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Comparison of N-terminal Pro-B type Natriuretic Peptide and Tissue Doppler in Diagnosing Diastolic Heart Failure

C. S. Thejanandan Reddy[1], D. Rajasekhar[1*], V. Vanajakshamma[1] and K. Latheef[1]

[1]*Department of Cardiology, SVIMS, Tirupati, Andhra Pradesh, India.*

Authors' contributions

This work was carried out in collaboration between all authors. Author CSTR designed the study, wrote the protocol, collected literature, collected data and wrote the first draft of the manuscript. Author DR designed the concept, analyzed the results, and corrected the manuscript. Author VV managed the experimental process, manuscript correction. Author KL managed the literature searches, statistical analysis, and manuscript preparation. All authors read and approved the final manuscript.

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ABSTRACT

Background: Heart failure (HF) has become a main cardiac problem. Doppler echocardiography has been used to examine left ventricular (LV) diastolic filling dynamics. Limitations of this modality suggest the need for other objective measures of diastolic HF.

Aim of the Study: The hypothesis of this study is to assess the utility of N-terminal pro-B type natriuretic peptide (NTproBNP) in the diagnostic evaluation of diastolic HF in comparison with tissue Doppler imaging (TDI) recordings.

Methods: A prospective study was carried out between May 2010 and December 2011. Patients with signs and symptoms of HF with normal LV systolic function by 2D-echocardiography were recruited. M-mode and 2-dimensional images, left atrial volume index (LAVI), spectral and TDI of the mitral annulus were obtained for all the patients. NTproBNP levels were measured with a

**Corresponding author: Email: cardiologysvims@gmail.com;*

bedside immunoassay.
Results: We found linear correlation between NTproBNP levels and grade of diastolic dysfunction (DD), LAVI, ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E') [r=0.72, p<0.001]. Patients with elevated left ventricular end diastolic pressure, defined as E/E'>15 (n =18), had the highest NTproBNP levels (3028±2674pg/mL). NTproBNP levels (4146±2887.43 pg/mL) were highest in patients with grade III DD. A receiver operator characteristic curve showed NTproBNP value, 286 pg/mL, the best cut-off for diagnosing diastolic HF with a sensitivity of 89% and a specificity of 100%.
Conclusions: Plasma NTproBNP levels can reliably estimate LV filling pressures in patients with HF and normal systolic function which might help to reinforce the diagnosis of "diastolic HF".

Keywords: Diastolic heart failure; N-terminal pro-B type natriuretic peptide; tissue Doppler imaging.

1. INTRODUCTION

Cardiovascular disease remains the leading cause of preventable death globally [1]. Heart failure (HF) is a worldwide growing epidemic and it is associated with increasing incidence and prevalence [1,2]. However, up to 50% of patients with HF have a preserved left ventricular ejection fraction (LVEF) suggesting that isolated diastolic dysfunction (DD) is the pathophysiological mechanism [a complex broadly referred to as heart failure with preserved left ventricular ejection fraction (HFpEF)] [3]. The data suggest that mortality rates among individuals with HFpEF are similar to those with HF and systolic dysfunction [4].

Clinical examination cannot differentiate between systolic and diastolic heart failure. Although Doppler echocardiography plays a vital role in examining the LV diastolic filling dynamics, but the limitations of this technique suggest the need for other objective measures of estimating diastolic function.

Tissue Doppler imaging (TDI) is a new Doppler ultrasound modality that records regional systolic and diastolic velocities within the myocardium. TDI of mitral annular motion may be correct parameter for checking the influence of myocardial relaxation on transmitral flows and has been shown to be an excellent predictor of diastolic filling in subsets of patients [5,6]. The early diastolic velocity at the annulus (E') has been shown to correlate well with indices of LV relaxation and is minimally influenced by preload [7]. But E' is also influenced by lengthening load and restoring forces. Since mitral peak early filling velocity (E) is preload dependent and E' is related to LV relaxation, the ratio E/E' can be used to estimate LV filling pressures. The combination of mitral annulus and mitral inflow velocities has been shown to provide better estimates of LV filling pressures than other methods [8]. However, this assessment of DD is more complex and requires expert interpretation.

Invasive investigations via left and right heart catheterization to measure LV filling pressures are more reliable, but load-dependent and not useful for wide spread clinical implementation. For these reasons, simple and reliable diagnostic criteria for diastolic heart failure are lacking and a rapid non-invasive diagnostic test would be of high clinical value.

Abnormal diastolic filling pressure, the key functional abnormality in diastolic heart failure, leads to a release of cardiac neurohormones including natriuretic peptides. Previous studies have reported that B type natriuretic peptide (BNP) and its biologically inactive fragment N-terminal pro BNP (NTproBNP), both release predominantly by the ventricles in response to stretch, may be used for the diagnosis of systolic heart failure [9,10]. However, the role of these peptides in patients with diastolic heart failure is still under investigation. As NTproBNP circulates at higher plasma concentration and has a longer half-life as compared to BNP [11], it could be useful for the detection of all degrees of diastolic dysfunction. Due to the limited availability of literature, the study was planned with an aim to assess the utility of NTproBNP in the evaluation of LV diastolic function in comparison with TDI recordings.

2. MATERIALS AND METHODS

A prospective study was carried out at an emergency department (ED) of Sri Venkateswara Institute of Medical Sciences, Tirupati between May 2010 and December 2011. Total of 60 patients was enrolled in the study.

The study was carried out as per the principles outlined in the Declaration of Helsinki. This study protocol was approved by the Institutional Ethics Committee of Sri Venkateswara Institute of Medical Sciences and written informed consent was obtained from all patients.

All patients presenting with signs and symptoms of heart failure (as per the Framingham criteria) and normal LV systolic function by 2D-echo were included in the study.Patients with E/E' > 15 were defined as Diastolic heart failure. Criteria for diagnosis of diastolicdys function or diastolic heart failure remain imprecise. A patient is said to have diastolicdys function if he has signs and symptoms of heart failure but the left ventricular ejection fraction is normal. A second approach is to use an elevated BNP level in the presence of normal ejection fraction to diagnose diastolic heart failure. Patients with valvular heart disease, acute coronary syndromes, chronic obstructive pulmonary disease, renal failure or atrial fibrillation (AF) were excluded from the study.

2.1 Doppler Echocardiographic Studies

M-mode and 2-dimensional images and spectral and color flow Doppler recordings were obtained (PHILIPS iE 33 2D echo and Doppler machine, USA). Two-dimensional imaging examination was performed in the standard fashion in parasternal long- and short-axis views and apical 4- and 2-chamber views. Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a 4 x 4 mm sample volume placed at the tips of mitral valves. All the echocardiographic observations were done by single operator (Concordance correlation coefficient = 0.9992; 95% CI: 0.9987 – 0.9995) to avoid inter-observer variability.

Echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV end-systolic and end-diastolic-volumes and EF were derived from biplane apical views using the modified Simpson's rule algorithm. Left atrial volume was calculated using the area/length method. The area was traced and length was measured in 2 orthogonal planes: the apical 4-chamber and 2-chamber views. The left atrial volume was then indexed to body surface area and an abnormal value was defined as >28 ml/m^2. The transmitral pulse Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: peak velocities reached in early diastole (E) and after atrial contraction (A), and deceleration time (DT).

The LV isovolumic relaxation time (IVRT) was obtained in the apical 5-chamber view with a continuous-wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or onset of transmitral flow.

TDI of the mitral annulus was obtained from the apical 4-chamber view after filters were set to exclude high-frequency signals. A 5-mm sample volume was placed sequentially at the lateral and medial mitral annulus. The resulting velocities were recorded for 3 consecutive cardiac cycles at a sweep speed of 100 mm/s. The following measurements were made from the recordings: peak systolic velocity (S'), early (E') and late (A') diastolic velocities. Analysis was performed for the early (E') and late diastolic velocities (A') as the average of the medial annulus.

The classification of diastolic function on echocardiography was according to Recommendations for the Evaluation of Left Ventricular Diastolic Function by American Society of Echocardiography [12,13]. The classification included the following categories: (a) normal, (b) relaxation abnormality (mild dysfunction), (c) pseudo-normal (moderate dysfunction), and (d) restrictive abnormality (severe dysfunction).

2.2 Measurement of NTproBNP Levels

The cobas h 232 (Roche Diagnostics Ltd., Switzerland) Point of Care (POC) systems is a portable device. All samples were collected by venipuncture into heparinised tubes within 2 hours of obtaining the echocardiogram. Two lines (signal and control line) in the detection zone of the test strip indicate the presence of analyte in the sample material. These lines were detected by the cobas h 232 systems with the help of a CMOS camera sensor and are displayed as "positive" prior to the quantitative evaluation. The reaction times for the assay are approximately 10 to 15 minutes; the sample volumes needed are 150 µL of heparinised venous whole blood. Detection range of the assay is 60-9000 pg/ml of NTproBNP.

2.3 Statistical Analysis

Statistical analysis was performed using Microsoft excel spread sheets, MedCalc and SPSS version 11.5 (SPSS Inc., Chicago, IL). The data was presented as mean ± SD (sometimes as mean ± SE) for continuous variables and as percentages for categorical variables. Multiple logistic regression analysis was performed to find out the factors that are influencing the diastolic dysfunction. Receiver operating characteristic (ROC) curves were constructed to determine the ability of NTproBNP throughout the range of concentrations (cut-off points) to identify diastolic dysfunction. Results were expressed in terms of the area under the curve (AUC) and 95% confidence interval (CI) for this area. A p-value of <0.05 was considered significant.

3. RESULTS

The study group consisted of 60 patients with majority of females (56.67%). Various demographic and echocardiographic characteristics of the study patients are illustrated in Table 1. Mean age of the patients was 60.52±9.5 years (range 43-94 years) with 24 (40%) patients in the age group of 60-69 years. Shortness of breath was the common symptom found in all patients. Hypertension, diabetes and coronary artery disease were more prevalent in DD patients with hypertension as the most common co-morbidity.Majority of the patients (36.7%) belonged to grade II DD. The E'/A' ratio was found to be 0.87±0.26 which is similar to the patients with diastolic dysfunction in similar studies [14].

Patients were divided into 3 groups of LAVI: <28, between 28 and 35, and >35. Among 60 patients, most patients (27) had LAVI in between 28-35 mL/m^2. NTproBNP levels were highest in patients with LAVI >35 mL/m^2 (mean ± SE: 3745±785.36pg/mL) (Table 2). Direct relationship was observed between the mean LAVI and grade of DD (Table 2), with the mean LAVI of 24.48 mL/m^2 in patients with normal diastolic function and 39.46 mL/m^2 in patients with restrictive filling.

All subgroups of DD had higher NTproBNP levels than subjects with normal diastolic function. Mean NTproBNP showed affirmative relation with the severity of diseases ranging from normal (107.27±17.73pg/mL) to grade III (4146.00±870.59pg/mL) (Fig. 1).

Table 1. Demographic and echocardiographic characteristics of patients with diastolic dysfunction

Variable	Population (n=60)
Age (yrs) [mean ± SD (range)]	60.52±9.5
Gender	
Male, n (%)	26 (43.33%)
Female, n (%)	34 (56.67%)
Diabetes, n (%)	23(38.3)
Hypertension, n (%)	42 (70)
Coronary artery disease, n (%)	21 (35)
Presenting complaints [n (%)]	
Edema	17 (28.3)
Shortness of breath	60 (100)
History of CHF	13 (21.67)
Grade of diastolic dysfunction [n (%)]	
Normal	15 (25)
Grade I	12 (20)
Grade II	22 (36.67)
Grade III	11 (18.33)
Echocardiography[mean ± SD (range)]	
IVRT (ms)	81.2±14.49
DT (ms)	187.75±58.47
E/A ratio	1.19±0.42
E'/A'	0.87±0.26
E/E'	12.39±5.72

CHF: congestive heart failure; IVRT: Isovolumic relaxation time; DT: Deceleration time; E: transmitral early diastolicvelocity; E': annular early diastolic velocity; A: transmitral late diastolic velocity: A': annular late diastolic velocity

Table 2. Comparison of mean plasma NTproBNP levels with different subgroups of LAVI and severity of disease [Variable expressed as mean ± SD (range)]

Comparison between mean plasma NTproBNP levels with different subgroups of LAVI		
LAVI (mL/m^2)	**No. of patients (n)**	**NTproBNP (pg/mL) (mean±SE)**
< 28	20	358.75 ± 89.50
28 - 35	27	664.92 ± 105.99
>35	13	3745 ± 785.36
Relation between NTproBNP levels and LAVI with the severity of disease		
Grades of diastolic dysfunction	**LAVI (mL/m^2) (mean)**	**NTproBNP (pg/mL) (mean±SE)**
Normal	24.48	107.27±17.73
Grade I	28.04	590.50±159.71
Grade II	30.29	886.91±118.02
Grade III	39.46	4146.00±870.59

LAVI: left a trial volume index; NTproBNP: N- terminal pro-B type natriuretic peptide

Patients identified with elevated LVEDP, defined as E/E'>15 (n=18), had the highest BNP levels (mean: 3028±2674 pg/mL). Those with E/E'<15 (n=42), had a mean BNP concentration of 459±453 pg/mL. There was a positive correlation between the NTproBNP levels and E/E' ratios derived from TDI for all patients (*r=0.72, p<0.001*) (Fig. 2). Patients with E/E' >8 (n=45) had higher BNP levels (1588.51±309.59pg/mL) when compared to patients with E/E' < 8 (n=15; BNP = 155.33±37.35 pg/mL).

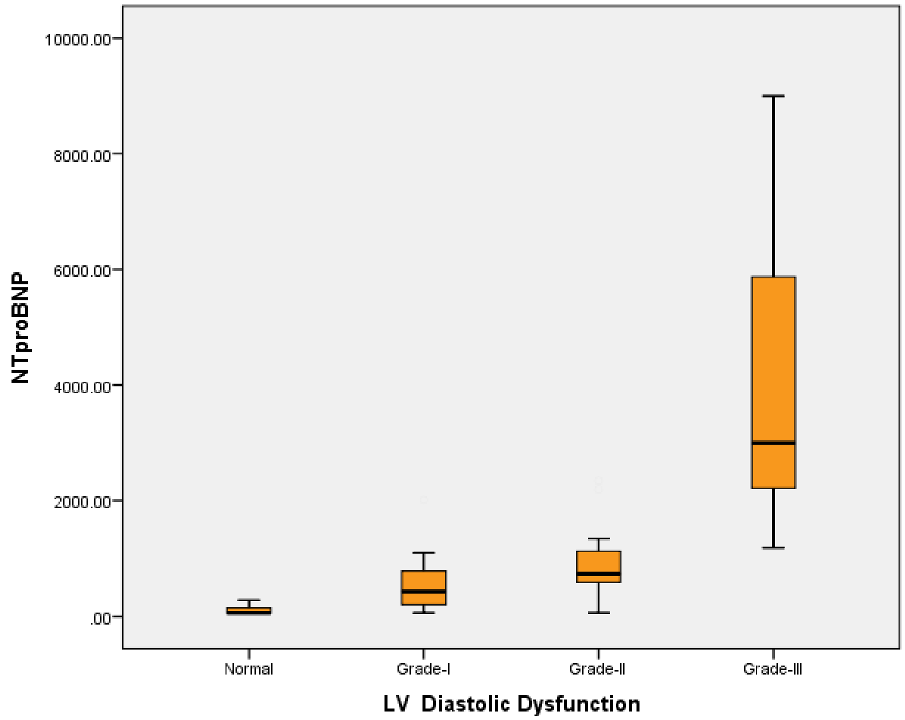

Fig. 1. Relation between NTproBNP levels in patients with diastolic dysfunction and severity of diseases

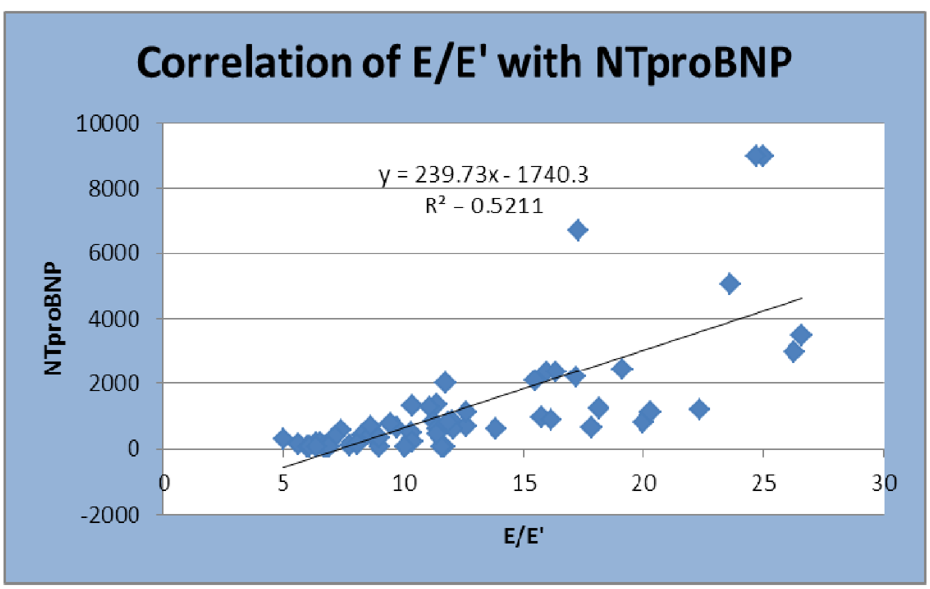

Fig. 2. Correlation graph between E/E' ratio and plasma NTproBNP levels (r = 0.72, p<0.001)

3.1 Diagnostic Accuracy of NTproBNP to Diagnose Isolated Diastolic Dysfunction

In differentiating normal and abnormal diastolic function, the area under the ROC curve was statistically significant (AUC=0.939, 95% CI: 0.846-0.985, p=0.0001). At a cut-off value 286 pg/mL, NTproBNP showed a high sensitivity of 89% and a specificity of 100% in diagnosing diastolic dysfunction (Fig. 3). NTproBNP has area under curve 0.939 whereas E/E' has area under curve 0.967 which are almost similar. With the above observations, E/E' is more accurate than NTproBNP in diagnosing diastolic dysfunction. But the advantage of NTproBNP assay is, it can be performed rapidly with a simple setting.

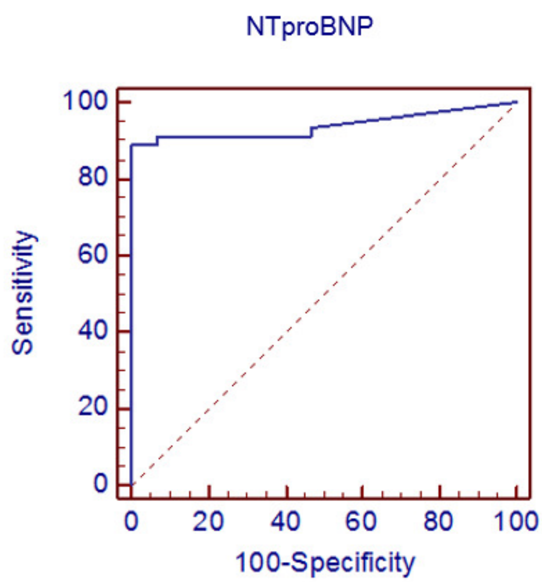

Fig. 3. Receiver-operating characteristic curve for NTproBNP level to identify isolated LV diastolic dysfunction (area under the curve [AUC] = 0.94, p<0.0001)

E/E' ratio was grouped into two based on ≤8 (normal) and >8 (abnormal). Logistic regression was used to study the impact of NTproBNP and other confounders like age, sex, diabetes, hypertension, body mass index (BMI) and smokingin diagnosing Diastolic dysfunction. After performing the multivariable logistic regression analysis, NTproBNP was an independent predictor of elevated filling pressures with an Odds ratio of 1.008 (95%CI: 1.003-1.014) (Table 3).

Table 3. Multivariable logistic regression for evaluating the ability of NTproBNP to identify diastolic dysfunction when compared with other indicators

Indicator	Odds ratio	p-value
NTproBNP	1.008	0.004
Age	0.922	0.258
Diabetes	0.111	0.057
Smoking	8.097	0.251
BMI	1.111	0.355
Hypertension	0.384	0.398
Sex	13.451	0.126

CI: Confidence interval; BMI-Body Mass Index; NTproBNP: N-terminal pro-B-type natriuretic peptide

4. DISCUSSION

Abnormalities of diastolic function may play a major role in patients with signs and symptoms of congestive heart failure [15,16]. The prevalence of diastolic heart failure increases with age, with an approximate incidence of 15% to 25% in patients <60 years of age, 35% to 40% in those between 60 and 70 years of age, and 50 % in patients >70 years of age [17,18]. Our study showed correlation between NTproBNP levels and E/E' ratio. Although conventional mitral inflow and pulmonary venous velocities had a weak relationship with filling pressures, the results of this study indicate that NTproBNP represents a blood marker providing positive evidence of the presence of diastolic dysfunction. Natriuretic peptides can therefore be used to provide objective evidence of prognostically important diastolic dysfunction in HFpEF. This would be especially useful in clinical settings where detailed and complex echocardiographic assessments are not possible.

Our findings are certainly complimentary to a consensus statement published by Paulus et al [19] who nicely outlined an algorithm for the diagnosis of HFpEF. The emphasis is on using a combination of elevated filling pressures as determined by TDI and natriuretic peptides (BNP>200 pg/ml and NTproBNP>220 pg/ml). He even suggested that increased left atrial volumes, AF or increased LV mass in addition to natriuretic peptides would increase the likelihood of HFpEF.

Iwanaga et al. [20] have demonstrated that BNP levels correlate very closely with LV end diastolic wall stress in the setting of HFNEF (r^2 =0.887), making it a good surrogate marker of worsening DD. Moreover, BNP was shown to strongly correlate with pulsed wave Doppler and tissue Doppler parameters in patients with HFpEF [21].

Our study findings confirmed that LAVI correlates with the grade of DD. Levels of NTproBNP also correlated well across the entire spectrum of LAVI values. LAVI is increasingly recognized as a relatively load-independent marker of LV filling pressures and has been shown to increase with worsening DD [22,23] and correlates closely with NTproBNP. The LA may become less spherical as it remodels. Thus LA volume is proposed as a better index of LA remodeling, more predictive for future AF and other CV events than LA dimension which was even concluded by Tsang et al. [24]. A study conducted by Lim et al. [25] reported that LAVI is an independent predictor of serum NTproBNP, in patients with a suspected history HFpEF. An extensive literature attests to the value of LAVI in both haemodynamic and prognostic assessment in a variety of settings.

Instant measurement of plasma natriuretic peptides that are normally increased as part of the neurohormonal activation in both diastolic and systolic heart failure is a powerful biochemical test. There are several reports on the efficacy of NTproBNP [26,27] in diagnosing chronic heart failure due to LV systolic dysfunction. A particular advantage of that test is its high negative predictive value, allowing ruling out systolic heart failure. The prospective, multicenter REDHOT (Rapid ED Heart Failure Outpatient Trial) of 464 patients presenting to the ED with HF showed that BNP provides prognostic value in the acute ED setting [28].

The highly negative predictive value of NTproBNP is the great advantage, as it allows in ruling out systolic heart failure. The usefulness of BNPs in detecting diastolic heart failure is still under investigation. Few studies have investigated the role of BNPs in diagnosing diastolic dysfunction in comparison with conventional echocardiography. Significantly higher BNP and NTproBNP levels were observed in diastolic dysfunction (restrictive and pseudo normal) patients, which are even favored by our study. In our study the diagnostic accuracy of NTproBNP to diagnose isolated diastolic dysfunction was done by ROC curve analyses which revealed an AUC for NTproBNP of 0.94. At a cut-off value, 286 pg/mL NTproBNP showed a high sensitivity of 89% and a specificity of 100% in diagnosing diastolic dysfunction which is analogous to the study done by Lubien et al [29]. According to PRIDE study by Januzzi et al. [30], NTproBNP at cut points of >450 pg/ml for patients <50 years of age and >900 pg/ml for patients >50 years of age were highly sensitive and specific for the diagnosis of acute CHF ($p < 0.001$).

The working group of European Society of Cardiology has proposed a BNP level >200pg/ml or an NTproBNP level >220 pg/ml to confirm the diagnosis of HFpEF in patients with symptoms of HF, LVEF >50%, and an ambiguous E/E' value between 8 and 15 [19]. One study by Tschope et al. [14] derived NTproBNP cutoff after combining echocardiography and invasive study among patients with both LV diastolic dysfunction, assessed by Doppler echocardiography and symptoms of HF and a control group without LV diastolic dysfunction or symptoms.

The role of these peptides in the detection of mild diastolic heart failure is uncertain [31], although it correlated with severe diastolic dysfunction. An elevated BNP levels were observed in patients with exertional dyspnea and impaired LV relaxation (202 pg/mL), which was reported by Lubien et al. [29]. A study by Mottram et al. [32] reported increased BNP levels in patients with hypertension-caused diastolic dysfunction correlated with controls, however in BNP levels were in the normal range (89 pg/mL) in about 75% patients with impaired relaxation in this study.

Previous studies used conventional echocardiographic parameters as the sole diagnostic criteria to identify isolated diastolic dysfunction. Obviously, the accuracy of transmitral flow analysis is limited. To overcome this key problem, we have defined diastolic dysfunction based on TDI findings.TDI parameters such as E' is more sensitive for identifying and grading DD than the transmitral flow pattern. The combined use of plasma BNP/NTproBNP level and E' may help more specific diagnosis of isolated LV DD.

5. LIMITATION

Our sample size is relatively small. This study findings may not be generalizable to entire population. This study findings are constricted to this study population only. It needs further research with large sample size to generalize these findings.

6. CONCLUSION

A rapid assay for NTproBNP can reliably detect the presence of diastolic abnormalities on echocardiography. In patients with heart failure and normal systolic function, elevated NT-pro-BNP levels and diastolic filling abnormalities can be considered as a tool for diagnosing "Diastolic Heart Failure".

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Institutional Ethics Committee of Sri Venkateswara Institute of Medical Sciences and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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