Correlation of NT-proBNP and Echocardiographic Parameters in Patients with Heart Failure with Preserved Left Ventricular Systolic Function

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Abstract

OBJECTIVE: Natriuretic peptides are increasingly used in clinical practice to diagnose myocardial dysfunction in heart failure (HF) with preserved ejection fraction (HFpEF). Recent studies indicate that plasma brain natriuretic peptide (BNP) may have a role in the diagnosis and management of HF. However, there is marked heterogeneity in BNP levels among subjects with HFpEF, which is only partially explained by differences in left ventricular (LV) dimensions or systolic function. This study aims to investigate if N-terminal proBNP (NT-proBNP) can be a useful tool to guide management in patients with HFpEF when echocardiography is not easily accessible.

MATERIALS AND METHODS: N-terminal proBNP in patients admitted in Chong Hua Hospital from July 2019 to July 2020 was collected from the hospital laboratory. Data of patients with HF symptoms with preserved LV systolic function and other echocardiographic parameters were collected from the hospital records. The correlation between the different echocardiographic parameters and NT-proBNP was determined.

RESULTS: The NT-proBNP levels increased significantly in HFpEF as the values of left atrial volume index (P <0.001), E/A ratio (P = 0.042), E/e′ (P <0.001), and tricuspid regurgitation velocity (P <0.001) increased. The mean NT-proBNP level was 5588 pg/mL. Highest levels were seen predominantly in diastolic dysfunction grade II.

CONCLUSION: Our findings indicate that NT-proBNP is positively correlated to echocardiographic parameters, namely, left atrial volume index, E/A ratio, E/e′, and tricuspid regurgitation velocity in patients with preserved LV systolic function.

INTRODUCTION

The incidence of heart failure (HF) is increasing. If for HF with reduced ejection fraction (EF), there are well-established methods of diagnosis and treatment. This is far from true in patients with HF with preserved EF (HFpEF). This increasing incidence justifies the need for proper diagnostic, therapeutic, and prognostic tools. In the era of cardiac biomarkers, natriuretic peptides (NPs) have a well-established role in HF pathophysiology and patient management. However, both the lack of consensus regarding NPs in HFpEF and the heterogeneous population make diagnosis and management difficult and unstandardized, leading to a decrease in quality of life and increase in mortality and hospitalization.[1]

Heart failure with preserved EF is associated with high mortality and morbidity.[1,2] In addition to the presence of typical symptoms and signs of HF, as well as the finding of nondilated left ventricle with preserved EF, the pivotal role in establishing a diagnosis of HFpEF has the evidence of left ventricular (LV) filling pressure elevation, indicative of a significant diastolic dysfunction.[3,4]

Brain NP (BNP) and its amino-terminal fragment, N-terminal proBNP (NT-proBNP), being peptide hormones released from the cardiac ventricles in response to myocyte stretch, have generated considerable attention in recent years and have been proposed as potential diagnostic and prognostic markers for cardiac disease. It accurately identifies HF in dyspneic patients.[5–7] Brain NP correlates with echocardiographic indices of diastolic function and right ventricular systolic function,[8–11] but the relationships between NT-proBNP and echocardiographic findings have not been established.

In the evaluation of patients with HF, echocardiography is a very important tool. A comprehensive two-dimensional and Doppler echocardiogram provides a reliable assessment of LV function. In addition to providing insight into the etiology of HF, echocardiographic data are valuable in assessing prognosis. The degree of impaired LV filling, LV dysfunction, and left atrial enlargement are all predictors of adverse outcomes.

This study aimed to determine the correlation of NT-proBNP and echocardiographic parameters in patients with HFpEF admitted in Chong Hua Hospital.

METHODOLOGY

This is a cross-sectional study done in Chong Hua Hospital, a tertiary care hospital with 660-bed capacity. This study included all patients with HFpEF admitted in Chong Hua Hospital from July 2019 to July 2020. This included admitted patients with HF with preserved LV systolic function, EF of greater than 50%, and adults older than 18 years. Admitted patients with HF with reduced LV systolic function and EF of less than 50% were excluded in this study.

Study Maneuver

N-terminal proBNP in patients admitted in Chong Hua Hospital from July 2019 to July 2020 were collected from the hospital laboratory. Patients with HF symptoms with preserved LV systolic function and other echocardiographic parameters were collected from the hospital records. The correlation between the different echocardiographic parameters and NT-proBNP was determined.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation. Associations of NT-proBNP with echocardiographic, demographic, and clinical indices were assessed using Spearman rank correl ation. Independent predictors of BNP were determined by multiple regression analysis. The Kruskal-Wallis test and Mann-Whitney *U* test were used to compare differences in BNP levels between subjects groups. Statistical significance will be set at a level of $P < 0.05$.

Sample size for frequency in the population was computed using OpenEpi version 3 (OpenEpi: Open Source Epidemiologic Statistics for Public Health, version 3. www.OpenEpi.com). *P* value of 50% was set as default in this study with a confidence level of 95%; thus, a sample size of 209 was obtained.

RESULTS

Data of a total of 1018 patients with NT-proBNP admitted in Chong Hua Hospital from July 2019- to July 2020 were collected from the hospital laboratory. The echocardiographic parameters were collected from hospital records, and 457 patients with preserved LV systolic function were determined by echocardiography record. Sample size was computed. Patients were assessed according to the criteria for diastolic dysfunction based on recent guidelines.[3] Demographic and clinical profiles were collected in the hospital records.

A total of 255 patients were included in the study. Table 1 shows the summary of demographic and clinical profiles of the patients. The patients had a mean age of 69 years and were predominantly male and New York Heart Association class III. Hypertension was common, comprising 82% of the population; diabetes and coronary artery disease comprise 48% and 45%, respectively, of the study population. Aortic valve disease, mitral valve disease, atrial fibrillation, chronic obstructive pulmonary disease, and asthma were noted in 9%, 7%, 29%, 18%, and 20%, respectively. Forty-six percent of the population was on β-blockers, 25% on loop diuretic, and 44% on angiotensin receptor blocker. N-terminal proBNP was determined, and mean value was 5588 pg/mL, shown in Table 1.

Among the 255 patients, these are the following mean echocardiographic parameters of the patients, shown in Table 2.

Left atrial volume index (LAVI), E/A ratio, E/e′, and tricuspid regurgitation (TR) velocity showed a $P < 0.05$. These echocardiographic indices showed statistical significance.

Diastolic indices are summarized and their mean values are shown in Table 3. It showed that diastolic dysfunction grade II has the highest mean NT-proBNP. *P* value was computed for the entire variable, which showed significant difference.

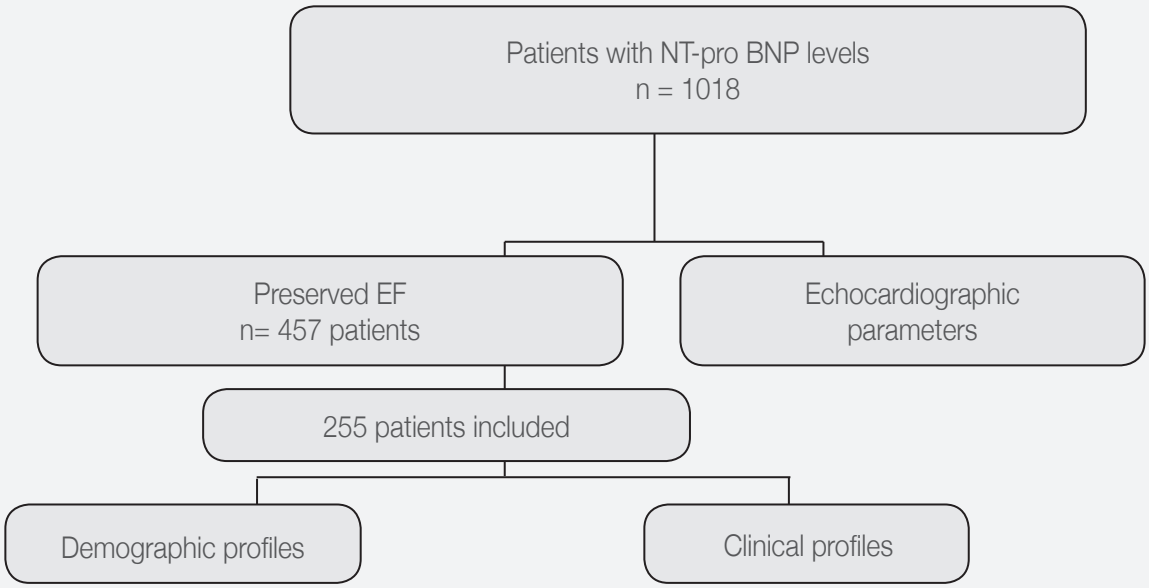


Figure 1. Scatter plots depicting the relationship of NT-proBNP to LAVI (left upper panel), E/A ratio (right upper panel), E/e′ (left lower panel), and TR velocity (right lower panel). All showed a positive and linear correlation. The relationship of NT-proBNP to LVEF (lowest left panel) showed a negative and linear correlation. LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–brain natriuretic peptide; TR, tricuspid regurgitation.

Comparison of the levels of NT-proBNP with diastolic dysfunction is shown in Figure 2 showing predominantly elevated NT-proBNP in diastolic dysfunction grade 2 in the study population.

DISCUSSION

The results of this study showed that there is positive correlation between NT- proBNP levels and the following diastolic echocardiographic parameters, namely, LAVI, E/A ratio, E/e□, and TR velocity. This means that as the NT-proBNP levels increase, there is also elevated values of LAVI, E/A ratio, E/e□, and TR velocity. Elevated BNP levels have previously been demonstrated in patients with abnormal relaxation and normal LV systolic function.[9] Stronger relationships were seen for NT-proBNP levels with noninvasive measures of LV filling pressure, such as LAVI, E/e□, and TR velocity, which is consistent with the understanding that LV wall stress is an important stimulus to BNP secretion. This is consistent with the latest 2016 recommendations for the evaluation of LV diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

N-terminal proBNP levels were directly correlated with diastolic dysfunction grade II. A pairwise comparison was done and showed that diastolic dysfunction grade 2 is significantly higher than the rest of the categories. Elevated BNP levels have previously been demonstrated in patients with abnormal relaxation and normal LV systolic function.[2] As seen in in a multivariate analysis, severity of overall diastolic dysfunction was independently related to BNP levels[1]; thus, it was noted in this study that diastolic dysfunction grade 2 has a positive correlation compared with diastolic dysfunction grades 1 and 3. These results provide a framework for interpreting NT-proBNP levels in patients with preserved LV systolic function.

Other findings showed that NT-proBNP has a positive correlation with weight, body mass index (BMI), and creatinine clearance. There are many variables that affect BNP levels in a patient, including gender and age, hypertension, renal disease, and atrial fibrillation.[12] The increase in NP levels with age likely reflects age-related decreases in LV compliance and glomerular filtration rate. These were seen in the study population. Recently, researchers have demonstrated a consistent inverse relationship between obesity (defined as having a BMI of ≥30 kg/m^2) and circulating BNP levels.[12] Wang et al first described the inverse relationship between obesity and BNP levels from the original Framingham Heart Study offspring cohort, none of whom had HF.[13] The mean BMI in the study population is 26 kg/m^2 (overweigh) and did not reflect indirect relationship. To date, few studies have compared NPs head-to-head in patients with chronic kidney disease.[12] Vickery et al showed increases in NP concentrations with declining glomerular filtration rate, which was greater for NT-proBNP.[14] Although median LVEF was normal for all chronic kidney disease strata, 6% of patients had prevalent HF, and 35% had known cardiovascular disease. This was seen in this study with a mean estimated glomerular filtration rate of 53 mL/min per 1.73 m^2.

Our findings suggest that NT-proBNP levels performed in the clinic may allow the clinician to rapidly identify patients

Table 1. Demographic and Clinical Profiles of the Study Population

Age, y	69 ± 14
Gender, n (%) Male Female	 135 (53) 120 (47)
Height, cm	158 ± 13
Weight, kg	66 ± 17
BMI	26 ± 6
Heart rate, beats/min	91 ± 23
Systolic blood pressure, mm Hg	131 ± 28
Diastolic blood pressure, mm Hg	77 ± 13
Creatinine clearance, mL/min per 1.73m^2	53 ± 29
NT-proBNP, pg/mL	5588 ± 7817
NYHA class, n (%) I II III IV	 1 (0.4) 113 (44) 138 (54) 3 (1.1)
Comorbidities, n (%) Hypertension Diabetes CAD Atrial fibrillation COPD Asthma	 209 (82) 122 (48) 116 (45) 74 (29) 46 (18) 51 (20)
Valvular heart disease, n (%) Aortic valve disease Mitral valve disease	 24 (9) 19 (7)
Medications, n (%) β-Blockers Loop diuretic ACE/ARB	 118 (46) 63 (25) 113 (44)
Diastolic dysfunction, n (%) Normal Grade 1 Grade 2 Grade 3	 30 (12) 150 (59) 61 (24) 12 (5)

ACE/ARB=angiotensin-converting enzyme/angiotensin receptor blocker; BMI=body mass index; CAD, coronary artery disease; COPD=chronic obstructive pulmonary disease; NYHA=New York Heart Association; NT-proBNP=N-terminal pro–brain natriuretic peptide.

Table 2. Correlation of NT-proBNP and Echocardiographic Parameters of Patients with Preserved LV Ejection Fraction

Echocardiographic Parameter	Mean ± SD	*P* Value
LAVI, mL/m^2	28.82 ± 15.003	<0.001
E/A ratio	1.0556 ± 0.74244	0.042
E/e′	13.45 ± 8.975	<0.001
TR velocity, m/s	2.4667 ± 0.76274	<0.001

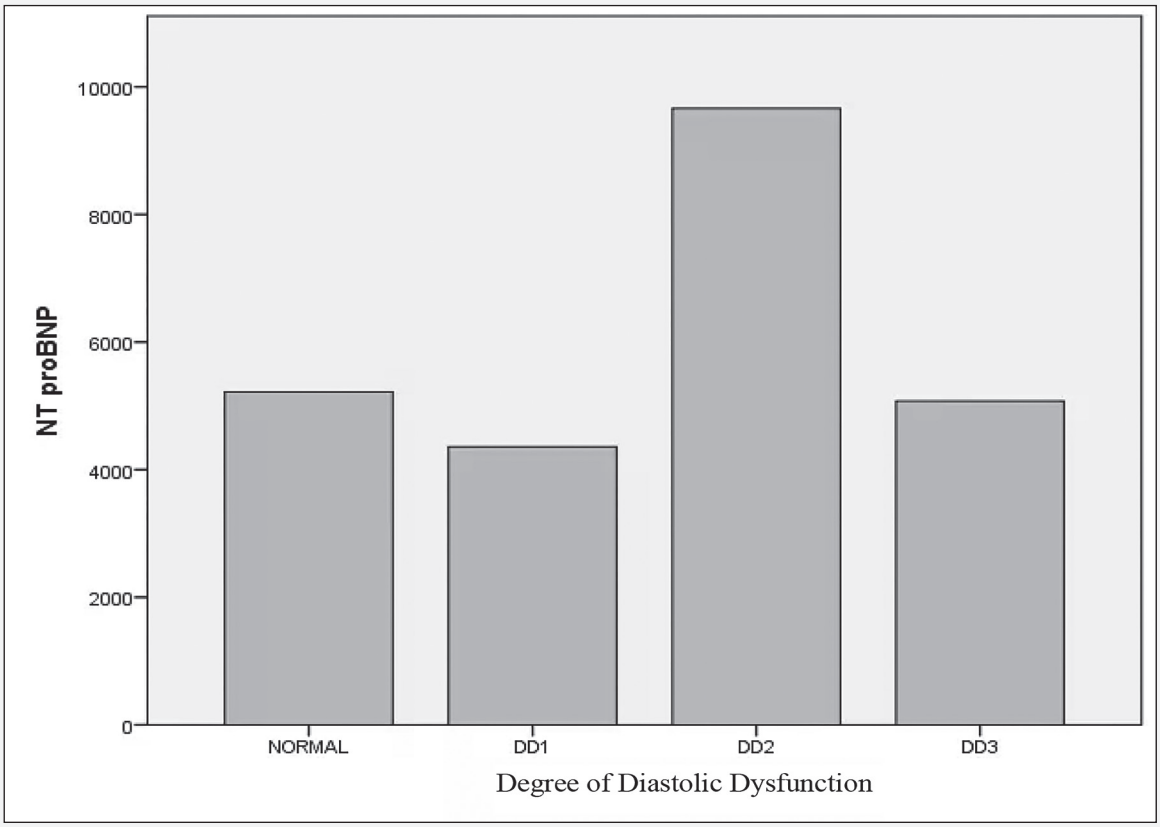
LAVI=left atrial volume index; LV=left ventricular; NT-proBNP=N-terminal pro–brain natriuretic peptide; TR=tricuspid regurgitation.

Table 3. Comparison Between the Degree of Diastolic Dysfunction and NT-proBNP (n = 255)

Diastolic Function	n	Mean NT-proBNP	*P* Value
Normal diastolic function	30	5216.00 ± 8253.670	*P* <0.001
Diastolic dysfunction grade I	150	4357.83 ± 6645.894	
Diastolic dysfunction grade II	61	9664.49 ± 9452.786	
Diastolic dysfunction grade III	14	5075.83 ± 4282.147	

NT-proBNP=N-terminal pro–brain natriuretic peptide; SD=standard deviation.

Figure 2. Comparison between the degree of diastolic dysfunction and NT-proBNP.



with preserved LV systolic function who may have more significant cardiac abnormalities. This, in turn, may facilitate the identification of patients who may benefit from more intensive investigation or therapy.[6] Plasma BNP-guided therapy has been tested in pilot studies with some success.[6] Our findings suggest that the ideal target BNP level may vary for individual patients and that the baseline BNP level and echocardiographic findings may be important in determining this target level.

STUDY LIMITATIONS

This study was limited to a duration of 1 year, limiting the sample size. Echocardiography and BNP assays were performed at only a single time point. The relationship of BNP to echocardiography parameters at serial time points following changes in therapy or in clinically decompensated patients cannot be deduced from our study, although it is possible that heterogeneity of BNP levels seen in acute HF[7] may be explained by our findings. Parameters of filling pressure were derived from echocardiography and not measured invasively. There were few patients with atrial fibrillation, which is known to influence BNP levels.

CONCLUSIONS

Our findings indicate that NT-proBNP is positively correlated to echocardiographic parameters, namely, LAVI, E/A ratio, E/e□, and TR velocity.

RECOMMENDATIONS

The researcher recommends increasing the duration of the study to increase the power of the sample size. Further analysis in patients with atrial fibrillation with HF and preserved ejection can be a future research interest.

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