95
LVIDd	0.06	0.74
E/A ratio	-0.01	0.94

[Table/Fig-3]: Correlations between BNP with other variables.
Pearson's correlation coefficient. *p-value ≤0.05 was considered as significant

DISCUSSION

The age of HF patients in groups 1 and 2 were 65.80±12.72 years and 66.56±11.72 years, respectively. Among the study participants males were affected more than the females. In patients with hypertension, cause for elevated blood pressure is mainly stiffening of arteries especially in older individuals. These age-related alterations pave the way for adverse cardiovascular events and death. Until the age of 60 years both systolic and diastolic blood pressures increase with age. Beyond 60 years, systolic blood pressure continues to increase whereas diastolic pressure remains the same or decreases [18].

Body mass index and WHR were in the obese category in both the groups. All the study participants were categorised under obese category based on WHR as per Asia-Pacific guidelines [17]. The prevalence and severity of blood pressure in hypertensives are directly proportional to the increasing BMI. Volume and pressure overload as found in hypertensives becomes worse when there is associated overweight or obesity. Hypertension leads to concentric Left Ventricular (LV) hypertrophy, but there is eccentric LV hypertrophy in the presence of obesity [19].

Random plasma glucose in groups 1 and 2 were 123 (104-140) and 176 (148-242) mg/dL (p-value=0.0041). Glycated haemoglobin (HbA1c) levels were significantly higher between the groups (p-value=0.0003). Diabetic patients present with two different phenotypes of HF based on the pathogenesis LV hypertrophy, insulin resistance and dislipidaemia contribute to HF with preserved EF. Factors such as oxidative injury, fibrosis, and apoptosis predispose to HF with reduced EF. In the initial stages, there is diastolic dysfunction, which in the long run leads to systolic dysfunction with poor prognosis [20].

In a cohort study by de Simone G et al., various mechanisms were attributed to heart failure in diabetic individuals. Although the authors have excluded patients with ECG of myocardial damage, it was not possible to exclude silent ischaemia. Presence of LV structural abnormalities such as concentric remodelling of LV with increased mass. There is found to be impaired energy metabolism with ineffective LV filling. All these factors contribute to impaired function of coronary vascular system in diabetic heart failure [21].

In the present study, the echocardiographic parameters of the patients showed that left ventricular internal dimension in diastole were 39.9±5.64 mm and 53.0±4.83 mm in groups 1 and 2, respectively (p-value=0.001); LVPW showed {9 (7-146)} mm and {9 (8-14)} mm in both the groups, respectively (p-value=0.006); and transmitral filling velocities-integrated (E/A ratio) were 2.32±1.13 and 1.22±0.63 in both the groups, respectively (p-value=0.009). The LV ejection fraction remains the diagnostic tool of HF diagnosis, prognosis, and treatment selection. The clinical use of EF has drawbacks, hence other parameters have been demonstrated to be better than the use of EF alone. The HF patients with ejection fraction ≤35% is defined as severe LV dysfunction [11].

The American Society of Echocardiography criteria classifies HF based on LV size as normal with no dilatation, mildly dilated, moderately dilated and severely dilated. The HF patients with LV dysfunction of moderate severity could present with low EF. This limits the utilisation of EF for stratifying HF patients. LV internal dimension in diastole (LVIDd) is an independent predictor of progression of HF and can be used to guide aggressive therapies [14]. The normal range of LV internal diameter end diastole is 3.5-5.6cm [13].

Mitral inflow pattern is a maker of diastolic function. Isovolumic relaxation time, ratio of E and A velocities, deceleration time of E velocity, and duration of A wave is used to assess diastolic dysfunction. Normally E/A ratio is more than 1.0 and is decreased in LV diastolic dysfunction. But with severe LV dysfunction, the ratio increases to more than 2.0, indicating adverse prognosis. E/A ratio is an independent predictor LV dysfunction [12]. The normal range of LV posterior wall thickness in end diastole is 60-110 mm [13]. In hypertensive individuals there is increased arterial stiffness, impaired relaxation, increased LV systolic overload and concentric remodelling/hypertrophy leading to increased LV stiffness as in HF [22].

In the present study, BNP levels were 1365 (243-3680) and 691 (44.7-4261) ng/L in in groups 1 and 2, respectively (p-value=0.23). The level of BNP is closely related to the occurrence and the severity of HF. There is predominantly LV concentric remodelling/hypertrophy and aortic stiffness in hypertensive patients. In response to stress, cardiac myocytes release BNP, thus can detect mild HF, as well as asymptomatic LV dysfunction [23]. The BNP stimulates transient receptor potential channel 6 causing increased intracellular calcium and cardiac hypertrophy [24]. The hypertrophic response in left ventricle, decreases LV wall stress back to normal [25].

In the present study, BNP was positively correlated with systolic blood pressure (r-value=0.33, p-value=0.05). The ARIC study by Hussain et al., was a prospective population-based study. The

study recruited participants of age 45-64 years of both genders from four US communities. The study identified individuals having high NT-proBNP but with minimally elevated blood pressures. These individuals were found to be at risk for cardiovascular events and stroke regardless of their blood pressure. Thus, BNP could serve as a prognostic marker in hypertensive individual and timely personalised management could be offered [26]. There was no correlation with BMI, WHR, diastolic blood pressure, and ECHO parameters probably due to small sample size.

Limitation(s)

In present study, calculated sample size was 270, out of which only 35 patients had BNP done at the time of emergency admission, this was the major limitation. Stratification of ejection fraction and their association with BNP levels could not be done.

CONCLUSION(S)

Plasma BNP levels were higher in hypertensives and BNP could predict heart failure in hypertensives. Also, it helps in assessing the severity of heart failure. BNP could not differentiate whether the heart failure was caused solely by hypertension or heart failure is due to associated with both metabolic conditions. BNP levels were positively correlated with systolic blood pressure. But echocardiographic findings such as LV internal dimension in diastole, LV posterior wall thickness in diastole and E/A ratio were not able to differentiate between HF due to hypertension alone or associated with diabetes mellitus also.

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