Original Research Article

The role of NT-proBNP in the diagnosis of diastolic heart failure and its correlation with echocardiography

Archana Toppo, Sanjay Varma*, Aneesh Karwa, Rajeev Lochan Khare, Yogendra Malhotra

Department of Medicine, Pt. JNM Medical College, Raipur, Chhattisgarh, India

*Correspondence:
Dr. Sanjay Varma,
E-mail: roopalisanjay@hotmail.com

ABSTRACT

Background: The primary aim of the current investigation was to evaluate the role of NT-proBNP in the diagnosis of diastolic heart failure and its correlation with echocardiography.
Methods: Hospital based observational and analytical study undertaken on a total of 65 patients of diastolic heart failure fulfilling clinical inclusion criteria. The enrolled patients had a mean age of 54.5 years with a female preponderance (33 females vs. 32 males). Patients underwent clinical evaluation and echocardiography examination. NT-proBNP estimation was done using autoanalyzer working on principle of electrochemiluminisense. Patients were divided into various grades of diastolic dysfunction on the basis of echocardiography. Statistical analysis was done to find the significance of levels of NT-proBNP and its correlation with the grading of diastolic heart failure.
Results: There was a statistically significant higher level of serum NT-proBNP in patients with diastolic heart failure and the increasing levels were directly proportional to severity of diastolic dysfunction. The mean level of NT-proBNP increased from 361.08 pg/ml to 3570 pg/ml in increasing severity of diastolic dysfunction.
Conclusions: Results suggested positive correlation of rising NT-proBNP levels with increasing severity of diastolic dysfunction.

Keywords: NT-proBNP, Diastolic heart failure, Echocardiography

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood develop a constellation of clinical symptoms and signs that lead to a poor quality of life, and a shortened life expectancy.[1]

Diastolic heart failure (DHF) is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction (EF), and abnormal diastolic function.[2] Diastolic dysfunction as a cause of left heart failure and as a powerful predictor of cardiovascular events is now well established.

Tissue Doppler imaging-derived early diastolic myocardial velocities (e'), measured at the mitral annulus, allow the assessment of myocardial relaxation. The E/e' ratio correlates with LV filling pressure. Echocardiographic evidence of LV diastolic dysfunction may consist of a reduced e' (e' average >9 cm/s) or an increased E/e' ratio (>15), or a combination of these parameters. The presence of at least two abnormal measurements and/or AF increases the likelihood of the diagnosis.[3]

NT-proBNP can be seen as a quantitative marker of HF that summarises the extent of systolic and diastolic left ventricular dysfunction. In general, levels of NT-proBNP are directly related to the severity of HF symptoms and to the severity of the cardiac abnormality.[4] Recently it was insisted that N-terminal proB-type natriuretic peptide (NT-proBNP) guided therapy reduces mortality and morbidity compared to clinically guided therapy of heart failure.

In the background of these, we studied the levels of plasma N-terminal proB-type natriuretic peptide in patients with diastolic heart failure. The objective of the study was to evaluate and correlate the levels of NT-proBNP with four grades (grade I to grade IV) of diastolic dysfunction as assessed by echocardiography (Figure-1). One sample from each patient is assessed along with echocardiography and is being correlated with the grades of diastolic dysfunction. Among patients with symptoms, Doppler, combined with two-dimensional echocardiography, is the best method to ascertain whether or not diastolic dysfunction is present and a likely cause of those symptoms. This provides a comprehensive, non-invasive approach to evaluate diastolic dysfunction and to assess its severity and hemodynamic consequences.[5]
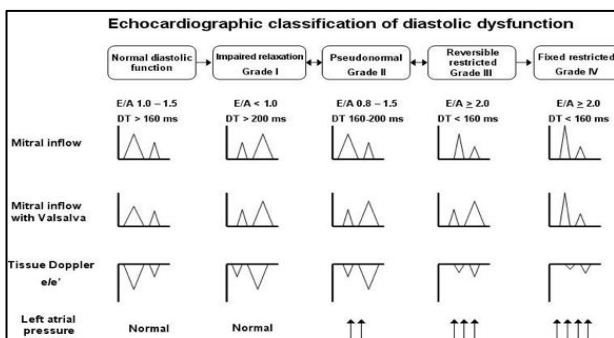

Figure 1: Echocardiographic classification of diastolic dysfunction.

Objective

The objective of the study was to evaluate and correlate the levels of NT-proBNP with four grades (grade I to grade IV) of diastolic dysfunction as assessed by echocardiography. Detailed clinical evaluation, blood biochemistry, electrocardiography, chest X-ray, echocardiography and plasma NT-proBNP were done in all the patients.

METHODS

The present study was conducted on 65 patients of DHF enrolled from outdoor and indoor patients in the Department of Medicine, Pt. JNM medical college, Dr. BRAM hospital, Raipur from January 2017 to September 2018.

Inclusion and exclusion criteria

Patients were included if there were symptoms and signs of heart failure, a preserved ejection fraction (EF ≥50%), and abnormal diastolic function. Patients were excluded if they had AMI (<7 days duration), unstable angina, serum creatinine >2 mg/dl, liver cirrhosis, Hb <10 g/dL, COPD, sepsis and atrial fibrillation. Echocardiographic parameters of isovolumic relaxation time (IVRT), mitral inflow, tissue doppler mitral annular velocity and pulmonary venous patterns were analysed to assess diastolic dysfunction.

IVRT is the interval between an aortic valve closure signal and mitral valve opening signal on a continuous wave Doppler. IVRT is increased when relaxation is prolonged; conversely IVRT is shortened when left atrial pressure is elevated. IVRT is an indicator of rate of myocardial relaxation.[5] Mitral inflow velocity is the single most important parameter for the assessment of diastolic function.[5] Pseudonormal stage of diastolic relaxation was unmasked with valsalva manoeuvre. Tissue Doppler imaging (TDI) is a relatively new echocardiographic technique that uses Doppler principles to measure the velocity of myocardial motion.[5] Pulmonary venous flow velocity can be recorded at the junction of the veins and left atrium, providing insight into the factors that affect left atrial filling.[5]

NT-proBNP analysis was done by Roche diagnostics cobas e-411 analyzer and ProBNP II© kit. It's an immunoassay for the in vitro quantitative determination of N-terminal pro B type natriuretic peptide in human serum and plasma and works on the principle of electrochemiluminescence. The sample used for analysis was human serum and plasma treated with type K2-EDTA. The ElecsysProBNP II© reagent contains two monoclonal antibodies directed against epitopes present on the N terminal part (1-76) of proBNP (108). Values were read on the monitor. NT-proBNP values ranges from 5-35,000 pg/ml. Values less than 5 were reported as <5 pg/ml and higher than 35000 pg/ml were reported as > 35,000 pg/ml. Cut off value in <50 years, 50-75 years and >75 years patients were 450 pg/ml, 900 pg/ml and 1800 pg/ml respectively. Values ≥3000 pg/ml were considered as extreme elevation.[6]

RESULTS

In the present study mean age for the 65 cases was 54.5 years with a female preponderance and female:male ratio of 1.032. In the present study 24 (36.9%) of the cases were in the age group of 51-60 years of which 13 were female and 11 were male. Amongst the rest of the case 20 (30.8%) were in the age group of 61-70 of which 9 were females and 11 were males, 13 (20%) were in the age group of 40-50 years in which there were 8 females and 5 males. In the age group >70 years constituting 8 (12.3%) subjects there were 3 females and 5 males.

In current study of 65 patients, 40 patients presented with dyspnea on exertion of which 22 were females and 18 were males. 18 (27.7%) presented with pedal oedema while 5 (7.7%) presented with heaviness of chest. Thus the most common presenting symptom was dyspnea and next to it was pedal oedema.
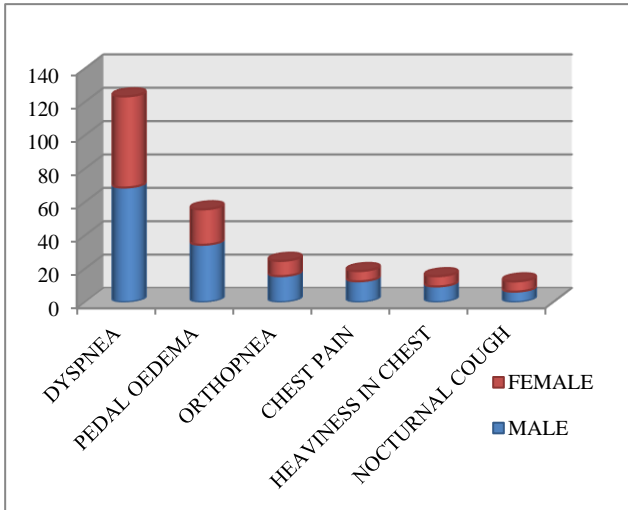

Figure 2: Distribution according to chief complaints.

In present study of 65 patients, 29.2% were diabetics and 70.8% were non diabetics. Out of 65 patients who were examined in the study, the most common chest X-ray finding was of normal chest X-ray in 53.8% (35 patients). The most common pathological chest X-ray finding was cardiomegaly found in 26.2% (17 patients) which is followed presence of pleural effusion in chest X-ray in 9.4% (5 patients) and lastly by increase in broncho-vascular margin in 6.1% (2 patients).

Table 1: Distribution of risk factor in 65 patients according to presence of DM.

		N	%
T2DM	No	46	70.8
	Yes	19	29.2
	Total	65	100.0

Table 2: Distribution according to chest X-ray finding in patients of diastolic heart failure.

X-ray findings	Female		Male		Total
	N	%	N	%	
Increased bronchovascular marking	1	3.0	1	3.1	1
Cardiomegaly	6	18.2	11	34.4	17
No abnormality detected	21	63.6	14	43.8	35
Pleural effusion	1	3.0	3	9.4	4

The most common ECG finding in the patients of diastolic heart failure was found to be features of Left

ventricular hypertrophy in 30.7% (20 patients). This was followed by sinus tachycardia in 18.46% (12 patients) and LAD in 6.1 % (4 patients). Normal ECG was found in 46.1% (30 patients). In present study subjects with LVH on ECG were compared with subjects without LVH with mean levels of NT-proBNP using student's t test. NT-proBNP level was found to be higher in LVH subjects compared to those without LVH (p<0.001) which is statistically significant.
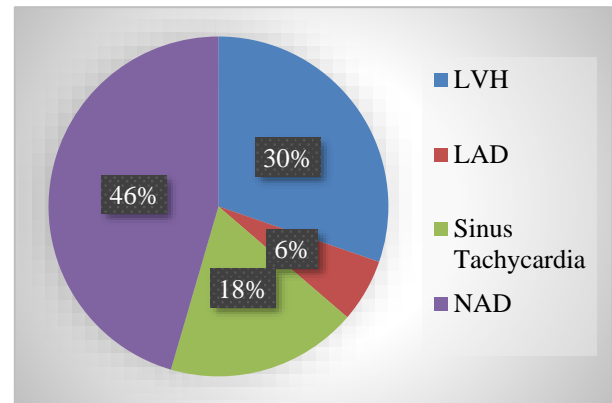

Figure 3: Distribution according to ECG findings.

In this study of 65 patients of diastolic heart failure there were no significant difference in the mean levels of NT-proBNP in males and females. The mean level of NT-proBNP in males was 839.6 pg/ml and in females was 743.9 pg/ml. In current study there was a statistical significance (p=0.008) found in the mean levels of NT-proBNP in patients with systemic hypertension compared with non-hypertensive patients .In our study there was no statistical significance (p=0.71) in the mean levels of NT-proBNP when compared in patient with diabetes and non diabetics.
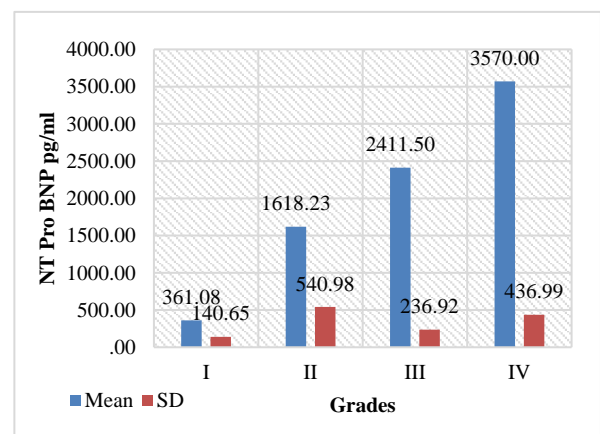

Figure 4: Comparison of mean NT-ProBNP in diastolic dysfunction grades.

In present study of 65 patients of diastolic heart failure, 32% (21 patients) of the study subject were smokers and the mean value of serum NT-proBNP in smokers was 1113.3 pg/ml. The mean value of NT-proBNP in non-

smokers was 683.95 pg/ml. There was a statistical significance value of NT-proBNP in smokers (p=0.006). In the current study 47 patients (72.3%) had Grade I diastolic dysfunction (mean NT-proBNP of 361.08 pg/ml), 12 patients (18.46%) had grade II diastolic dysfunction (mean NT-proBNP of 1618.23 pg/ml), 4 patients (6%) had grade III.

Diastolic dysfunction (mean NT-proBNP of 2411.5 pg/ml) and 2 patients (3%) had grade IV diastolic dysfunction (mean NT-proBNP of 3570 pg/ml) and there was a significant statistical correlation (p<0.0001) observed between increasing diastolic heart failure and serum NT-proBNP levels.

Table 3: Comparison of mean NT-proBNP in LVH.

	LVH on ECG	N	Mean	Std. deviation	t	df	P value	Inference
NT-proBNP pg/ml	Present	16	1352.63	783.48	3.53	63	0.001 (≤0.001)	Highly significant
	Absent	49	607.68	713.92				

Table 4: Comparison of mean levels of NT-proBNP in males and females.

	Sex	N	Mean	Std. deviation	t	P value	Inference
NT-proBNP pg/ml	Male	32	839.6	872.0	0.48000	0.63 (>0.05)	Not significant
	Female	33	743.9	721.2			

Table 5: Comparison of mean level of NT-proBNP in patients with systemic hypertension.

Systemic hypertension	N	Mean NT-proBNP pg/ml	Std. deviation	t	df	P value	Inference
Present	51	925.08	844.56	7.42	2	0.008 (<0.05)	Significant
Absent	14	302.80	185.76				
Total	65	791.05	794.18				

Table 6: Comparison of mean level of NT-proBNP in smokers.

Smoking	N	Mean NT-proBNP pg/ml	t	df	P value	Inference
Yes	21	1113.3	7.42	2	0.006 (<0.05)	Significant
No	44	683.95				
Total	65	822.6				

DISCUSSION

Heart failure is one of the most common diseases in this century. The estimated prevalence of heart failure in India is 1.3 to 4.6 million and incidence is about 491 600-1.8 million. The estimated prevalence of heart failure in India remains lower than in USA (5.8 million).[7]

Patients with diastolic heart failure have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures. Most have additional evidence of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (hence the term diastolic HF).[8]

The measurement of cardiac biomarkers has emerged as an important adjunct to the initial and subsequent evaluations of patients with suspected or proven heart failure. There are nearly 5 types of cardiovascular natriuretic peptides. ANP (A-type), BNP (B-type), CNP (C-type), urodilation-renal peptide and DNP (D-type) (dendroaspis natriuretic peptide). All types of NPs share structural similarities in a 17-amino acid core ring and a cysteine bridge.[9,10] Markers such as BNP and NT-proBNP have acquired a prime role in the diagnosis and management of heart failure, because of difficulty in diagnosis, assessment of severity and to be able to provide optimal therapy in such cases. Biomarkers can identify structural changes in heart at an earliest phase.[9] Even though the heart is the major source of BNP it is called brain-type natriuretic peptide because it was described in 1988 after isolation from the porcine brain. Now it is mainly called B-type natriuretic peptide. BNP may also be produced by cardiac fibroblasts.[11] In the healthy heart, BNP gene expression occurs mainly in the atria. However, ventricular BNP gene expression is up-regulated in diseases that affect the ventricles, such as heart failure.[12]

The physiological effects of BNP comprise natriuresis/diuresis, peripheral vasodilatation, and

inhibition of the rennin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS).[13] BNP is produced in the form of PreproBNP containing 134 amino acids. After removing the signal peptide of 26 amino acids proBNP is formed. ProBNP is then processed into active form BNP and inactive form NT-proBNP.[14] NT-proBNP has a longer half-life than BNP and has more stability and apparently less intra patient variability. Grewal et al found a significant correlation with NT-proBNP with diastolic heart failure with the initial cut off of 300 pg/ml.[15] Hobbs et al found elevated concentrations of NT-proBNP and if ventricular systolic dysfunction is excluded, elevated concentrations of NT-proBNP indicates diastolic dysfunction.[16] In current study most of the patients (36.9%) were in the age group of 51-60 years. Amongst the rest of the cases, 20 (30.8%) were in the age group of 61-70, 13 (20%) were in the age group of 40-50 years and the least were between the age group >70 years constituting 8 (12.3%).

The mean age of patient were 51.57 years with a standard deviation of ±16.81 years as observed in the study by Panjiyar et al.[17] In the present study females were most commonly affected by diastolic heart failure and 49.2 % were male and 50.8% were female with F:M ratio 1.032. The female preponderance is supported in the studies conducted by Panjiyar et al.[17] In present study 78% of patients had hypertension. Hypertension is found to be the single most important risk factor associated with diastolic heart failure in our study. There was a statistically significant ($p<0.05$) higher mean levels of NT-proBNP in patients with systemic hypertension (925.08 pg/ml) as compared with non-hypertensive patients (302.85 pg/ml). This result correlates with findings by Panjiyar et al (78.94 %) and McMurray et al (64 %).[17,18] Hypertension is the most common risk factor and the principal precursor of diastolic heart failure as it results in a compensatory thickening of ventricular wall.

Current study revealed 29.2% prevalence of diabetes in the subjects, there was no statistical significant correlation found between presence of diabetes and serum NT-proBNP level. The prevalence of smoking was found to be 32.3% and the mean value of serum NT-proBNP in smokers was 1113.3 pg/ml which was found to be statistically significant ($p<0.05$). In the present study the most common presenting symptom was dyspnea (61%) which was followed by pedal oedema (38.5%), pulmonary rales (33.84%) raised JVP (24.6%), sinus tachycardia (18.46%) and orthopnoea (12.3%). Pleural effusion was present in 6% and cardiomegaly was present in 26.15% of patients.

In present study subjects with LVH on ECG were compared with subjects without LVH with respect to mean levels of NT-proBNP using student's t test. Patients having LVH on ECG examination had a statistically significant ($p<0.001$) higher NT-proBNP level (1352.63 pg/ml) compared to those without LVH (607.68pg/ml). In current study of 65 patients of diastolic heart failure , 47

patients (72.3%) of the study subjects had grade I diastolic Dysfunction with a mean value of NT-proBNP of 361.08 pg/ml. 12 patients (18.46%) of the study subjects had grade II diastolic diastolic dysfunction with a mean value of NT-proBNP of 1618.23 pg/ml, 4 patients (6%) of the study subjects had a grade III diastolic dysfunction with a mean value of NT-proBNP of 2411.5 pg/ml and 2 patients (3%) had grade IV diastolic dysfunction with a mean value of NT-proBNP of 3570 pg/ml. In the study by Tschope et al NT-proBNP levels increased significantly according to the severity of diastolic dysfunction, ranging from impaired relaxation with mean of 151.6 pg/ml, pseudonormal filling with mean of 308.1 pg/ml and restrictive filling with mean of 2307.1 pg/ml.[19]

In summary of the findings of the present study, diastolic heart failure was seen more commonly in females and in the subjects in the age group of 51 to 60 years. Diastolic dysfunction was found to have a statistically significant association with hypertension and smokers. Mean levels of serum NT-proBNP was higher in hypertensive patients as compared to normotensive patients. In the study subjects, serum NT-proBNP was found to be higher in the age group of 70 years and above, as compared to other age groups. In current study no statistically significant correlation could be found in diabetics and serum NT-proBNP level, this finding can be attributed to a higher level of mean blood pressure in the non-diabetic group.

NT-proBNP was found to be statistically significantly raised in patients of diastolic heart failure and it correlated with increasing severity of diastolic dysfunction. NT-proBNP levels were higher in grade-IV diastolic dysfunction as compared to grade-I diastolic dysfunction.

Limitations

Limitations in the study could be ascribed to the fact that it was a single centre study and its statistical power could be increased with recruitment of more study subjects. As echocardiography findings are dependent on observer variations this can also theoretically affect the results.

CONCLUSION

Serum NT-proBNP levels provide reliable diagnostic accuracy to detect diastolic heart failure and it correlates well with increasing severity of diastolic dysfunction as assessed by well-established modality of echocardiography.

REFERENCES

1. Ramakrishnan S. Heart failure-definition and diagnosis. Heart Fail. 2005;13-20.
2. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: Diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105(11):1387-93.
3. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. 2009;22:165-93.
4. Mueller C, Breidthardt T, Laule-Kilian K, Christ M, Perruchoud AP. The integration of BNP and NT-proBNP into clinical medicine. Swiss Med Wkly. 2007;137(1-2):4-12.
5. Armstrong WiF, Ryan T, Feigenbaum H. Feignebaum's Echocardiography. 6th ed. USA: Lippincott Williams & Wilkins; 2010:816.
6. Downie PF, Talwar S, Squire IB, Davies JE, Barnett DB, Ng LL, et al. Assessment of the stability of N-terminal pro-brain natriuretic peptide in vitro : implications for assessment of left ventricular dysfunction. Clin Sci. 1999;258:255-8.
7. Stimson NF. National Institutes of Health public access policy assistance: one library's approach. J Med Libr Assoc. 2009;97(4):238-40.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016; 37(27):2129-200.
9. Hill SA, Booth RA, Santaguida PL, Don-Wauchope A, Brown JA, Oremus M, Ali U, Bustamam A, Sohel N, McKelvie R, Balion C, Raina P. Use of BNP and NT-proBNP for the diagnosis of heart failure in the emergency department: a systematic review of the evidence. Heart Fail Rev. 2014;19(4):421-38.
10. Lee CY, Burnett JC. Natriuretic peptides and therapeutic applications. Heart Fail Rev. 2007;12(2): 131-42.
11. Hall C. Essential biochemistry and physiology of (NT-pro) BNP. Eur J Heart Fail. 2004;6(3):257-60.
12. Goetze JP. Biochemistry of pro-B-type natriuretic peptide-derived peptides: The endocrine heart revisited. Clin Chem. 2004;50(9):1503-10.
13. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006;92(6):843-9.
14. Gunning M, Ballermann BJ, Silva P, Brenner BM, Zeidel ML. Brain natriuretic peptide: interaction with renal ANP system. Am J Physiol. 1990;258(3):F467-72.
15. Grewal J, McKelvie R, Lonn E, Tait P, Carlsson J, Gianni M, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. Eur J Heart Fail. 2008;10(3):252-9.
16. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ. 2002;324(7352):1498.
17. Panjiyar RK, Rs T, Laudari S, Gupta M, Dhungel S, Dubey L, et al. A clinical study of heart failure with preserved ejection fraction in patients at college of medical sciences , teaching hospital : a tertiary centre from. Int J Sci Res Pub. 2017;7(12):58-62.
18. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, Staiger C, Donovan JM, Massie BM. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail. 2008;10(2):149-56.
19. Tschöpe C, Kašner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: Correlation with echocardiographic and invasive measurements. Eur Heart J. 2005;26(21):2277-84.