Original Article

Role of B Type Natriuretic Peptide in the Early Diagnosis of Left Ventricular Diastolic Dysfunction in High Risk Subjects

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Abstract

Key words:
BNP,
Diastolic
dysfunction.

Background: Brain natriuretic peptide (BNP) reflects left ventricular pressure. It increases in systolic dysfunction. Our aim was to evaluate role of plasma BNP level in early diagnosis of left ventricular isolated diastolic dysfunction.

Methods: We studied 60 patients (male=18, female=42) with hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia. The Doppler parameters used for evaluation of diastolic dysfunction are: isovolumetric relaxation time (IVRT), Transmitral flow velocities (E/A) ratio, deceleration time (DT) & pulmonary vein Doppler findings. 49 patients (group-1) had diastolic dysfunction whereas 11 patients (group-2) had normal flow patterns. Plasma BNP level was done in all patients.

Results: Mean plasma BNP levels were 40.41±6.82 pg/ml in individuals with normal filling patterns and 183.36±25.28 pg/ml in subjects with abnormal diastolic dysfunction (p<0.001).The accuracy of BNP in detecting diastolic dysfunction was assessed with receiver-operating characteristic(ROC) analysis. The area under the ROC curve for BNP test accuracy in detection of any abnormal diastolic dysfunction was 0.928 (95% CI, 0.861 to 0.994;p<0.001).A BNP value of 63 pg/ml had the sensitivity of 89.9%,specificity of 91.9% and accuracy of 90.3%.PPVwas 97.8% and NPV-66.7% for detecting diastolic dysfunction.

Conclusion: Raised plasma BNP level is useful for early diagnosis of isolated left ventricular Diastolic dysfunction.

Introduction:

 Diastolic dysfunction is characterized by impaired energy-dependent active relaxation, increased stiffness and resultant pulmonary congestion and low cardiac output state. Isolated diastolic dysfunction is a relatively common problem and accounts for up to 30% of heart failure.[1]

Prognosis of the patient with diastolic dysfunction is better than those with systolic heart failure.[2]

The one year readmission rate approaches 50% in patients with diastolic heart failure. This morbidity rate is nearly identical to that for patients with systolic heart failure.[3,4,5].

Risk factors for diastolic dysfunction are: i) high blood pressure (i.e. hypertension, where, as a result of left ventricular muscle hypertrophy to deal with the high pressure, the left ventricle has become stiff), ii) scarred heart muscle (e.g. occurring after

a heart attack, iii) scars are relatively stiff), diabetes (stiffening occurs presumably as a result of glycosylation of heart muscle), iv) severe systolic dysfunction that has led to ventricular dilation i.e. when the ventricle has been stretched to a certain point, any further attempt to stretch it more, as by blood trying to enter it from the left atrium, meets with increased resistance - it has become stiff, v) reversible stiffening as can occur during periods of cardiac ischemia, vi) ageing.[6] Jossup M et al 2003, showed that it is frequently common in female.

So early diagnosis of diastolic dysfunction in high risk individuals is important to prevent overt heart failure.[7]

Although Doppler echocardiography has been used to examine left ventricular diastolic filling dynamics, the limitations of this technique suggest the need for other measures of diastolic dysfunction.[8]

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Recent studies have demonstrated that LV diastolic dysfunction contributes to BNP level, thus it is useful in the diagnosis of diastolic dysfunction,[9] although there are limited data.

The strongest correlations have been reported for BNP with LV diastolic wall stress consistent with stretch-mediated BNP secretion.[8,9] BNP levels increase with diastolic dysfunction, independent of LVEF, age, sex, body mass index, and renal function, and the highest levels are seen in subjects with restrictive filling patterns.[9,10,11]

Peptide levels correlate with indexes of filling pressure—including transmitral early filling velocity (E)—as well as with indexes of compliance and myocardial relaxation. In subjects with normal LVEF, BNP (>100 pg/ml) are the strongest independent predictor of severe diastolic dysfunction; low peptide levels (<140 pg/ml) exhibit very high negative predictive value (>90%) for diastolic dysfunction.[9]

Our aim was to evaluate the performance of plasma BNP level for early diagnosis of isolated diastolic dysfunction identified by echocardiography in high risk subjects.

Materials & Methods:
It is a Cross sectional study, done in the Department of Cardiology S.S.M.C, Mitford Hospital, Dhaka, from Sep 2009- March 2010.60 patients with risk factors for diastolic dysfunction like HTN,DM,IHD were enrolled in the study.

Selection criteria:
Patients of both sexes
Patients of ≥18 years of age. <80 years.
Clinically suspected diastolic dysfunction in patients having risk factors like HTN, DM, and IHD.

Exclusion criteria:
Patients with EF<55%

Patients with LVED dimension >55mm

Patients with ACS, acute heart failure,

Cardiac cause of stroke,

Poor echo window,

Patients with renal failure,

Hepatic failure,

Patients having undue tachycardia.

Consents from all patients were taken before the study. The study protocol was approved by medical college Research Ethics Committee.

All patients first underwent M-mode, 2D echocardiography by parasternal long axis ,apical 2- and 4- chamber views for careful visual analysis to detect regional wall motion abnormalities, LV systolic and diastolic volumes and ejection fraction, chamber enlargement, ventricular hypertrophy. Apical 4- chamber view was used to assess the transmitral flow and pulmonary venous flow parameters. To see the transmitral flow parameter, pulsed Doppler sample volume was positioned at the tip of the mitral leaflets and in the right upper pulmonary vein for assessment of venous inflow. All echocardiograms were interpreted by experienced cardiologists who were blinded to the plasma BNP levels. As per the values of transmitral and pulmonary venous inflow parameters, different types of diastolic dysfunction were classified. All Doppler values were recorded. Flow spectral was also printed on Polaroid paper with a printer.

Normal ventricular function:
LV end-diastolic dimension (35-55mm), End-systolic dimension (25-36mm)
No major wall motion abnormalities, Ejection fraction>55%,
No evidence of impaired or restrictive relaxation abnormalities.

Diastolic dysfunction: Classified as following:
Impaired relaxation:
E/A ratio of<1 or DT>240ms in patients<55 years of age, or
E/A<0.8 and DT>240ms in patients >55years age
IVRT > 90ms with abnormal E/A ratio.

Pseudo normal:
E/A ratio 1 to 1.5 and DT>240ms.
Confirmation included Pvd/Pvs>1.5 or IVRT<90ms or
By reversal of the E/A ratio <1 by valsalva when possible.

Restrictive like:
DT<160ms with ≥ of the followings:
Left atrial size>50mm,
E/A ratio>1.5 or
IVRT<70ms,
Pvd/Pvs>1.5, and
Pulmonary A" reversal duration exceeding forward mitral A-wave duration.

Plasma BNP assay:

Collection of blood sample:

With full aseptic precaution 3ml of venous blood taken from antecubital vein of each study subject and collected in a tube containing EDTA (axis shield diagnostic, 2003). Plasma separated by centrifuging the blood at 3000 rpm for 10 minutes and 1.8 ml of plasma taken in eppendrofs tube and preserved at -35ºC until analysis.

Estimation of Plasma BNP level:

By micro particle enzyme immune assay (MEIA) principle in AxSYM system (Axis-Shield diagnostics, 2003).

Statistical analysis:

The statistical data were evaluated using SPSS 12(Chicago, IL, USA) package software. General descriptive characteristics were assessed as means ±SD and percentage (%). Normally distributed continuous variables were compared by Student t test and discrete variables were compared using chi- square test. Group comparisons of BNP values were made by using Mann-Whitney test because BNP values were not normally distributed. Significant level was accepted as $p<0.05$. Sensitivity, specificity and accuracy were computed for BNP by use of possible cut points. The diagnostic role of BNP in prediction of echocardiographic probability of diastolic dysfunction was performed by using ROC curve analysis. Results were expressed in terms of the area under the curve (AUC) and 95% CI for this area.

Results:

In our study, Plasma BNP level was found high in individuals with isolated diastolic dysfunction evaluated by echocardiographically. We found that diastolic dysfunction was meaningfully high in individuals with hypertension (Fig: 1) compared with other risk factors. The BNP cut off value was 63 pg/ml with sensitivity 89.8% and specificity 90.9%.

Mean plasma BNP levels (Fig:3) were 40.41±6.82 pg/ml in individuals with normal filling patterns and 183.36±25.28 pg/ml in individuals with abnormal diastolic dysfunction (p<0.001).The accuracy of plasma BNP in detection of diastolic dysfunction was assessed with receiver-operating characteristic (ROC) analysis.

The Area under the ROC curve (Fig: 5) for BNP test accuracy in detection of any abnormal diastolic dysfunction was 0.928(95% CI, o.861 to .994; p<0.001.) A BNP cut of value of 63 pg/ml had a sensitivity of 89.9%, a specificity of 90.9% and an accuracy of 90.3%, PPV – 97.8% NPV-66.7% for detecting diastolic dysfunction.
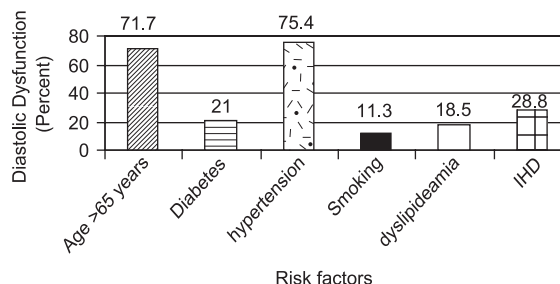

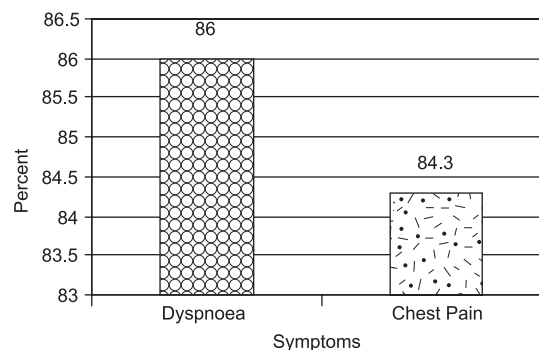**Fig-1:** *Percentage of diastolic dysfunction according to risk factors. In 60 study subjects*

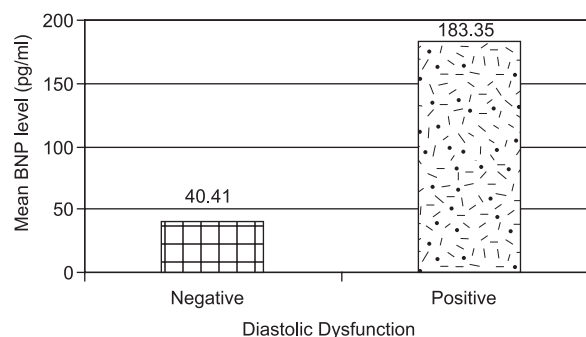**Fig-2:** *Prevalence of dyspnoea and chest pain in study population.*

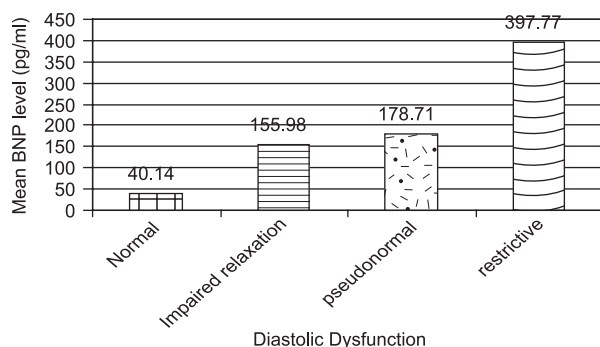**Fig-3:** *Mean BNP value in Normal subjects having no Diastolic dysfunction & in Diastolic dysfunction subjects*

Fig-4: *Mean plasma BNP value in Different types of diastolic Dysfunction.*
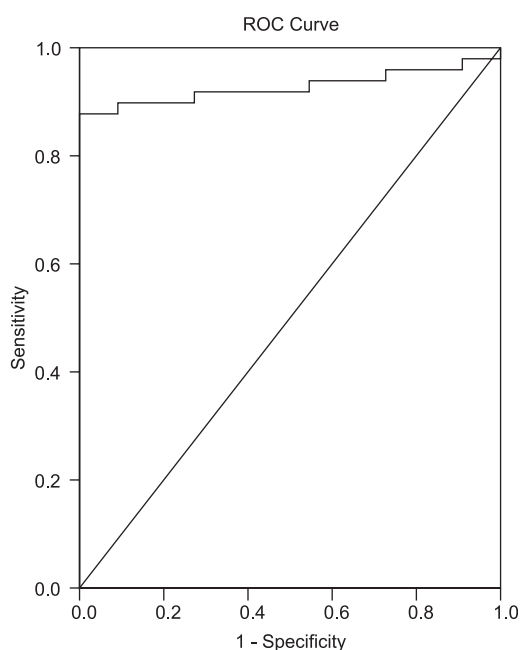

Fig-5: *ROC curve showing sensitivity & specificity*

Discussion:

Systolic functions are normal on echocardiography in one third of patients with heart failure. In these patients diastolic dysfunction was shown to underlie the development of symptoms.[12]

It is known that the prevalence of diastolic dysfunction increases with age. Its incidence is reported to be 15-25% in patients <60 years of age, 35-40% between 60-70 years and above 50% over 70 years.[13,14,15] In our study we found that above 65 years the incidence is about 71.7%.

Wei et al[15] reported that BNP at cut off value>40pg/ml had the 79% sensitivity and 92% specificity in diagnosing LV diastolic dysfunction. Suzuki et al[16] reported cut off value for BNP as 41pg/ml, whereas

Lubien et al[10] demonstrated that BNP cut off value of 62pg/ml could be a predictive marker in showing diastolic dysfunction in patients with heart failure. In our study we found that at BNP value of 63 pg/ml had a sensitivity of 89.9%, and specificity of 90.9%. So it is necessary to determine new cut off values for patients with diastolic dysfunction.

Definitive diagnosis of diastolic dysfunction requires measuring left ventricular pressure and showing the pressure-volume relation. However, invasive and time- consuming nature of these methods hinders its use for the diagnosis of diastolic dysfunction. Evaluation of left ventricular filling through indirect, non-invasive tests is the approach preferred in the emergency clinics for the diagnosis of LV diastolic dysfunction.[17,18]

Very few works in Bangladesh on diastolic dysfunction & Plasma BNP in heart failure have been done. Syed Azizul Haque[19] had shown LV diastolic dysfunction in acute coronary syndrome, 14(20%) having restrictive pattern, whereas 56(80%) impaired relaxation and 2(37.5%) pseudo normal pattern. Smoking was found as the most common risk factor followed by hypertension, hyperlipidaemia and diabetes mellitus. In another study, Dr. Md. Safiul Alam[20] showed significant rise of plasma BNP in heart failure. Very recently MM Hoque et al showed role of plasma BNP for clinical staging of heart failure.[21]

Study Limitation:

The number of our study population is not very large.

Conclusion:

In our study, Plasma BNP level was found high in isolated diastolic dysfunction and it also increases with severity of diastolic dysfunction. We found that diastolic dysfunction was meaningfully high in individuals with hypertension compared with other risk factors. The data obtained from this study indicated that plasma BNP level can be a determining marker of isolated diastolic dysfunction without overt heart failure. So early diagnosis of diastolic dysfunction through plasma BNP level will help in risk factors identification and appropriate treatment that will prevent irreversible structural changes in the heart.

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