ORIGINAL ARTICLE

Plasma B-type Natriuretic Peptide Levels in Stable Heart Failure Patients

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Abstract

Introduction: Heart failure (HF) is a major and growing public health problem among the global population. Cardiac biomarkers are a promising tool for the early and specific detection of heart failure. B-type natriuretic peptide (BNP) is one such cardiac biomarker released in response to ventricular myocyte stretch.

Aim: The aim of the present study was to estimate the levels of plasma BNP in patients with stable chronic heart failure (CHF) and to compare them with controls. Further to correlate the relationship between plasma BNP levels and factors like age, gender and left ventricular ejection fraction (LVEF), in the two groups.

Materials and methods: A case-control study conducted in Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India consisting of 55 stable CHF patients on treatment and 35 controls. Serum creatinine was estimated adopting modified Jaffe's method. eGFR was calculated using the modification of diet in renal disease (MDRD) formula. Plasma BNP levels were measured by ELISA.

Results: The mean BNP concentration in patients with stable CHF was 60.46 ± 16.13 pg/mL, while in controls it was 20.94 ± 5.81pg/mL and the difference was highly significant (p= 0.001). As the age increases an increasing trend in the values of plasma BNP was observed in both groups. There was a strong negative linear relationship (r = -0.798) observed between LVEF and BNP levels in the study population. A cut-off level of 30.2pg/mL for plasma BNP had a 100% sensitivity and specificity to predict CHF.

Conclusion: Our study concludes that plasma BNP was significantly higher in patients with stable chronic heart failure than in the controls. Plasma BNP as a biomarker will help in identifying stable CHF patients who are asymptomatic, on their adequacy of treatment.

Keywords: B-type natriuretic peptide, Biomarker, Case-control study, Heart failure.

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Introduction

A structural or functional abnormality of the heart, which is long-standing and impairing its ability to pump adequate blood to the peripheral tissues to meet their metabolic demands, results in chronic heart failure (CHF).[1] Worldwide around 26 million people suffer from HF.[2] Diverse molecular pathways like an injury to the cardiomyocytes, activation of the neuro-hormones, inflammation, oxidative stress, fibrosis and remodeling of the extracellular matrix are involved in the pathogenesis of HF.[3] The major cause for symptoms in CHF is the excessive circulating blood volume. In humans, Renin-angiotensin Aldosterone system and Natriuretic peptides act antagonistically and maintain euvolemia.

When the circulating blood volume is increased causing cardiac ventricles to stretch, pro-BNP is cleaved into the active fragment BNP (32 amino acids) and the inactive fragment NT pro-BNP which are released into the blood in equimolar amounts.[4] BNP acts via NPRA cell surface receptors and raises the intracellular cGMP levels in the effector cells. The physiologic actions of BNP are to promote natriuresis, diuresis and vasodilation. The concentration of BNP in an untreated HF patient can be as high as in thousands.[5] Precise monitoring of the short-term ventricular stress response together with its stability in HF patients with early renal failure,[6] makes BNP estimation advantageous over NT-pro-BNP. Periodic assessment of BNP in patients with CHF gives an objective data which provides clues for anticipating cardiac decompensation and facilitating therapeutic adjustment in advance.[7] The aim of the present study was to estimate the levels of plasma BNP in patients with stable CHF and to compare them with controls. Further to correlate the relationship between plasma BNP levels and factors like age, gender and left ventricular ejection fraction (LVEF), in the two groups.

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Materials and Methods

A case-control investigation on the levels of plasma BNP in stable chronic heart failure patients was carried out between October 2012 and October 2013 in Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India.

Data Collection

The study was conducted after obtaining Institutional Ethical committee clearance. The study group comprised of 55 known cases of stable CHF patients who attended the review outpatient department of cardiology. There were 39 adult males and 16 females. The control group comprised of 35 adults attending the cardiology outpatient department for cardiac evaluation under anesthetic fitness for surgeries. There were 23 males and 12 females in the control group.

Inclusion Criteria

Cases

- Stable CHF patients with Left ventricular ejection fraction < 45% by echocardiography.
- Patients were on treatment for CHF with Diuretics, β-blockers, ACE inhibitors and statins.

Controls

Patients having no symptoms of heart failure with LVEF ≥ 60% by Echocardiogram.

Exclusion Criteria

- Newly diagnosed heart failure patients of < 6months duration,
- Acute or decompensated heart failure patients,
- Renal failure (eGFR < 90 mL/min)
- Anemia (Hb < 10g/dL),
- Thyroid dysfunction.

Procedure

Four mL of blood was collected from the anti-cubital vein of the patients and was aliquoted in EDTA tube and red-capped tube. The samples were centrifuged within 30 minutes of collection and were stored at –70°C until further processing. Plasma and serum samples were used for BNP and creatinine estimations respectively. Serum creatinine was estimated first by modified Jaffe's method, using an IDMS traceable calibrator and eGFR was calculated using the MDRD formula. Patients with eGFR > 90 mL/min/1.73 m^2 were only included in the study as case or control. The plasma B-type Natriuretic Peptide levels were estimated using the Competitive ELISA method (RayBiotech, Inc, USA) using ELISA plate analyzer and ELISA plate washer (Robonik, India).

Results

All the results obtained were statistically analyzed using SPSS software 17.0v. Mean and the standard deviation was found for all parameters. Chi-square test was used to compare factors like smoking, alcohol intake, the presence of diabetes mellitus and hypertension. The concentration of plasma BNP and LVEF levels in stable CHF patients and controls were compared using independent "t" test. Relationship of plasma BNP and age sub-groups was determined using one-way analysis of variance (ANOVA). Pearson's correlation coefficient value for plasma BNP and LVEF was done. Diagnostic value for plasma BNP for CHF was analysed with ROC curve.

Discussion

Heart failure results from the activation of multiple pathogenic pathways. BNP estimation has a role in the diagnosis of heart failure and guiding heart failure therapy.[8] In the present study, the plasma concentration of B-type natriuretic peptide in patients with stable chronic heart failure and controls was estimated. While comparing the characteristics of the participants in the present study, there was a significant difference in left ventricular ejection fraction (LVEF) among the study groups. Insignificant p values were obtained for smoking, alcohol intake, BMI, the presence of diabetes mellitus and hypertension between the stable CHF and the control group (Table 1).

The mean and standard deviation of serum creatinine among stable CHF patients and controls was 0.75 ± 0.09 mg/dL and 0.65 ± 0.08 mg/dL. Their eGFR was 100.24 ± 8.81 mL/min and 117.31 ± 10.34 mL/min respectively. The levels of serum creatinine and the estimated glomerular filtration (eGFR) were within the normal limits in all the participants in the present study. This indicates that the participants included in the study had a normal renal function, thus, excluding early occult renal failure as a cause for alterations in plasma BNP level in both the study groups. The mean and standard deviation values of age among patients with stable CHF and controls were 54.49 ± 9.38 and 52.51 ± 10.40, respectively. The mean and standard deviation of the plasma BNP concentration in patients with CHF was 60.46 ± 16.13 pg/mL, while in controls it was 20.94 ± 5.81 pg/mL which were statistically significant. A similar result was also obtained by Tsutamoto et al.[9]

According to the European Society of Cardiology (2012 guidelines), the concentration of BNP ≥100 pg/mL is required for the diagnosis of CHF.[10] However, in our study in stable CHF patients, it was lower than the above-prescribed cut-off because BNP levels reduce with adequate treatment.[11] Thus, BNP aids in guiding adequacy of drug therapy in CHF patients. In 2013, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) HF guidelines have recommended the use of BNP for guiding chronic HF management (level of evidence: B).[12] More recently, several meta-analyses have suggested that Natriuretic Peptide-guided therapy strategies could be associated with a reduction in all-cause mortality in CHF patients less than 75 years.[13-15] However, the 2017 update guideline task force makes no recommendation regarding the use of BNP testing to guide HF therapy.[16]

As in Table 2, significant differences in plasma BNP concentrations were also observed between stable CHF patients and controls when they were classified into five sub-groups based on their age ($p = 0.001$*). In addition, an increase in the concentration of plasma BNP with advancing age was observed in both stable CHF patients ($p = 0.03$) and in control ($p = 0.001$) groups. Studies by Laura,[8] Braunwald,[17] Redfield,[18] and Wang et al.[19] also observed a moderate increase in the levels of circulating BNP with advancing age. A study by Nishikimi in 2013 showed that total BNP levels increased with aging and the possibility could be an increased cardiac muscle mass together with a reduction in the normal renal clearance of BNP during aging.[20]

Table 1: Characteristics of patients in the study population

Variable	*Stable CHF patients* (n = *55)*	*Control* (n = *35)*	*p value*
Smoking	27 (49%)	11 (31.4%)	0.829
Alcohol intake	22 (40%)	10 (33.3%)	0.992
Presence of diabetes mellitus	18 (32.7%)	5 (14.3%)	0.051
Presence of hypertension	23 (41.8%)	16 (45.7%)	0.716
BMI	27.19 ± 2.56	26.02 ± 2.44	0.254
LVEF (%)	35.51 ± 5.88	71.23 ± 4.61	< 0.0001[b]
Plasma BNP (pg/mL)	60.46 ± 16.13	20.94 ± 5.81	0.001[a]

[a]$p < 0.001$; [b]$p < 0.0001$

Table 2: Concentration of BNP in case and controls in age sub-groups

	Plasma BNP (pg/mL)				
	Stable CHF patients		*Controls*		
Age (in years)	*Mean*	*SD*	*Mean*	*SD*	*Independent t-test*
< 40	46.32	7.69	12.95	2.30	t = 10.18 p = 0.001[a]
41–50	54.77	15.33	19.19	3.66	t = 8.45 p = 0.001[a]
51–60	64.95	14.77	23.30	4.76	t = 6.14 p = 0.001[a]
61–70	64.99	19.84	26.66	1.63	t = 5.77 p = 0.001[a]
> 70	70.67	7.66	30.20	0.0	t = 4.57 p = 0.001[a]
(ANOVA)	F = 2.87 p = 0.03		F = 20.02 p = 0.001[a]		

[a]p < 0.001

Table 3: Comparison of plasma BNP levels in male and female

		Gender				
		Male		*Female*		
Analyte	*Group*	*Mean*	*SD*	*Mean*	*SD*	*Independent t-test*
Plasma BNP (pg/mL)	Stable CHF patients	63.12	16.79	53.98	12.65	t = 1.95 *p* = 0.06
	Control	20.77	5.95	21.28	5.75	t = 0.24 *p* = 0.08

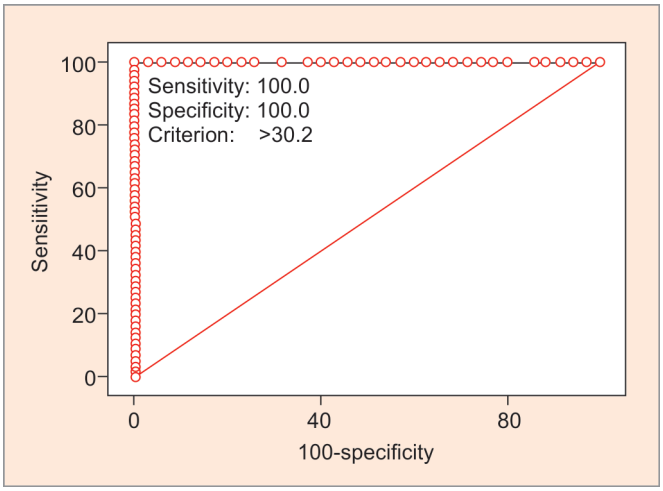
Table 4: Comparison of plasma BNP values in sub-groups of LVEF in case and controls

Study population	*LVEF (%)*	*No of participants*	*Mean and SD BNP (pg/mL)*	*p value*
Stable CHF patients	25–30	18	60.53 ± 15.99	0.679
	31–35	12	59.21 ± 16.30	
	36–40	15	64.33 ± 19.11	
	41–45	10	56.00 ± 11.68	
Controls	60–65	6	27.05 ± 2.39	0.003
	66–70	8	20.61 ± 3.97	
	71–75	15	20.56 ± 6.02	
	76–80	6	16.22 ± 5.27	

Redfield et al. reported higher plasma BNP levels in healthy women than in men.[18] Nishikimi[20] in his study analyzed the effects of gender on BNP and found that females had higher BNP levels and opined that further studies are necessary to elucidate the mechanism of increased BNP levels in females. However, in our study, the levels of BNP did not vary significantly with gender in both the groups (Table 3).

Left ventricular ejection fraction (LVEF) was classified into sub-groups and BNP concentration in each sub-group was analyzed (Table 4). An increase in LVEF caused a significant decrease in plasma BNP levels in the control group (p = 0.003). However, it was not significant in stable CHF patients (p = 0.679). The Pearson's correlation coefficient value for plasma BNP and LVEF in the study population showed a strong negative linear correlation with r = –0.798. Veena V et al. in 2016 reported a strong negative correlation between BNP levels and LVEF% in heart failure with reduced ejection fraction [21].

Graph 1 shows the ROC curve which was plotted according to the data of 55 CHF patients and 35 controls. When the cut-off level of plasma BNP was higher than 30.2 pg/mL, the sensitivity to predict CHF was 100%, and the specificity was 100%. AUC was 1.00 (0.96–1.00) for BNP. Hence, plasma BNP is sensitive and specific for identifying stable heart failure.



Graph 1: Analysis of the diagnostic value of plasma BNP for CHF with ROC curve

Limitations of the Study

The present study was done in a short duration of one year period involving a small number of participants. Echocardiography was done by a different cardiologist on different patients; hence there is a possibility of subjective variation while determining the left ventricular ejection fraction. Clinical examination and previous records of hemoglobin > 10 g/dL were used to include participants in the study rather than objectively estimating hemoglobin to exclude anemia in the participants. Periodic assessment of plasma BNP at various time intervals in stable patients was not done in the present study.

Conclusion

In conclusion, plasma BNP was significantly higher in patients with stable chronic heart failure than in the controls. The concentrations of plasma BNP increased as the age of the participants increased. There was a strong negative correlation between plasma BNP levels and LVEF. A cut-off level of 30.2 pg/mL for plasma BNP had a 100% sensitivity and specificity to predict CHF. Plasma BNP as a biomarker will help in identifying stable CHF patients who are asymptomatic, on their adequacy of treatment.

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