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ORIGINAL ARTICLE

Potential use of Brain Natriuretic Peptide in patients with asymptomatic significant mitral stenosis

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KEYWORDS

Brain Natriuretic Peptide;
Rheumatic mitral stenosis;
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Abstract *Objective:* To evaluate the ability of BNP to identify a subset of patients with asymptomatic significant rheumatic MS, who get symptoms on stress exercise testing.
Methods: Seventy asymptomatic patients with significant rheumatic MS (MVA $\leqslant 1.5\ cm^2$) were included in the study. All patients underwent resting echo-Doppler study, exercise echocardiography and BNP level assessment pre- and one week post-balloon dilatation (for group I patients who had PMC).
Patients were divided into two groups. Group I included 33 patients who became symptomatic on exercise and had low exercise capacity. Group II included 37 patients who were asymptomatic on exercise and had reasonable exercise capacity.
Results: BNP level in group I was 92 ± 12 compared to 40 ± 10 pg/ml in group II, $P < 0.001$. Post PMC, BNP in group I significantly decreased (92 ± 12, compared to 31 ± 9 pg/dl, $P < 0.001$). LA dimension was significantly different between both groups (50 ± 2.9 in group I compared to 46 ± 3.1 mm in group II, $P < 0.001$). Post-exercise SPAP was 72 ± 12 in group I compared to 46 ± 13 mmHg in group II, $P < 0.001$. Post-exercise MV gradient was 28 ± 9

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; AF, atrial fibrillation; ANP, Atrial Natriuretic Peptide; AS, aortic stenosis; BNP, Brain Natriuretic Peptide; EF, ejection fraction; ESC, European Society of Cardiology; LA, left atrium; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; NT-Pro-BNP, N terminal-pro brain natriuretic peptide; PAP, pulmonary artery pressure; PMC, percutaneous mitral commissurotomy; SPAP, systolic pulmonary artery pressure; WMA, wall motion abnormality.

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compared to 20 ± 12 mmHg, $P = 0.002$. BNP significantly correlated with post-exercise SPAP ($r = 0.635$; $P < 0.001$). Area under the ROC curve for BNP as a predictor of low exercise capacity and development of symptoms on exercise was 0.98 [CI 95% 0.96–1.0]. When using a cutoff value of 55 pg/mL for BNP, sensitivity was 93.9% and specificity was 91.9%.

Conclusion: BNP may be used to approach asymptomatic patients with significant MS. BNP may identify a subset of patients with exercise-induced clinical and echo-Doppler criteria that meet the contemporary guidelines for intervention.

1. Introduction

Current European Society of Cardiology (ESC) guidelines for management of valvular heart diseases (2012), recommend doing percutaneous mitral commissurotomy (PMC) for patients with clinically significant mitral stenosis (MS) (mitral valve area $\leqslant 1.5\ cm^2$) with suitable valve scores if patients are symptomatic. In asymptomatic patients, intervention is justified for those who become symptomatic on exercise testing and those who had low exercise capacity [achieve < 5 Metabolic Equivalents (METs)].[1]

Rheumatic valvular heart diseases continue to be a major health problem in developing countries. Mitral stenosis is one of the most frequently encountered rheumatic valvular heart disease affections.[2,3] Regular follow up for patients with significant mitral stenosis is crucial to take the proper decision of intervention in the proper time (either surgical replacement or alternatively balloon commissurotomy if the valve morphology is suitable). It is frequently encountered that rheumatic MS patients describe equivocal symptoms. Due to the long latent period between onset of the initial rheumatic valvular affection and development of significant mitral stenosis, it is difficult for the treating physician to truly identify patients with symptoms that could be attributed to either hemodynamically significant stenosis or non cardiac dyspnea. Some patients have a sedentary life style that may result in physical deconditioning and subsequently exertional symptoms. On the other hand, other patients who are considered asymptomatic adapt their level of exertion and thereby do not get symptoms. Symptomatic status is mainly subjective, and hence a better risk stratification objective tool is required to be implemented in regular follow up of rheumatic MS patients.[4]

Several studies have reported an association between natriuretic peptides and severity of mitral stenosis.[5] Other studies have remarked a significant drop of Brain Natriuretic Peptide (BNP) post PMC.[5,6]

The predominant cardiac source of Atrial Natriuretic Peptide (ANP) is the atria, while the ventricles are the main source of BNP, although both can be synthesized in either chamber.[7–10] Both ANP and BNP are released into the circulation following primarily myocyte stretch. ANP release is more closely related to increased left atrial pressure while BNP release is more dependent on increased left ventricular pressure.[11,12,10,13–16]

In previous studies, a strong correlation between plasma BNP level and left atrial area suggested atrial secretion of BNP in MS. This was supported by evidence for synthesis of BNP by atrial myocytes in response to chronic increase in wall stress and co-storage of BNP with ANP in atrial granules.[14]

In valvular heart diseases, BNP serum level was found to be related to functional class and prognosis, particularly in aortic stenosis (AS) and mitral regurgitation (MR). In patients with chronic asymptomatic MR, several studies suggested the value of elevated BNP levels and a change in BNP as predictors of outcome. A cut-off BNP value $\geqslant 105$ pg/ml determined in a derivation cohort was prospectively validated in a separate cohort and helped to identify asymptomatic patients at higher risk of developing heart failure, LV dysfunction or death on mid-term follow-up.[17] Another study found that low-plasma BNP had a high negative predictive value and might be helpful for the follow-up of asymptomatic organic MR patients.[18]

The aim of our study was to evaluate the ability of a single baseline BNP level assessment to truly identify an important subset of asymptomatic clinically-significant rheumatic MS patients (with suitable valve scores for PMC) whose exercise stress criteria (clinical and echo-Doppler) meet the ESC contemporary guidelines for intervention.

2. Patients and methods

In this single center study, seventy asymptomatic patients with clinically significant rheumatic mitral stenosis (MVA $\leqslant 1.5\ cm^2$ and $> 1\ cm^2$) were prospectively included. All patients had suitable mitral valve scores for percutaneous dilation (mitral valve scores of $\leqslant 8$). All patients had a resting systolic pulmonary artery pressure < 50 mmHg. All patients underwent treadmill exercise testing and post-exercise echo-Doppler study. Patients were divided into two groups based on symptomatic status on exercise and exercise capacity. Group I included 33 patients who were symptomatic on exercise and had low exercise capacity (< 5 METs).[19] Group II included 37 patients who were asymptomatic on exercise and had a reasonable exercise capacity (> 5 METs).

Exclusion criteria were poor echocardiography window, significant renal impairment, presence of ischemic heart disease by history or resting wall motion abnormality (WMA) on echo-Doppler study, previous cardiac surgery or valve intervention, coexistent heart muscle disease or other valvular lesion (if graded more than mild) or inability to exercise (inability to walk on treadmill).

This study was carried out in the Cardiology Department, Faculty of Medicine, Zagazig University Hospitals, in the period from July 2011 to November 2013. All patients gave an informed consent to participate in the study.

2.1. BNP measurement

All samples were collected by veni-puncture into EDTA tubes within 2 h of obtaining the baseline echocardiogram and one week after PMC (for group I). The blood samples were kept at room temperature and analyzed within 4 h of sampling

using the Triage BNP assay (Biosite diagnostics). Before analysis, each tube was inverted several times to ensure homogeneity. The BNP assay was a sandwich immuno-assay that consisted of a disposable device to which EDTA-anticoagulated whole blood or plasma was added. The triage meter was used to measure the BNP concentration by detecting a fluorescent signal that reflected the amount of BNP in the sample, the cells were separated from the plasma by a filter, and the plasma containing BNP entered a reaction chamber that contained fluorescent-tagged BNP antibodies to form a reaction mixture. The reaction mixture was incubated for 2 min and then migrated through the diagnostic lane by capillary action to a zone of immobilized antibody that would bind the desired BNP-fluorescent antibody complex. The unbound fluorescent antibodies were washed away by excess sample fluid. After 15 min, the device was placed in a Triage meter, which measured the fluorescence intensity of the BNP assay zone. The Triage meter then correlated the fluorescence measurement to BNP concentration by use of an internal calibration curve. The assay was completed in 15 min.[20]

2.2. Baseline echocardiography study

All patients underwent resting echocardiography study using SONOS 5500 machine (Philips technologies). The mitral valve area (MVA) was calculated using pressure half time and direct planimetry and the median MVA was calculated. The Wilkins scores for MV suitability for PMC were calculated. This scoring system assigns a point value from 1 to 4 for each of (1) valve calcification, (2) leaflet mobility, (3) leaflet thickening, and (4) disease of the subvalvular apparatus.[21] By tracing the continuous wave Doppler signal across the mitral valve, mean transmitral pressure gradients were obtained. Left atrial dimensions were obtained from the long axis parasternal view using the m-mode. Systolic pulmonary artery pressure (SPAP) was obtained using the simplified Bernoulli equation (the peak tricuspid regurgitation (TR) jet was added to an estimate of right atrial pressure obtained by imaging the inferior vena cava). The left ventricular ejection fraction was measured from the apical four-chamber view using the modified Simpson's rule.[22,23] All values were obtained by averaging three cycles (five in cases of atrial fibrillation). All data were analyzed by a single operator who was blind to patients' symptomatic status and BNP values.

2.3. Exercise treadmill test and post-exercise echo-Doppler study

Symptom-limited treadmill test was done using a modified Bruce protocol. Continuous 12 lead ECG monitoring and blood pressure checking at three minutes interval were done. Indications to stop treadmill were significant arrhythmia, significant dyspnea, and fatigue or upon patient's request. An experienced cardiologist supervised the test.[24]

Within one minute of peak exercise, formal echo-Doppler study was done with special emphasis on the apical four-chamber view with continuous wave Doppler across mitral valve for mean pressure gradient and the tricuspid valve for tricuspid jet velocity and assessment of systolic pulmonary artery pressure. Treadmill exercise test and post-treadmill echocardiogram assessments were performed blinded to the BNP levels. Low exercise capacity was defined as achieving <5 METs on treadmill exercise.[19]

Patients were either referred for PMC or to continue annual regular follow up assessments according to the symptomatic status on exercise testing and the exercise capacity.

For group I patients, PMC was done after exclusion of left atrial or left atrial appendage clots and confirmation of MR severity by trans-esophageal echocardiography.[21,25]

2.4. Statistical analysis

Baseline demographic and analytical information are presented as absolute number (percentage for categorical variables). Comparison of categorical and continuous variables between the 2 groups was performed using chi-square and unpaired *t*-test, respectively. Correlations between variables were calculated by Pearson correlation coefficient. To evaluate the ability of BNP to predict low exercise capacity and development of symptoms on exercise, the area under the receiver-operating characteristic (ROC) curve was used. An optimal cutoff value was calculated from analyses of the ROC curve.

Statistical analysis was performed using SPSS for windows (version 19 SSPS Inc, Chicago, IL, USA). All P values were evaluated and a result of <0.05 was considered significant. P values <0.001 were considered highly significant.

3. Results

3.1. Baseline demographic and echo-Doppler characteristics

As shown in Table 1, both study groups were comparable regarding baseline demographic characteristics and medications (beta-blockers, loop diuretics), ($P > 0.05$). 54.5% in-group I had AF compared to 59.4% in-group II, $P > 0.05$. There was no statistically significant difference between the two groups regarding any of the studied baseline echo-Doppler criteria apart from left atrial (LA) dimension

Table 1 Demographic and resting echo-Doppler characteristics in the two groups.

	Group I (n = 33)	Group II (n = 37)	P value
Age (years)	29 ± 10.1	32 ± 9.3	0.33
Males (n, %)	10 (30.3%)	12 (32.4%)	0.84
Systolic blood pressure	115 ± 13	118 ± 11	0.32
Diastolic blood pressure	65 ± 5	68 ± 7	0.44
Beta-blockers (n, %)	12 (36.4%)	10 (27%)	0.40
Loop diuretics (n, %)	20 (60.6%)	18 (48.6%)	0.31
Atrial fibrillation (n, %)	18 (54.5%)	22 (59.4%)	0.74
Resting echocardiographic findings			
LVEF (%)	59 ± 7	63 ± 9.1	0.14
Left atrial dimension (mm)	50 + 2.9	46 + 3.1	<0.001
Right ventricle (mm)	33.2	33.8	0.36
MV area(cm^2)	1.29 ± 0.2	1.33 ± 0.1	0.31
Mean MV gradient (mmHg)	9 ± 3.2	10 ± 2.4	0.26
Systolic PAP (mmHg)	33 ± 12.3	35 ± 8.4	0.53

LVEF: left ventricular ejection fraction; MV: mitral valve; SPAP: systolic pulmonary artery pressure.

(50 ± 2.9 in group I compared to 46 ± 3.1 mm in group II, $P < 0.001$).

3.2. Treadmill exercise test (as shown in Table 2)

Peak exercise heart rate was not statistically significant on comparing both groups (139 ± 17.4 compared to 145 ± 19.5 b/m, respectively, $P > 0.05$). Peak-exercise SPAP was 72 ± 12, compared to 46 ± 13 mmHg respectively, $P < 0.001$. Peak-exercise mean gradient across mitral valve was 28 ± 9 compared to 20 ± 12 mmHg respectively, $P = 0.002$.

3.3. BNP levels

As shown in Table 3, baseline BNP levels were significantly higher in group I patients compared to group II (92 ± 12 compared to 40 ± 10 pg/ml, respectively, $P < 0.001$). The upper limit of the normal lab reference for BNP was 42 pg/ml.[20]

In group I, all patients underwent PMC. The procedure was successful in all patients. Procedural success was defined as post-procedure MVA $\geqslant$1.5 cm^2 and MR severity $<$2/4 or a 50% gain in relation to the measured area before the procedure.[19] BNP levels one-week post balloon valvuloplasty dropped significantly compared to baseline values (92 ± 12 compared to 31 ± 9 pg/ml, $P < 0.001$).

As shown in Fig. 1, analysis of the receiver-operating characteristic curve for BNP as a predictor of low exercise capacity and development of symptoms on exercise showed an area under the curve of 0.98 [confidence interval 95%, 0.96–1.0], kappa measure of agreement 0.85, $P < 0.001$.

When using a BNP cut-off value of 55 pg/ml, derived from the receiver-operating characteristic curve as a predictor of low exercise capacity and development of symptoms on exercise, sensitivity was 93.9%, specificity was 91.9%, positive predictive value was 91.2% and negative predictive value was 94.4%.

Correlation analysis between some studied variables and post-exercise elevation of systolic pulmonary artery pressure $>$60 mmHg is shown in Table 4. There was a positive correlation between resting mitral valve area ($r = 0.327$, $P < 0.01$), left atrial dimension ($r = 0.285$, $P < 0.05$), resting mean transmitral gradient ($r = 0.319$, $P < 0.01$), baseline BNP level($r = 0.635$, $P < 0.001$) and post-exercise elevation of SPAP $>$60 mmHg.

4. Discussion

In this study, we demonstrated that in asymptomatic patients with clinically significant MS, a baseline BNP assessment could predict symptomatic status on exercise and low exercise capacity. A cut-off point for BNP that was concluded from the ROC curve (55 pg/ml) was found to have a reasonable sensitivity and specificity. We found also a significant positive correlation between BNP levels and exercise induced elevation of SPAP $>$60 mmHg.

Contrary to the 2008 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of valvular heart diseases [where PMC was class I indication in asymptomatic moderate to severe MS (MVA

Table 2 Exercise treadmill test and post exercise echo-Doppler results in both study groups.

	Group I	Group II	*P* value
Peak PAP (mmHg)	72 ± 12	46 ± 13	<0.001
Mean MV gradient (mmHg)	28 ± 9	20 ± 12	0.002
LVEF (%)	69 ± 12.5	72 ± 11.3	0.43
Peak heart rate (b/m)	139 ± 17.4	145 ± 19.5	0.32

LVEF: left ventricular ejection fraction; MV: mitral valve; PAP: pulmonary artery pressure.

Table 3 Baseline BNP levels in group I versus group II; plus pre and one week post balloon dilatation (PMC) in group I patients.

	Group I	Group II	*P* value
BNP level (pg/ml) (Baseline)	92 ± 12	40 ± 10	<0.001
BNP level (pg/ml) post-PMC	31 ± 9		
P value	<0.001		

BNP: Brain Natriuretic Peptide; PMC: percutaneous mitral commissurotomy.

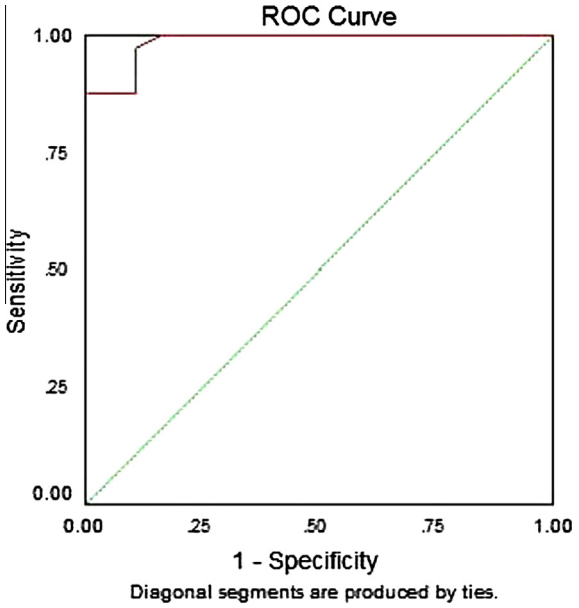

Figure 1 Receiver-operating characteristic curve for BNP to predict low exercise capacity and development of symptoms on exercise.

Table 4 Correlation analysis of some studied variables (at rest) and exercise–induced elevation of systolic pulmonary artery pressure $>$60 mmHg.

Variable	*r*	*P* value
Age (year)	0.108	>0.05
MVA (cm^2)	0.327	<0.01
LAD (cm)	0.285	<0.05
mPG (mmHg)	0.319	<0.01
BNP (pg/ml)	0.635	<0.001

MVA: mitral valve area; LAD: left atrial dimension; mPG: mean pressure gradient; BNP: Brain Natriuretic Peptide.

$\leqslant$1.5 cm^2 with suitable valve morphology), if resting SPAP is $>$50 mmHg, $>$60 mmHg on exercise or when patients have poor exercise tolerance], ACC/AHA 2014 guidelines state that although exercise-induced pulmonary hypertension does not have a formal place in those guidelines, a rise in RV systolic pressure to $>$60 mmHg to 70 mmHg should prompt the clinician to carefully consider the patient's symptoms.[26,27]

Rheumatic heart diseases are most prevalent in developing countries where patients who need regular follow up and proper risk stratification may have limited access to echocardiography or exercise testing. On the other hand, it is clear from the currently available evidence that better risk stratification of asymptomatic patients with significant valvular disease is still required. Symptomatic status is totally subjective and some patients may simply avoid symptoms by limiting their exertion over years while others may get symptoms on mild exertion due to noncardiac dyspnea or due to physical deconditioning. A simple objective tool that could be used in regular follow up of a subset of MS patients (asymptomatic with MVA $\leqslant$1.5 and $>$1 cm^2) and that could predict development of symptoms on exercise would be clinically very helpful. A useful biomarker would reflect disease severity, increase with progression of disease, reflect subclinical myocardial dysfunction, discriminate between patients in whom symptoms do and do not develop in the short to medium term, and be easily and reliably measured.[28]

Natriuretic peptides (ANP, BNP, and NT-pro-BNP) have been studied in MS patients in several trails[29–31] and a correlation between natriuretic peptide level and severity of mitral stenosis and patients' symptoms was found.

Sharma, et al. studied 30 patients with moderate to severe MS versus 13 normal controls. They found that BNP was higher in MS patients compared to controls (BNP 58 [34, 93] vs. 16 [14, 25 pg/ml], $P < 0.0001$). They divided patients into groups according to the BNP level (control, normal BNP, BNP $<$84 pg/ml and BNP $>$84 pg/ml). Their results match those of our study as they found an association between BNP and development of symptoms on exercise, exercise capacity, and SPAP $>$50 at rest or $>$60 mmHg on exercise.[4]

Our results agree with those of Kilickesmez, et al. who found a correlation between NT pro-BNP level and exercise-induced augmentation of pulmonary artery pressure in patients with moderate to severe, asymptomatic or mildly symptomatic mitral stenosis. They studied 41 asymptomatic or mildly symptomatic moderate to severe mitral stenosis patients versus 21 age and sex-matched control healthy subjects. They found that the plasma concentrations of NT pro-BNP levels were significantly higher in patients with mitral stenosis than in control subjects before and after exercise ($P < 0.001$).They concluded that NT pro-BNP levels correlated with functional class and echocardiographic findings in patients with mitral stenosis and indicated exercise induced augmentation of peak PAP $>$60 mmHg compared to control subjects. They also found a significant correlation between NT Pro BNP and the left atrial dimension, right ventricular end diastolic diameter, exercise duration, heart rate, rest, and exercise pulmonary artery systolic pressure and after exercise mitral valve mean gradient.[32]

We found that left atrial dimensions were larger in group I compared to group II. This could explain the higher levels of BNP in group I and augment the already available evidence of BNP co-storage and secretion from the left atrium.[7–10] We found that BNP levels dropped significantly one week post balloon valvuloplasty in group I patients. This drop could be explained by the expected drop in the mean left atrial diameter, pressure and also the expected drop in the pulmonary artery pressure and subsequently the right ventricular pressure. After PMC, pulmonary pressures fall soon because elevated pulmonary vascular resistance is usually due to reactive vasoconstriction rather than permanent histopathologic changes.[33] Concordant with our results, a study done by Selcuk, et al. found a significant drop of NT pro-BNP post PMC.[5] This again could prove a causal relationship between natriuretic peptides and severity of MS. Also, concordant with our results, a study done by Shang, et al. found a significant drop in the BNP levels when pre and post percutaneous mitral balloon valvuloplasty BNP levels were compared.[6]

We did not include patients with MVA $<$1 cm^2 (very severe MS, as defined by ACC/AHA 2014 guidelines) where intervention by PMC is justified regardless of symptomatic status if valve scores were suitable.[26]

A cut-off point of 55 pg/ml for BNP to predict development of symptoms on exercise in MS is lower than that set by the ESC/Heart Failure guidelines to exclude heart failure as a cause of dyspnea (100 pg/ml).[34] This may be explained by the source of BNP secretion (left atrium in MS where BNP is co-secreted in addition to ANP), and the left ventricle in case of left ventricular failure. On the other hand, Pizzaro, et al. concluded a BNP cut-off value of $\geqslant$105 pg/ml to identify asymptomatic MR patients at higher risk of developing heart failure, LV dysfunction or death on mid-term follow-up[17], a cut-off value that was higher than that set by the current study. This again could be explained by the source of BNP secretion (both LA and LV in case of MR).

To the best of our knowledge, this is the first study of BNP assessment in asymptomatic significant MS that (1) identified patients who fulfilled intervention criteria set by the ESC, and (2) assessed BNP level after PMC in the same study. Moreover, this is the first study to set a cutoff value for BNP level that could predict low exercise capacity and development of symptoms on exercise.

5. Suggestion for future research

Larger caliber studies recruiting more patients with an intention to validate the set cut-off BNP value that could predict a justified intervention by PMC in patients with asymptomatic significant MS are strongly suggested. Further studies on the same patients' cohort may result in sufficient evidence to implement BNP use in regular follow up and decision making in future guidelines. An interesting area of research would be whether BNP cut-off value could be confounded be medications (e.g. loop diuretics) or arrhythmia as atrial fibrillation.

6. Conclusion

Brain Natriuretic Peptide may be used as a risk stratification tool for asymptomatic patients with significant mitral stenosis whose resting echo-Doppler assessments do not meet criteria for intervention. BNP may be used to identify an important subset of patients with exercise-induced clinical and echo-Doppler criteria that meet the contemporary guidelines for intervention.

Conflict of interest

All authors have no conflict of interests to declare.

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