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Original Article

NT-proBNP in Mitral Stenosis: Can It Be a Predictor of Hemodynamic Status?

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ABSTRACT

Background: Mitral valve area (MVA) and other indices of the severity of mitral stenosis poorly reflect the functional status, systolic pulmonary artery pressure, and cardiac output in patients with severe mitral stenosis. In the present study, we aimed to compare the strength of conventional stenosis indices and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in the prediction of major functional and hemodynamic consequences of mitral stenosis in a group of patients with a severe form of this disease.

Methods: Patients with severe symptomatic rheumatic mitral stenosis (MVA< 1.5 cm^2) were enrolled. Comprehensive echocardiography and catheterization were performed for all the patients. MVA was measured via the 2D planimetry method, and NT-proBNP levels were measured during admission.

Results: Forty-one patients, 88% of whom were female, were enrolled in our study. The NT-proBNP level and MVA had a significantly negative correlation ($\rho = -0.450$ and $P = 0.003$). The NT-proBNP level had a significant correlation with systolic pulmonary artery pressure ($\rho = -0.423$ and $P = 0.006$) and MV resistance ($\rho = -0.506$ and $P = 0.001$); however, the mean transmitral pressure gradient and the NT-proBNP level did not show a significant relationship. The strongest relationships were found between the NT-proBNP level and stroke volume and cardiac output, which were negatively significant ($P = -0.601$ and $P = 0.000$) and ($\rho = -0.587$ and $P = 0.000$), respectively.

Conclusions: It appears that the NT-proBNP level can be a good predictor of patients' hemodynamic status such as cardiac output in addition to the echocardiographic features of mitral stenosis. ***(Iranian Heart Journal 2020; 21(3): 89-95)***

KEYWORDS: Mitral stenosis, Brain natriuretic peptide, Echocardiography, Cardiac output

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Rheumatic involvement of the mitral valve, which results in mitral stenosis (MS) is still one of the major causes of disability and mortality among young patients in developing countries. [1, 2] Even asymptomatic or mildly symptomatic patients are at risk of adverse hemodynamic consequences, including pulmonary hypertension and atrial arrhythmia.

The severity of MS is mainly measured by echocardiographic and Doppler examinations, and these studies are essential for the diagnosis and quantification of the severity of the stenosis. [3]

Based on current recommendations, valve area planimetry via 2D echocardiography, valve area calculation via the pressure half-time method, the measurement of the mean transmitral pressure gradient (TMPG), and the measurement of systolic pulmonary artery pressure are appropriate tools for the classification of MS severity. [3]

Natriuretic peptides (NPs) are synthesized and secreted by cardiac myocytes in response to increases in wall stress. [4,5]

Brain natriuretic peptide (BNP) levels are used for the diagnosis of patients with dyspnea and heart failure symptoms as part of the guideline for the diagnosis and management of heart failure. [6,7]

MS affects the right heart along with the left atrium and increases the BNP level in patients with MS. [8-11]

N-terminal pro B-type natriuretic peptide (NT-proBNP) is secreted in a proportion equivalent to BNP and is thought to be more sensitive because of its longer half-life. [12]

In this study, we sought to evaluate NT-proBNP levels in patients with MS and to determine its correlation with the echocardiographic and hemodynamic parameters of MS such as mitral valve area (MVA), systolic pulmonary artery pressure, mitral valve resistance, left atrial diameter, and cardiac output.

METHODS

Study Population

From September 2013 to December 2014, patients with symptomatic severe native MS (MVA < 1.5 cm^2) admitted to Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, for further diagnostic and therapeutic workup were enrolled via the convenient sampling methods. Patients were excluded if they had moderate or severe mitral or aortic valve regurgitation or a left ventricular ejection fraction of less than 50%.

All the patients provided written informed consent, and the Review Board of Rajaie Cardiovascular Medical and Research Center approved the study protocol.

Echocardiographic Examination

Comprehensive transthoracic echocardiography was performed by a single echocardiography specialist using a Vivid 3 ultrasound system (GE Medical System, Horton, Norway) and a 1.7/3.4-MHz transducer. Images were acquired with the subjects at rest, lying in the left lateral supine position at the end of expiration. Two-dimensional electrocardiography (ECG) was superimposed on the images, and end-diastole was considered at the peak R-wave of the ECG. Left ventricular global systolic function was evaluated using a modified biplane Simpson method for calculating left ventricular ejection fraction by measuring end-diastolic and end-systolic volumes in 2D images. In all the patients, MVA was assessed using the 2D planimetry method in the parasternal short-axis view at the valve tips as was described previously. [13] Systolic pulmonary artery pressure was also measured by echocardiography. All the measurements were performed in keeping with the protocols and standards of the latest American Society of Echocardiography (ASE) guidelines for native valve disease. [3] Intraobserver and interobserver variabilities were calculated to 1.5% and 3.5%, respectively.

Biochemical Measurements

Serum NT-proBNP levels were determined by enzyme immunoassay (Siemens Healthcare Diagnostic Inc, USA), with intra- and inter-assay coefficient of variations of 5% and 6.5%, respectively.

Statistical Analysis

All the data analyses were conducted using the SPSS software, version 23, (SPSS Inc, Chicago, IL, USA). All the data were initially analyzed using the Kolmogorov–Smirnov test to assess normality. The categorical variables were presented as numbers (percentages) and analyzed using the χ^2 test. The normally-distributed quantitative variables were presented as the mean ± the standard deviation (SD), and those with non-Gaussian distributions were presented as the median (the interquartile range [IQR]). For the analysis of the quantitative variables, the Student *t*-test, the Mann–Whitney *U* test, and the Kruskal–Wallis test were employed, depending on the data distribution. Relationships were assessed using the Spearman rank correlation coefficient (ρ). All *P* values were 2-tailed, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 41 patients with pure rheumatic MS, including 36 (88%) women, were enrolled. The age distribution of the study population was between 23 and 77 years, with a mean of 50 ± 12 years. Twenty-four (58.5 %) patients were on diuretic therapy, and 30 (73.2%) were taking beta-blockers. The median MVA and the median NT-proBNP level were 0.80 cm^2 (IQR: 0.65 to 1.01) and 396 pg/mL (IQR: 139 to 1331), respectively. The baseline characteristics of the patients are summarized in Table 1, and the echocardiographic data are summarized in Table 2.

Table 1: Baseline characteristics of the study population

Characteristic	Value
Age	50±12
Gender	
male	5 (12%)
female	36 (88%)
Cardiac Rhythm	
sinus	21 (51.2%)
atrial fibrillation	20 (48.8%)
Cardiac Axis (ECG)	
normal	33 (80.5%)
RAD	7 (17.1%)
LAD	1 (2.4%)
Bundle Branch Block	
No	34 (82.9%)
RBBB	7 (17.1%)
Creatinine (mg/dL)	0.8 (0.6-0.9)
NT-proBNP (pg/mL)	396 (139-1331)

ECG, Electrocardiography; RAD, Right axis deviation; LAD, Left axis deviation; RBBB, Right bundle branch block

Table 2: Echocardiographic characteristics of the study population

Characteristic	Value
MVA (cm^2)	0.8 (0.65-1.01)
MVR (dyne.s.cm-5)	151.2 (06.05-236.75)
PHT (ms)	249 (211.75-334.75)
sPAP (mm Hg)	45.00 (40.00-55.00)
Mean TMPG (mm Hg)	10.00 (8.25-15.00)
LA diameter (cm)	4.57 (4.00-4.97)
LVEDD (cm)	4.78 (4.4-5.00)
RV size (cm)	3.20 (2.90-3.38)
CO (lit/min)	3153.30 (2629.65-3795.40)
SV (mL)	40.70 (35.25-50.10)
LVEF (%)	55 (50-60)

MVA, Mitral valve area; MVR, mitral valve resistance; PHT, Pressure half-time; sPAP, Systolic pulmonary artery pressure; TMPG, Transmitral pressure gradient; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; RV, Right ventricle; SV, Stroke volume; LVEF, Left ventricular ejection fraction; CO, Cardiac output

The NT-proBNP level and MVA had a significantly negative correlation (ρ = −0.450 and *P* = 0.003) (Fig. 1). The relationship between the NT-proBNP level and systolic pulmonary artery pressure was also significant (ρ = −0.423 and *P* = 0.006) (Fig. 2). The NT-proBNP level and MV resistance (another marker for the severity of MS) also exhibited a strong correlation (ρ = −0.506 and *P* = 0.001) (Fig. 3). The relationship between the mean TMPG and NT-proBNP was not significant (*P* = 0.106), but MVA and the mean TMPG showed a significant negative correlation (ρ = −0.478 and *P* = 0.002). The strongest relationships between the NT-proBNP level and echocardiographic data were with stroke volume and cardiac output, which were negatively significant (ρ = −0.601 and *P* = 0.000 and ρ = −0.587 and *P* = 0.000, respectively) (Fig. 4). Left atrial diameter and NT-proBNP had a significant relationship (*P* = 0.342 and *P* =0.031), while left ventricular end-diastolic diameter and the NT-proBNP level showed no significant relationship (*P* = 0.945). Table 3 depicts the relationship between the NT-proBNP level and the echocardiographic findings of the patients.

Table 3: Correlations between NT-proBNP and echocardiographic measures

	NT-proBNP	
	Correlation Coefficient (ρ)	*P* value
MVA	-0.437	0.003
MVR	0.506	0.001
PHT	0.541	0.000
Mean TMPG	0.256	0.106
sPAP	0.423	0.006
SV	-0.601	0.000
LA diameter	0.342	0.031
LVEDD	-0.011	0.945
LVEF	-0.453	0.003
CO	-0.587	0.000

MVA, Mitral valve area; MVR, mitral valve resistance; PHT, Pressure half-time; sPAP, Systolic pulmonary artery pressure; TMPG, Transmitral pressure gradient; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; RV, Right ventricle; SV, Stroke volume; LVEF, Left ventricular ejection fraction; CO, Cardiac output

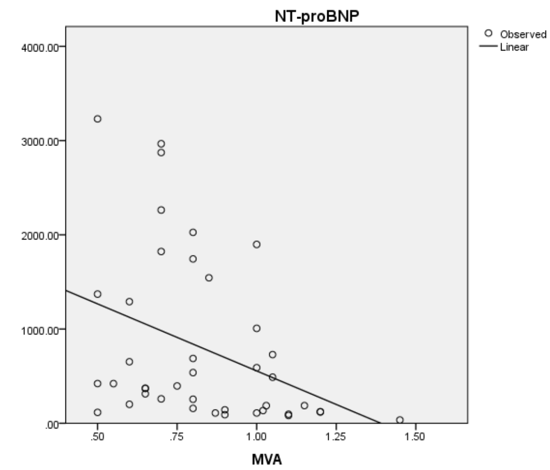

Figure 1: Correlation between NT-proBNP and mitral valve area (MVA)

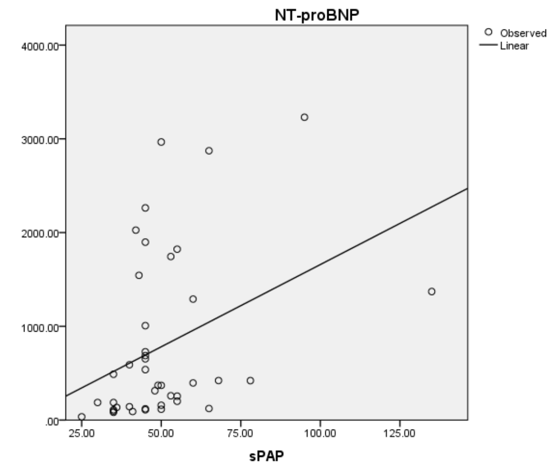

Figure 2: Correlation between NT-proBNP and systolic pulmonary artery pressure (sPAP)

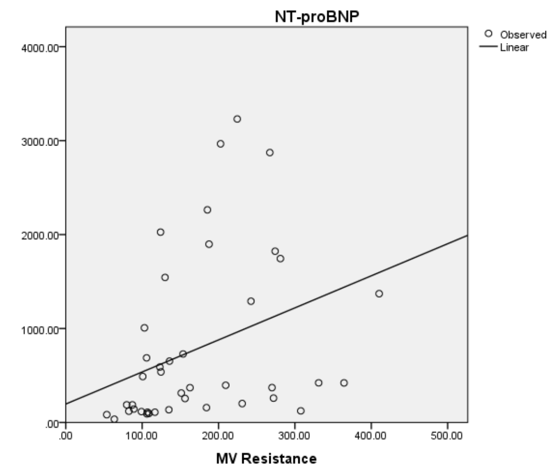

Figure 3: Correlation between NT-proBNP and mitral valve resistance (MVR)

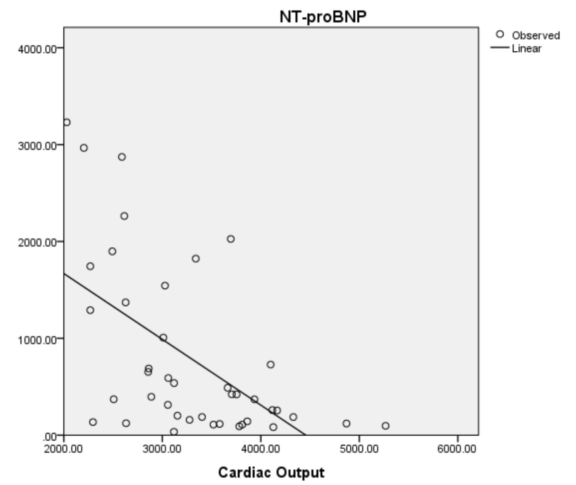

Figure 4: Correlation between NT-proBNP and cardiac output

Nearly half of the patients (48.8%) were in atrial fibrillation rhythm, and the NT-proBNP level was significantly higher in those with atrial fibrillation rhythm than in those in sinus rhythm (868 pg/mL, IQR: 501.25 to 1975.25 vs 143 pg/mL, IQR: 109 to 383; *P* = 0.000). Further, 17% of the patients had a right bundle branch block pattern in their surface ECG, and the NT-proBNP level was higher in this group than in the group without this pattern (1744 pg/mL, IQR: 422 to 2873 vs 314 pg/mL, IQR: 122.25 to 698.25; *P* = 0.009).

DISCUSSION

The use of BNP and NT-proBNP in diagnosing patients with heart failure, monitoring their treatment, and predicting their outcome is growing fast, and it has an important role in the current guidelines for the management of patients with heart failure. [6, 7] BNP and its N-terminal pro-form have shown predictive values in various diseases that have direct or indirect influences on cardiac functions in many non-heart failure circumstances, even in the absence of depressed cardiac function. [14] BNP adds important incremental prognostic information that is useful for the management of patients with valvular diseases, particularly for the optimal timing of surgery. [15]

The relationships between NPs (eg, ANP, BNP, and NT-proBNP) and the severity of MS have been studied in several trials; these relationships have also been shown to have correlations with patients' symptoms and exercise capacity. [8-11,16-19]

Previous studies have reported an association between the echocardiographic findings of MS and the plasma BNP level and also between the functional capacity of patients and the BNP level. Arat-Ozkan et al [16] studied 29 patients with isolated MS and compared them with 20 normal control subjects and found that the NT-proBNP level was elevated in the patients with MS compared with the controls (325 ± 249 pg/dL [19.9 to 890] vs 43 ± 36 pg/dL [5.76 to 193.3]; *P* < 0.0001). Also in their study, patients with atrial fibrillation had higher NT-proBNP levels. The authors concluded that NT-proBNP correlated with left atrial diameter, right ventricular diameter, MVA, mean mitral gradient, peak pulmonary artery pressure, and New York Heart Association functional class.

Sharma et al [17] studied 30 patients with moderate-to-severe MS and compared them with 13 normal controls and reported that BNP was higher in the patients with MS than in the controls (BNP 58 [34, 93] vs 16 [14, 25 pg/mL]; *P* < 0.0001). [17]

A study conducted by Kilickesmez et al [18] showed a correlation between NT-proBNP and exercise-induced augmentation in pulmonary artery pressure in patients with moderate-to-severe, asymptomatic, or mildly symptomatic MS.

In our study, similar to other studies, we found significant relationships between the echocardiographic parameters of MS severity such as MVA, pressure half-time, systolic pulmonary artery pressure, and mitral valve resistance and NT-proBNP

levels; nevertheless, there was no statically significant relationship between the NT-proBNP level and the mean TMPG, although the relationship between MVA and the mean TMPG was significant. We also found a significant relationship between left atrial diameter and the NT-proBNP level.
Patients with similar MVA are considered in the same class of severity. Still, in clinical practice, we frequently witness patients with the same MVA but with a significantly wide range of clinical symptoms. Thus, it appears that other indices may be needed to classify patients with the same degree of MS based on the hemodynamic consequences of their disease. One of these indices could be the NT-proBNP level. As the severity of stenosis increases, cardiac output becomes subnormal at rest and fails to increase during exercise. [3] In our study, the relationship between cardiac output and the NT-proBNP level was stronger than that with MS severity parameters, which may suggest that in patients with severe MS, the NT-proBNP level may be more helpful in predicting the hemodynamic effects of MS such as a low cardiac output state. To that end and to extend the availability of NT-proBNP measurements, we need further research to determine whether this biomarker can be used as a hemodynamic predictor of MS.

CONCLUSIONS

It has been proven previously that the NT-proBNP level correlates with MS severity and functional class. Be that as it may, based on our study, it could also be a precise predictor of patients' hemodynamic status parameters such as cardiac output.

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