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Comparison of N-Terminal Pro B-Natriuretic Peptide and Echocardiographic Indices in Patients with Mitral Regurgitation

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Abstract

Introduction: Echocardiographic indices can form the basis of the diagnosis of systolic and diastolic left ventricular (LV) dysfunction in patients with Mitral regurgitation (MR). However, using echocardiography alone may bring us to a diagnostic dead-end. The aim of this study was to compare N-Terminal pro B-natriuretic peptide (BNP) and echocardiographic indices in patients with mitral regurgitation.

Methods: 2D and Doppler echocardiography and BNP serum level were obtained from 54 patients with organic mild, moderate and severe MR.

Results: BNP levels were increased with symptoms in patients with mitral regurgitation (NYHAI: 5.7 ± 1.1 , NYHAII: 6.9 ± 1.5 , NYHAIII: 8.3 ± 2 pg/ml, $P < 0.001$). BNP plasma level were significantly correlated with MPI (myocardial performance index) ($r = 0.399$, $P = 0.004$), and following echocardiographic indices: LVEDV ($r = 0.45$, $P < 0.001$), LVESV ($r = 0.54$, $P < 0.001$), LVEDD ($r = 0.48$, $P < 0.001$), LVESD ($r = 0.54$, $P < 0.001$), dp/dt ($r = -0.32$, $P = 0.019$) and SPAP ($r = 0.4$, $P = 0.006$).

Conclusion: The present study showed that BNP may be useful in patients with MR and may confirm echocardiographic indices.

Keywords: mitral regurgitation, N-Terminal pro-B natriuretic peptide, echocardiographic indices

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Introduction

Mitral regurgitation (MR) causes progressive systolic and diastolic left ventricular (LV) dysfunction,^{1,2} and has negative impacts on the prognosis of patients with MR.^{3–6} Understanding the degree of this dysfunction and severity of regurgitation would be helpful to establish the best treatment strategy and improve patients' survival.

Echocardiographic indices detection of significant regurgitation of mitral valves can form the basis of the diagnosis of mitral regurgitation and LV systolic and diastolic dysfunction. Although assessment of ventricular function using echocardiography may be difficult and can bring us to a diagnostic dead-end,^{7–9} the use of multiple echocardiographic and hormonal parameters in combination can provide an accurate assessment of MR severity and LV dysfunction in most cases.

N-Terminal pro B-Natriuretic Peptides (NT-pro BNP) are synthesized and secreted in response to increases in wall stress by cardiac myocytes.^{10,11} It has been shown that plasma levels of the NT-pro BNP which are elevated in myocardial infarction and heart failure patients are independent prognostic factors in numerous studies.^{12–14} In contrast, only a few studies have evaluated NT-pro BNP in valvular heart diseases. So the purpose of this study was to compare NT-pro BNP and echocardiographic indices in patients with mitral regurgitation.

Methods

Patients

The subjects included 259 patients who were referred to the Echocardiography Department of Shaheed Rajaei Cardiovascular Medical Centre (Tehran, Islamic Republic of Iran) for evaluation of severity of mitral regurgitation from April 2009 to March 2010. 205 patients were excluded (17 patients had mitral stenosis, 13 patients had right ventricular ischemia, 29 patients had pulmonary hypertension, 10 patients had aortic stenosis, 35 patients had pulmonary disease, 16 patients had hyperthyroidism, 22 patients had severe renal disease, 13 patients had age <18, 20 had poor imaging and 30 patients did not submit their informed consent). This left a study population of 54 patients with mitral regurgitation (33 females and 21 males; mean age, 52 ± 17 years).

Inclusion criteria for the study were: i) sinus rhythm on electrocardiography with no conduction disorder; ii) absence of cardiovascular or other systemic disease; and iii) an upper limit of 120/80 for blood pressure at rest. All participants gave written informed consent for inclusion in the study. The study protocol was approved by the local Medical Ethics Committee.

N-terminal Pro-BNP measurement

Before the performance of echocardiography, a polyethylene catheter was inserted percutaneously in a forearm vein for blood sampling and patient had been in a supine position. Samples were collected in EDTA tubes, immediately placed on ice, and transferred to the laboratory. Plasma levels of NT—pro-BNP were determined with Elecsys proBNP analyzer (measuring range 5–35,000 pg/mL) using a chemiluminescent immunoassay kit (Roche Diagnostics).

Echocardiograph

All patients underwent 2-dimensional echocardiography using Vivid 7 (GE Vingmed Ultrasound, Horten, Norway), with the patient in left lateral decubitus. LV end systolic dimension (LVESD), volume (LVESV) and end diastolic volume (LVEDV) and dimension (LVEDD) were measured as recommended by the American society of echocardiography.¹⁵ The ejection fraction was calculated using the modified Simpson biplane method. LA volume was assessed using the biplane area-length method from apical 4- and 2-chamber views at end systole from the frame preceding mitral valve opening and all other indices were measured according to American Society of Echocardiography guidelines.¹⁶

Myocardial performance index(MPI) which is defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time was calculated (normal range: 0.39 ± 0.05) as described by Tei et al.¹⁷

Statistical analysis

The Independent sample *t*-test was used for comparison of parametric variables, one-way ANOVA for comparison of values of echocardiographic indices and N-terminal pro BNP between three groups with MR. Distribution of BNP levels were skewed but were normal after logarithmic (Ln) transformation. Pearson



test is used to assess the correlation between plasma BNP levels and echocardiographic parameters. The areas under the receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of NT—pro-BNP and echocardiographic variables for the prediction of abnormality of MPI ($\text{MPI} > 0.45$) and were compared according to the method of Hanley and McNeil. Data are mean \pm SD. $P < 0.05$ was considered significant. All tests were done with SPSS 16.0 (Statistical Package for Social Sciences) for Microsoft Windows.

Results

The characteristics of 54 patients with mild ($n = 8$), moderate ($n = 25$) and severe ($n = 21$) MR are listed in Table 1.

BNP levels in groups with mild, moderate and severe MR were 5.5 ± 1.6 , 6.5 ± 1.5 , 6.8 ± 1.6 pg/ml, respectively ($P = 0.162$). Myocardial performance index were 0.44 ± 0.24 , 0.42 ± 0.23 and 0.53 ± 0.28 in patients with mild, moderate and severe MR, respectively. But there were no significant difference among 3 groups ($P = 0.404$). BNP levels were increased with symptoms in patients with mitral regurgitation (NYHAI: 5.7 ± 1.1 , NYHAII: 6.9 ± 1.5 , NYHAIII: 8.3 ± 2 pg/ml, $P < 0.001$). BNP plasma level were significantly correlated with MPI ($r = 0.399$, $P = 0.004$), and following echocardiographic indices: LVEDV ($r = 0.45$,

$P < 0.001$), LVESV ($r = 0.54$, $P < 0.001$), LVEDD ($r = 0.48$, $P < 0.001$), LVESD ($r = 0.54$, $P < 0.001$), dp/dt ($r = -0.32$, $P = 0.019$), SPAP ($r = 0.4$, $P = 0.006$), LA dimension ($r = 0.41$, $P = 0.004$), LV mass ($r = 0.34$, $P = 0.016$) and negative correlation with LV ejection fraction ($r = -0.543$, $P < 0.001$), but there were no significant correlations between BNP plasma level and MR volume ($P = 0.33$), MR VC ($P = 0.23$), MR EROA ($P = 0.34$) and LA volume ($P = 0.6$). Univariate analysis between MPI and echocardiographic indices are summarized in Table 2.

We categorized patients into two groups according to MPI cutoff level of 0.45. The areas under the ROC curve for NT—pro-BNP and echocardiographic measures to predict MPI abnormality are shown in Figure 1. The areas were 0.722 (95% confidence interval [CI] 0.57 to 0.87) for NT—pro-BNP, 0.792 (95% CI 0.65 to 0.93) for LV end-systolic diameter, 0.49 (95% CI 0.38 to 0.60) for LV end-diastolic diameter, 0.79 (95% CI 0.65 to 0.93) for LV end-systolic volume, and 0.76 (95% CI 0.62 to 0.90) for LV end-diastolic volume. The sensitivity, specificity, and area under the ROC curve for abnormality of MPI by natriuretic peptide levels and echocardiographic measures are shown in Table 3.

Discussion

In the present study, we showed that BNP levels were increased with MR symptoms, and correlates with left

Table 1. Baseline clinical characteristics.

	Group 1 (mild) (n = 8)	Group 2 (moderate) (n = 25)	Group 3 (severe) (n = 21)
Men:Women	4:4	9:16	8:13
Age (years)	34 ± 16	59 ± 12	51 ± 19
Heart rate (beat/min)	75 ± 18	75 ± 17	83 ± 22
BSA (m^2)	1.6 ± 0.1	1.7 ± 0.2	1.6 ± 0.1
Ejection fraction (%)	54 ± 9	43 ± 15	47 ± 16
LVEDD (mm)	5.1 ± 0.7	5.6 ± 0.9	5.8 ± 0.9
LVESD (mm)	3.1 ± 0.8	3.9 ± 1	3.9 ± 1
LVESV (ml)	57 ± 30	75 ± 41	76 ± 33
LVEDV (ml)	122 ± 38	131 ± 48	145 ± 44
LV mass (g/m^2)	118 ± 54	141 ± 47	154 ± 65
LA dimension (mm)	3.8 ± 1	3.6 ± 0.6	4.3 ± 0.9
LA volume (ml)	48 ± 40	31 ± 18	62 ± 40
SPAP (mm Hg)	27 ± 5	34 ± 9	40 ± 11
dp/dt	1830 ± 954	1609 ± 1056	1448 ± 927
Mitral annular diameter	3.5 ± 0.8	3.3 ± 0.4	3.5 ± 0.6

Abbreviations: LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume; LV, left ventricular; LA, left atrium; SPAP, systolic pulmonary atrial pressure.

Table 2. Univariate analysis between MPI and other echocardiographic indices.

	<i>r</i>	<i>P</i>
Ejection fraction	−0.54	<0.001
LVEDD	0.54	<0.001
LVESD	0.55	<0.001
LVESV	0.6	<0.001
LVEDV	0.47	<0.001
LV mass	0.36	0.009
LA dimension	0.31	0.029
LA volume	−0.57	0.7
MR EROA	0.252	0.08
MR VC	0.17	0.23
MR volume	0.114	0.43
SPAP	0.31	0.03
dp/dt	−0.34	0.013
Mitral annular diameter	0.440	0.002

Abbreviations: LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LV, left ventricular; LA, left atrium; SPAP, systolic pulmonary atrial pressure; MR, mitral regurgitation.

ventricular volumes and dimensions both in systole and diastole and some of the other echocardiographic indices. Also we showed that BNP levels had a same sensitivity and specificity in prediction of MPI abnormality in comparison with other echocardiographic indices. Mitral regurgitation is a progressive disorder that leads to LV dilatation and dysfunction and reduced functional capacity in these patients, and obtaining an accurate quantitative assessment of the severity and LV function of MR is technically demanding.^{18,19} The most internationally accepted methods to demonstrate

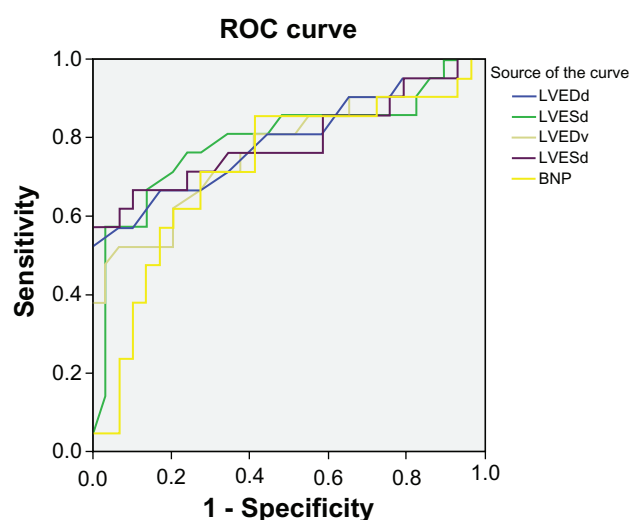
prognosis of MR was LVEF but it has been seen that this index is more dependent on LV geometry and isn't accurate. Previous study has shown that Tei index, a Doppler-derived echocardiographic index, is independent of ventricular geometry, blood pressure and age. Since Tei index incorporates both systolic and diastolic ventricular function may provide a better assessment of the global LV function than LVEF.²⁰

In the present study, we found that MPI correlates positively with left ventricular volumes and dimensions both in systole and diastole, SPAP, LA dimension. Dependency of MPI to preload was seen in previous studies: Lutz and colleagues²¹ found that Tei index is only affected by the increase in preload in mechanically ventilated patients. Similarly, Moller and colleagues²² reported that Tei index is only affected by changes in load conditions in healthy volunteers. Bruch et al²³ supported our result, describing positive correlation between MPI and LV end systolic volume. Correlation of MPI and dp/dt may indirectly describe parallel relation between dp/dt and isovolumic contraction time.

BNP as a neurohormone is secreted by the myocardium and previous studies have shown that its serum level elevated in patients with MR.^{24,25} We found that BNP were increased by symptoms severity and this is concordant to other studies showing increased plasma BNP levels with higher NYHA classes.^{26,27} We also found positive relation between MPI and BNP level which both increased by systolic and diastolic dysfunction.

Our data showed that there is no statistically significant difference in myocardial performance index and BNP of the patients with mild, moderate or severe MR. In other words, neither myocardial performance index nor BNP levels can predict the severity of mitral regurgitation. This finding supports the previous studies which believed in patients with mitral regurgitation BNP activation is a result of alterations in hemodynamic, atrial and ventricular status rather than the degree of regurgitation alone.

When we have chosen cut point level of 0.45 for MPI based on Ono and colleague's²⁰ study we could define a cut point for N-terminal pro BNP serum level and some of the mentioned echocardiographic indices to differentiate normal and abnormal MPI. To the best of our knowledge, this study is the first one in the medical literature that gives such information in mitral

**Figure 1.** Diagonal segments are produced by ties.

**Table 3.** Sensitivity and specificity of natriuretic peptide levels and echocardiographic parameters for patients with normal and abnormal MPI.

Variable	Cut point	Sensitivity (%)	Specificity (%)	AUC
N Terminal -proBNP (pmol/L)	603	71	73	0.76
LV end-systolic volume (mL)	63.5	72	76	0.79
LV end-diastolic volume (mL)	118	76	63	0.76
LV end-systolic dimension (cm)	3.7	76	76	0.79
LV end-diastolic dimension (cm)	5.4	71	76	0.79

Abbreviations: LV, left ventricle; AUC, area under curve.

regurgitation. Based on our results, an N-Terminal proBNP serum level of more than 603 pmol/l can show the abnormality of MPI with 71% sensitivity and 73% specificity.

Furthermore, calculation and comparison of area under ROC curves for N-Terminal proBNP and echocardiographic measures such as LV end-diastolic volume, LV end-systolic volume, LV end-systolic dimension and LV end-diastolic dimension showed that there is no significant clinical difference between these indices such that one may be chosen as the best one for prediction of MPI abnormality. And because BNP measurement is easier, it costs less than echocardiography and intra observer viability may be useful to use as a hormonal marker in patients with MR.

Limitation

It may be better to measure diastolic echocardiographic indices due to systolic and demonstrated relation of them with BNP which representative both systolic and diastolic function. Also further studies with larger population may lead to more accurate results.

Conclusion

This study showed that BNP measurement has the same sensitivity and specificity as echocardiographic indices and may be used as a hormonal factor for the evaluation of patients with MR in combination with echocardiography.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest.

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