Correlation Between N-terminal Pro Brain Natriuretic Peptide and Right Ventricular Performance Measured by Doppler Echocardiography after Successful Percutaneous Balloon Mitral Valvuloplasty

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ABSTRACT
Mitrail stenosis leads to a passive rise of both pulmonary venous and arterial pressures which cause Right Ventricular (RV) pressure overload and RV failure. Brain Natriuretic Peptide (BNP) increases in cases of RV pressure or volume overload. This study aimed to investigate the relationship between N-terminal proBNP (NT-Pro BNP) and echocardiographic determinants of RV function post successful PBMV. A total number of 35 patients with rheumatic mitral stenosis planned for Percutaneous Balloon Mitral Valvuloplasty (PBMV). The control group was composed of 30 age and gender matched healthy volunteers who underwent transthoracic echocardiography and proved to have a normal Left Ventricular (LV) function without valvular heart disease. Both patients and control groups were subjected to thorough history, physical examination and echocardiography with emphasis on mitral valve area, Trans-Mitral Gradient (TMG), pulmonary artery systolic pressure and Tricuspid Annular Plane Systolic Excursion (TAPSE). On the other hand, PW-TDI on lateral side of tricuspid annulus was performed and Sa, Ea, Aa and RV Tei index were calculated. N-terminal proBNP was determined, echocardiographic evaluation and NT-proBNP measurements were performed before and 24-48 h after PBMV. Pulmonary artery systolic pressure, RV Tei index and NT-ProBNP were significantly decreased while Sa, Ea/Aa and TAPSE were significantly increased (p<0.05) after the increasing MVA post PBMV. The decreased plasma level of NT-ProBNP post PMBV correlated positively with decreased PASP and RV Tei index (p<0.001) and negatively with increased TPASE (p<0.001). The decrease of NT-ProBNP level was correlated with decreased pulmonary artery systolic pressure and improved right ventricular function after PBMV.

Key words: N-Terminal pro brain natriuretic peptide, right ventricular performance measured, doppler echocardiography, percutaneous balloon mitral valvuloplasty

INTRODUCTION
Rheumatic Mitral Stenosis (MS) that develops as a late sequel of rheumatic fever (Bonow and Braunwald, 2012; Otto and Bonow, 2014) still represents an important problem in developing countries. Type of treatment, as well as its timing, should be decided on the basis of clinical,
Percutaneous Balloon Mitral Valvuloplasty (PBMV) is a well accepted treatment option for symptomatic and uncomplicated rheumatic MS with favorable valve morphology (Maoqin et al., 2005).

Mitral stenosis leads to an increase in left atrial pressure which results in a passive rise in both pulmonary venous and arterial pressures (Vahanian et al., 2013).

Marked increase in pulmonary pressures causes right ventricular pressure overload and eventually leads to right ventricular dilatation and failure. Hence, right ventricular dysfunction is an important indicator to evaluate the severity of MS (Tayyareci et al., 2008).

A successful PBMV provides an immediate and long-term hemodynamic and symptomatic improvement by increasing the mitral valve area and reducing the mitral valve gradient, left atrial pressure and mean pulmonary artery pressure (Reyes et al., 1994; Dean et al., 1996; Sanchez et al., 2005).

The issue of RV geometry is usually overcome by using geometry independent parameters such as tricuspid annular velocity and Tei index (Coghlan and Davar, 2007).

Brain Natriuretic Peptide (BNP), a cardiac neurohormone secreted by ventricles in response to the excessive stretching of the ventricular myocytes. It may be co secreted from some atrial granules (Mukoyama et al., 1991; Ritchie et al., 2009). BNP has diagnostic and prognostic role in LV dysfunction of different etiologies (Hasegawa et al., 1993; Talwar et al., 2000). NT-pro BNP is secreted in proportion equivalent to BNP and it was thought to be more sensitive because of its longer half life (Pfister et al., 2004) BNP plasma concentrations increase in pathologic conditions that cause RV pressure or volume overload (Nagaya et al., 1998; Tulevski et al., 2001).

The aim of this study was to investigate the relationship between NT-Pro BNP and echocardiographic determinants of RV function (mainly TAPSE and tissue Doppler derived RV Tei-index) post successful PBMV.

MATERIAL AND METHODS

A total number of 35 patients (28 females, 7 males) with mean age 31.94 years with symptomatic rheumatic Mitral Stenosis (MS) who were planned for Balloon Mitral Valvuloplasty (BMV) in Mansoura Cath Lab. Mansoura University, Egypt. From December 2013 to June 2014.

The control group was composed of 30 age and gender matched healthy volunteers with mean age 31.53 years who underwent transthoracic echocardiography and proved to have a normal Left Ventricular (LV) function without valvular heart disease. The protocol was approved by our ethics committee.

Inclusion criteria:

- Patients with MS which fulfilled the following criteria for PBMV
- New York Heart Association functional class ≥II or ≤IV
- Moderate to severe MS (mitral valve area ≤1 cm²/m² body surface area or <1.5 cm² in normal sized adult (Otto, 2004; Nishimura et al., 2014)
- Absence of any cardiovascular disease which required surgical intervention
- Suitable valve morphology according to Wilkins score (Wilkins et al., 1988)

Exclusion criteria:

- More than mild mitral or aortic regurgitation and/or aortic stenosis
- Atrial fibrillation
Diabetes mellitus
Systemic hypertension
Pulmonary valve disease
Organic tricuspid valve disease
Coronary artery disease, lung diseases and cardiomyopathies
Echocardiographic contraindications for PBMV (e.g., MR Grade III or IV, left atrial thrombus, heavily calcified mitral valve annulus)

**Percutaneous Balloon Mitral Valvuloplasty (PBMV):** After a written consent was taken, all patients underwent PBMV by the antegrade trans-septal approach using an Multi-track and Inoue balloons with a stepwise dilatation strategy (Inoue *et al.*, 1984; Bonhoeffer *et al.*, 1999; Schievano *et al.*, 2009; Sakr *et al.*, 2013; Farman *et al.*, 2014).

A successful PBMV was defined as MVA ≥ 1.5 cm²/m² with =grade II mitral regurgitation (Nishimura *et al.*, 2014).

**Echocardiography:** Two-dimensional echocardiography and Doppler studies were performed one-day before and 24-48 h after PBMV using a GE-Vivid 3 (Norway) machine. All measurements were obtained according to the recommendations of the American Society of echocardiography (Schiller *et al.*, 1989; Lang *et al.*, 2005, 2006) Morphology features of the mitral valve were classified according to the echocardiographic scoring system described by Wilkins *et al.* (1988).

The following echocardiographic parameters were measured:

- Conventional echo doppler
  
  Left Atrial Diameter (LAD), Mitral Valve Area (MVA) by planimetry and pressure half time, left ventricular ejection fraction and Right Ventricular Diastolic Diameter (RVDD) was measured from apical four-chamber view. Mean and maximal trans-mitral diastolic gradients were determined by a Doppler method from apical views as recommended (Hatle *et al.*, 1979; Baumgartner *et al.*, 2009).

  Pulmonary artery systolic pressure was determined from the tricuspid regurgitant jet.

  The Tricuspid Annular Plane Systolic Excursion (TAPSE) was determined by the difference in the displacement of the RV base during systole and diastole (Ghio *et al.*, 2000).

- Tissue Doppler Imaging (TDI) measurements
  
  A sample volume was placed at the lateral side of the tricuspid annulus for estimation of systolic and diastolic velocities (Sa, Ea and Aa).

  Right ventricular Tei index by TDI: The time interval from the end to the onset of tricuspid annular velocity pattern during diastole (a) were equal to the sum of isovolumic contraction time (ICT), isovolumic relaxation time (IRT) and ejection time (ET). ET (b) was measured as the duration of Sa wave. RV Tei index was calculated as follows (iovolumic contraction time+isovolumic relaxation time)/RV ejection time or (a-b)/b (Tei *et al.*, 1996).

- Neurohormonal evaluation

  N-Terminal proBNP measurements: NT-proBNP was determined by ECLIA (Electrochemilumimeneceht immunoassay) method using ELECYS 2010, Roche, Germany.
**Statistical analysis:** Data was analyzed using SPSS (Statistical Package for Social Sciences) version 14. Qualitative data was presented as number and percent. The quantitative data was tested for normality by Kolmogrov-Smirnov test. The normally distributed data was presented as Mean±SD. Student t-test was used to compare between two groups and paired t-test was used within a group. Pearson’s correlation coefficient was used to test the correlation between variables. The p<0.05 was considered to be statistically significant.

**RESULTS**

In the patients with MS RVDD, PASP, Tei-index and NT-ProBNP were significantly increased whereas Sa, Ea/Ea and TAPSE were significantly reduced compared to the control group (Table 1) (p<0.05).

Table 2 shows that PASP, RV Tei-index and NT-ProBNP were significantly decreased and Sa, Ea/Aa and TAPSE were significantly increased after increasing MVA post PBMV (p<0.05).

The decreased plasma level of NT-ProBNP post PMBV correlated positively with the decreased LAD, PASP and RV Tei-index (p = 0.001, <0.001 and <0.001, respectively) and negatively with the increased TPASE (p<0.001) (Table 3).

**DISCUSSION**

In the patients with mitral stenosis, RV function is closely related to symptoms, functional capacity, the need and timing for interventions, perioperative mortality and postoperative results (Tayyareci et al., 2008).

The quantitative echocardiographic assessment of RV function is difficult because of the ventricle’s complex trapezoidal anatomy. A wide variety of techniques have been used but none is currently considered the gold standard. In practice, clinicians largely rely on two modalities: two-dimensional echocardiography and Tissue Doppler Echocardiography (TDE). From the first modality Ejection Fraction (EF) and TAPSE are considered to reflect the global systolic function (Ghio et al., 2000; Schenk et al., 2000; Miller et al., 2004). TAPSE showed an excellent correlation

| Parameters          | Patients with MS | Control   | t    | p-value |
|---------------------|------------------|-----------|------|---------|
| Age (years)         | 31.94±6.73       | 31.53±5.96| 0.258| 0.798   |
| LAD (cm)            | 5.00±0.46        | 2.87±0.41 | 19.586| 0.000   |
| LVEDD (cm)          | 4.55±0.62        | 4.41±0.55 | 0.970| 0.336   |
| LVESD (cm)          | 3.02±0.45        | 2.84±0.37 | 1.700| 0.094   |
| EF%                 | 64.66±5.29       | 65.17±4.15| 0.427| 0.671   |
| RVDD (cm)           | 3.46±0.65        | 1.63±0.28 | 15.114| 0.000   |
| PASP (mmHg)         | 49.23±8.19       | 18.63±3.60| 19.978| 0.000   |
| TAPSE (mm)          | 16.86±1.52       | 23.77±2.86| 11.874| 0.000   |
| Sa (cm/s)           | 11.03±1.50       | 15.17±1.26| 11.896| 0.000   |
| Ea/Aa               | 1.12±0.16        | 1.80±0.30 | 11.132| 0.000   |
| RV Tei index        | 0.44±0.10        | 0.20±0.07 | 11.505| 0.000   |
| NT-ProBNP (pg/ml)   | 434.23±199.52    | 148.70±67.79| 7.948| 0.000   |

**Table 1: Clinical and echocardiographic data of both patients and control groups**

LAD: Left atrial diameter, RVDD: Right ventricular diastolic diameter, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF%: Ejection fraction, MVA: Mitral valve area, TMG: Transmitral gradient, PASP: Pulmonary artery systolic pressure, TAPSE: Tricuspid annular plane systolic excursion, Sa: Peak tricuspid annular systolic velocity, Ea/Aa: Ratio of early to late tricuspid diastolic velocity, NT-ProBNP: N-terminal pro-brain natriuretic peptide
Table 2: Doppler echocardiographic parameters (conventional and TDI) and NT-proBNP before and after PBMV

| Parameter          | Pre PBMV       | Post PBMV      | t    | p-value |
|--------------------|----------------|----------------|------|---------|
| LAD (cm)           | 5.00±0.46      | 4.35±0.50      | 5.534| 0.000   |
| LVEDD (cm)         | 4.55±0.62      | 4.53±0.58      | 0.122| 0.903   |
| LVESD (cm)         | 3.02±0.45      | 3.17±0.44      | 1.566| 0.127   |
| EF (%)             | 64.66±5.29     | 65.00±4.74     | 1.063| 0.295   |
| RVDD (cm)          | 3.46±0.65      | 3.37±0.66      | 0.755| 0.455   |
| MVA_PLM (cm²)      | 1.00±0.17      | 1.69±0.27      | 20.403| 0.000   |
| MVA_PHT            | 1.04±0.14      | 1.73±0.27      | 19.427| 0.000   |
| TMG Mean (mmHg)    | 17.29±5.41     | 6.63±1.85      | 15.267| 0.000   |
| TMG Maximum (mmHg) | 29.57±9.56     | 10.34±2.20     | 14.392| 0.000   |
| PASP (mmHg)        | 49.23±8.19     | 30.09±4.99     | 11.042| 0.000   |
| TAPSE (mm)         | 16.86±1.52     | 19.49±1.63     | 5.517| 0.000   |
| Sa (cm/s)          | 11.03±1.50     | 12.83±1.58     | 15.721| 0.000   |
| Ea/Aa              | 1.12±0.16      | 1.39±0.20      | 6.237| 0.000   |
| RV-Tei index       | 0.44±0.10      | 0.31±0.06      | 5.582| 0.000   |
| NT ProBNP (pg/ml)  | 434.23±199.52  | 313.86±151.25  | 2.714| 0.010   |

LAD: Left atrial diameter, RVDD = Right ventricular diastolic diameter, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF%: Ejection fraction, MVA_PLM: Mitral valve area planimetry, MVA_PHT: Mitral valve area pressure half time, TMG: Transmitral gradient, PASP: Pulmonary artery systolic pressure, Sa: Peak tricuspid annular systolic velocity, TAPSE: Tricuspid annular plane systolic excursion, Ea/Aa: Ratio of early to late tricuspid diastolic velocity, NT-ProBNP: N-terminal pro-brain natriuretic peptide

Table 3: Correlation between NT-ProBNP and RV Performance Measured by Doppler echocardiography post successful PBMV

| Parameter of RV performance | r     | P    |
|-----------------------------|-------|------|
| LAD                         | 0.527 | 0.001|
| LEVDD                       | -0.007| 0.967|
| LVESD                       | -0.117| 0.503|
| EF                          | 0.190 | 0.275|
| RVDD                        | 0.497 | 0.002|
| MVA_PLM                     | 0.173 | 0.309|
| MVA_PHT                     | 0.173 | 0.321|
| TMG Mean                    | -0.113| 0.518|
| TMG Maximum                 | -0.128| 0.465|
| PASP                        | 0.733 | 0.000|
| TAPSE                       | -0.732| 0.000|
| Sa                          | 0.221 | 0.203|
| RV-Tei index                | 0.539 | 0.001|

LAD: Left atrial diameter, RVDD: Right ventricular diastolic diameter, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF%: Ejection fraction, MVA_PLM: Mitral valve area planimetry, MVA_PHT: Mitral valve area pressure half time, TMG: Transmitral gradient, PASP: Pulmonary artery systolic pressure, Sa: Peak tricuspid annular systolic velocity, TAPSE: Tricuspid annular plane systolic excursion, NT-ProBNP: N-terminal pro-brain natriuretic peptide

with RV ejection fraction calculated using echocardiography or radionuclide angiography and its measurement has been proven to be highly reproducible and easy to obtain (Kaul et al., 1984; Ueti et al., 2002; Lamia et al., 2007).

Tissue Doppler Imaging (TDI) measures velocities of cardiac tissue and reflects directly myocardial function and is considered a promising technique for evaluating the RV function.
(You et al., 2007). For example, many studies have shown Sm to reflect RV systolic function. This parameter was found to have a very good correlation with RV fractional area and RVEF assessed by radionuclide ventriculography Harada et al. (2004). Also, tricuspid annular Em and Am may be used for the detection of RV diastolic abnormality in the isolated mitral stenosis (Saricam et al., 2007).

The Tei index; a combined measurement of systolic and diastolic myocardial performance, is more reflective of overall cardiac function than systolic or diastolic function alone in both ventricles and provides a relatively new concept about the measurement of the global RV function (Tekten et al., 2003).

In present study it was decided to utilize multiple parameters to study RV functional changes before and after PBMV. Our results showed that the patients with MS have depressed RV function compared with the control subjects (Table 1), findings in accordance with previous radionuclide and hemodynamic studies (Cohen et al., 1985; Mohan et al., 1999; Sade, 2014).

The reasons for the impaired RV function in pure MS are controversial (Lee et al., 1996; Pamir et al., 1997). Some studies conclude that the rheumatic pathologic process may directly affect the myocardium to cause dysfunction (Borer et al., 1991; Malhotra et al., 1987a). In a histo-morphological study of the cases with rheumatic heart disease, Malhotra et al. (1987b) found that intramyocardial branches of coronary vessels were involved in a form of active rheumatic vasculitis or inactive lesions characterized by medial hypertrophy and replacement fibrosis. They speculated that these changes might affect myocardial function. Also, the passive increase in left atrial pressure and reactive changes in pulmonary arteriolar resistance may lead to increased RV afterload and RV failure (Iskandrian et al., 1984).

The present study showed that plasma NT-proBNP levels were significantly elevated in patients with rheumatic MS when compared to control subjects (Table 1) and this agreed with the results of previous studies that investigated the relationship between MS and plasma BNP levels (Iltumur et al., 2005). As our patient group was composed of a homogeneous group of patients with MS and preserved left ventricular systolic function, it is possible that the left atrium and right side of the heart are responsible for the elevated NT-proBNP levels rather than the left ventricle.

The present results demonstrated a positive correlation between elevated BNP levels and left atrial dimension, PASP and RV dysfunction (Table 3), indicating that BNP level is more related to the stretch of atrial myocytes and to ventricular volume rather than an increase in LA pressure. Similar to our results, in the study of Golbasy et al. (2004), NYHA functional class and systolic pulmonary artery pressure were demonstrated to be independent determinants of higher BNP levels. Another study by Arat-Ozkan et al. (2005) supported the presence of an association between serum NT-proBNP levels and echocardiographic findings and functional class in patients with MS. Accordingly, they claimed that NT-proBNP may be a valuable marker in monitoring disease progression (Arat-Ozkan et al., 2005).

The present findings revealed that TAPSE, Tei index and tricuspid annular pulsed TDI velocities showed a significant improvement after successful PBMV (Table 2), like the in a study significant improvement was found in RV Sm and Em whereas RV Am was relatively unaltered and concluded that pure MS affects the long-axis function of the LV and RV and the extent of involvement seems to correlate with MVA and the adequacy of the result of PBMV. On the other hand some researchers noticed an non significant increase in RV free wall annular velocities in 25 patients studied following PBMV and concluded that RV dysfunction persists in the period immediately following PBMV despite significant changes in pulmonary artery pressures and this could explain the persistence of right sided congestion in some of these patients.
The present study showed that there was a significant decrease in LA diameter, mitral peak pressure gradient, mitral mean pressure gradient and pulmonary artery systolic pressure from pre to post PBMV and was associated with a significant decrease in NT-proBNP from 434.23 pg mL\(^{-1}\) pre PBMV to 313.86 pg mL\(^{-1}\) post PBMV (Table 2).

The decrease in RV Tei index and peak pulmonary artery systolic pressure together with the increase in TAPSE immediately post-PBMV suggest that RV systolic function improved as a result of an acute decrease in RV after load. This is concordant with the study by Borges et al. (2006) who demonstrated an improvement in Tei index after vasodilator therapy in patients with chronic pulmonary hypertension. Ragab et al. (2011) also concluded that both TAPSE and RV tissue Doppler indices are able to assess early RV dysfunction in patients with similar degrees of MS and able to precociously recognize patients with worse prognosis specially after successful PBMV.

In the current study, the decrease in systolic pulmonary artery pressure, the decrease in Tei index and increase of TAPSE were found to be correlated with the decrease in NT-proBNP level (Table 3).

N-terminal proBNP has shown to correlate with mitral valve pressure gradients, left atrial pressures and peak pulmonary artery pressures in various studies. Chadha et al. (2010) investigated the change in NT-proBNP levels among 44 consecutive patients with mitral stenosis, 10 min before and 24 h after undergoing percutaneous transvenous mitral commissurotomy. Reduction of NT-proBNP was more marked in patients in sinus rhythm as compared to those with atrial fibrillation. The only hemodynamic parameter that correlated significantly with NT-proBNP was PAP, a surrogate for RV pressure. They concluded that RV may be the most important source of BNP in these patients. Selcuk et al. (2007) showed that the decrease in NT-pro BNP correlated with the decrease in pulmonary systolic pressure but did not correlate with mitral valve pressure gradients and left atrial pressures in patients undergoing PBMV. Shang et al. (2005) measured plasma BNP levels before PBMV, at 20 min and at 24 h post PBMV. In patients in sinus rhythm, plasma BNP levels decreased significantly post PBMV and significantly correlated with mean LA pressure and pulmonary systolic pressure but in patients in atrial fibrillation, plasma BNP levels remained unchanged post PBMV.

Finally, although the examination of LV function was not included in our study, we noted that mean LVEF of our patients and normal controls was normal possibly because we selected only young patients and young controls with sinus rhythm. After PBMV the ejection fraction showed no significant change implying that the overall LV function was unchanged. A limitation of this study was the lack of a repeated measurement of NT-proBNP levels and repeated assessment of RV function that would add further information to present findings as further substantial hemodynamic improvement occurs over time. A follow-up study including the serial measurements of NT-proBNP levels and serial echocardiography would confirm present results.

Small number of cases due to relatively decreased number of MS patients suitable for PBMV in our catheterization laboratory.

**CONCLUSION**

Patients with MS have abnormal right ventricular functions which can be early assessed by TAPSE, Tei index and RV tissue Doppler indices. Also those patients have elevated plasma level of NT-proBNP concentration. After PBMV plasma level of NT-proBNP was decreased and RV performance was improved and the decrease in NT-proBNP level was correlated with decreased LAD, systolic pulmonary artery pressure and improved right ventricular function.
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