Correlation between plasma N-terminal pro-brain natriuretic peptide levels and changes in New York Heart Association functional class, left atrial size, left ventricular size and function after mitral and/or aortic valve replacement

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BACKGROUND and OBJECTIVES: Elevated plasma brain natriuretic peptide (BNP) levels have been demonstrated in patients with chronic valvular disease. We designed the present study to assess whether changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels after mitral, aortic and double mitral and aortic valve replacement reflect changes in heart failure (HF) symptoms including New York Heart Association (NYHA) class and changes in left atrium (LA) size, left ventricle (LV) size and LV function.

DESIGN and SETTING: A prospective observational nonrandomized study among consecutive patients undergoing mitral and/or aortic valve replacement in our center.

PATIENTS AND METHODS: The study population consisted of 24 patients (mean [SD] age of 55.3 [16.2] years, 58% were males) who underwent surgical mitral valve replacement (12 patients), aortic valve replacement (8 patients) and combined mitral and aortic valve replacement (4 patients). NT-proBNP measurements, transthoracic echocardiography and NYHA class assessments were performed before and 6 months after surgery.

RESULTS: The decrease in NT-proBNP was associated with decrease in left atrial dimension (r = 0.73, P < .002), LV end-diastolic dimension (r=0.65, P=.001), LV end-systolic dimension (r=0.53, P=.036), and increase in ejection fraction (r=–0.65, P=.001) after 6 months postoperatively. Furthermore, a decreasing NT-proBNP was associated with improvement in NYHA class.

CONCLUSIONS: NT-proBNP levels after mitral, aortic and double valve replacement correlates with changes in HF manifestations as well as changes in LA size and LV dimension and function. Thus, we hypothesize that interval measurement of the NT-proBNP level at clinic visits can allow early detection of any clinical deterioration as well as the possibility of assessment of the long-term outcome of those patients.

The natriuretic peptides are endogenous cardiac hormones that are synthesized and released from the myocardium in response to wall stress.1-3 Brain natriuretic peptide (BNP) and its amino-terminal portion N-terminal pro-brain natriuretic peptide (NT-proBNP) are the commonest among these peptides used in clinical settings.4-6 Both BNP and NT-proBNP have been demonstrated to provide important diagnostic and prognostic information as well as guided therapy in patients with heart failure (HF).7 Recently, elevated plasma BNP levels have been demonstrated in patients with chronic valvular disease.8 The severity of valvular disease was directly related to the BNP levels.9 For surgery in severe mitral regurgitation, BNP levels correlated with HF symptoms and left atrial (LA) dimensions.10 Data about NT-proBNP and correlation with the same parameters following valve replacement are limited. Accordingly, we conducted this study to evaluate the changes in NT-proBNP levels after mitral, aortic and DVR and to correlate these changes
with New York Heart Association (NYHA) class, LA diameter, left ventricular (LV) diameter and LV ejection fraction (EF).

PATIENTS AND METHODS

Between April 2009 and August 2010, 24 consecutive patients undergoing valve replacement surgery (12 with mitral valve [MV], 8 with aortic valve [AV] and 4 with double mitral [DM] and aortic valve [AV] replacement) were prospectively enrolled. The study was approved by the Institutional Review Board. All patients gave informed consent to participate in the study. Rheumatic etiology was defined in 12 patients, degenerative etiology in 11 cases and Marfan syndrome in 1 case. Patients with combined coronary artery bypass graft (CABG) and valve surgery were excluded. Clinical evaluation and assessment of symptoms using NYHA class was conducted by the patient’s referring cardiologist and was confirmed by a cardiothoracic surgeon during hospital admission for surgery. A clinical follow-up was performed at 6 months to evaluate the change in NYHA class and also changes in the echocardiographic parameters of remodeling. During the 6-month follow-up period, adverse events, including non-fatal myocardial infarction, repeat valve surgery, cerebrovascular events, renal dysfunction and hospitalization for HF were noted.

Prior to surgery, transthoracic echocardiography was performed in all patients. Patients were imaged in the left lateral decubitus position by using a commercially available system (Vingmed Vivid Seven, General Electric—Vingmed, Milwaukee, WI, United States). Using a 3.5 MHz transducer, images were obtained at a depth of 16 cm in the parasternal (long- and short-axis images) and apical views (2-, 3- and 4-chamber images). From parasternal M-mode acquisitions, the LA dimension and LV dimensions (end-systolic and end-diastolic diameter) and EF were determined. The severity of valve lesions was already assessed and the decision to operate on those patients was a combined decision between the referring cardiologist, echocardiographer and cardiac surgeon. Immediately after surgery, transesophageal echocardiography was performed to assess residual valve lesions. A transthoracic echocardiogram was repeated at 6 months follow-up to assess LA and ventricular dimensions, EF, the presence of any residual valve lesions and the trans-valvular gradient.

NT-proBNP measurement (Acute Care NT-proBNP Test, Stratus STAT Fluorometric Analyzer, Siemens, Germany) is a quantitative measurement of NT-proBNP in heparinized plasma. It is a sandwich assay based scheme upon solid phase radial partition immunoassay technology. A specific monoclonal antibody is added to the center portion of a piece of glass fiber paper in the NT-proBNP test pack. This antibody recognizes a distinct antigenic site in the NT-proBNP molecule. The sample is then added onto the paper where it reacts with the immobilized antibody. The reaction rate can then be measured by an optical system that monitors the reaction rate via front surface fluorescence. Reference normal values of NT-proBNP are shown in Table 1.11

All analyses were performed using SPSS 16.0 statistical software (IBM Corp, Armonk, NY, United States). The changes in NT-proBNP levels from baseline to 6 months follow-up were calculated and expressed as a percentage. Changes in LA dimension, LV end-systolic and end-diastolic dimensions and ejection fraction were also calculated and expressed as a percentage. Continuous variables were expressed as mean (SD) or median (interquartile range) and compared using the t test. Categorical data were compared using the Fisher exact test. The Pearson correlation coefficient was used to assess the association between changes in NT-proBNP levels and changes in echocardiographic variables. For all tests, a P<.05 was considered significant.

RESULTS

The baseline characteristics of the 24 patients (mean [SD] age of 55.3 [16.2] years, 58% were males) are summarized in Table 2. Pre- and post-operative NYHA class, echocardiographic parameters and NT-proBNP changes are shown in Table 3. Seven patients (29%) were in NYHA class II, 12 (50%) in class III and 5 (21%) in class IV. The mean (SD) length of hospital stay was 6.8 (5.2) days. Transesophageal echocardiography was done immediately after surgery. All patients survived the 6-month follow-up period and no patients were lost to follow-up. During hospital stay and follow-up period, none of the patients were required to repeat a valve surgery. NYHA class deteriorated in 4 patients (16.6%), remained unchanged in 6 (25%) and improved in 14 (58.3%). The 16 patients with a decrease in NTproBNP level exhibited a mean (SD) improvement of 8.47±pg/ml.11

Table 1. Reference normal values of NT-proBNP (pmol/L).

| Age   | Male | Female |
|-------|------|--------|
| <54   | <13.73 | <15.39 |
| 55-64 | <18.57 | <23.87 |
| 65-74 | <19.29 | <25.83 |
| >74   | <22.42 | <35.66 |

Conversion Factor: pmol/L×8.47→pg/mL.11
in NYHA class of 1.8 (1.1), whereas the 8 patients with unchanged/increased NT-proBNP levels revealed a small but significant mean (SD) worsening in NYHA class of 0.3 (0.9) with $P<.001$ versus baseline.

There was correlation between changes in NT-proBNP level and changes in echocardiographic variables during the 6-month follow-up period after valve surgery (Table 3). The decrease in NT-proBNP was associated with decrease in LA dimension ($r=0.73$, $P<.002$), LV end-diastolic dimension ($r=0.65$, $P=.001$), LV end-systolic dimension ($r=0.53$, $P=.036$), and increase in ejection fraction ($r=-0.65$, $P<.001$). Decreasing NT-proBNP was associated with improvement in NYHA class.

Adverse events, including nonfatal myocardial infarction, cerebrovascular events, hospitalization for HF or endocarditis happened in two patients during the 6 months of follow up. During the 6-month follow up two patients (9%) developed renal dysfunction in the post-operative period, which was successfully treated with a short period of renal dialysis. None of the patients presented with renal dysfunction during the 6-month follow-up period.

**DISCUSSION**

BNP has been used extensively in the diagnosis and prognosis of patients with HF. Also, BNP and its N-terminal pro-PNP are increasingly used now in assessing patients with valvular heart disease even before the occurrence of overt HF. These natriuretic peptides start to leak into the circulation with the increase in the filling pressures in different chambers of the heart especially LV. More recently, Sutton and colleagues demonstrated in 49 patients with mitral regurgitation and preserved LV ejection fraction that plasma levels of BNP and NT-proBNP levels were directly related to the severity of mitral valve regurgitation. In addition, Detaint et al evaluated 124 patients with chronic mitral regurgitation and demonstrated that BNP levels were correlated with long-term outcome. Moreover, the authors demonstrated that BNP levels in chronic mitral regurgitation were related to LA volume, LV end-systolic volume index, atrial fibrillation and HF symptoms.

Data about NT-proBNP and valve replacement are scarce. In the present study, NT-proBNP was assessed in patients with mitral, aortic and double valve replacement and re-assessed after surgical correction of the valve lesions. The patient population consisted of 24 patients with mitral, aortic and double valve replacement who were prospectively enrolled.
underwent successful surgical correction and demonstrated competent replaced valves on echocardiography at 6-months follow-up.

Our aim was to report the association between NT-proBNP changes and changes in HF symptoms and echocardiographic outcome after surgical mitral, aortic and DVR. The changes in NT-proBNP levels were directly related to changes in NYHA class, LA dimension, LV dimension and systolic function (as indicated by the EF). In particular, the patients with a significant decrease in NT-proBNP levels exhibited a significant reduction in LA size, with reverse LV remodeling. In addition, the patients with a reduction in NT-proBNP levels demonstrated an improvement in symptoms (reduction in NYHA class), whereas patients with an increase in NT-proBNP did not show a significant change in symptoms or even worsening. In addition to the HF population, NT-proBNP may be of use to reflect clinical status after valve surgeries, with a decrease in NT-proBNP indicating an improvement in symptoms and reverse LV remodeling; conversely, an increase in NT-proBNP should alert the clinician, since it was associated with absence of reverse remodeling and absence of improvement in symptoms.

Nils et al studied the effect of AVR on plasma B-type natriuretic peptide in patients with severe aortic stenosis and the 6 months and one year follow-up after AVR in 22 patients. BNP levels decreased at six and twelve months after AVR. BNP correlated with LV mass index preoperatively, and with age both preoperatively and at twelve months. Pfister et al studied the utility of NT-pro-BNP in patients undergoing transapical aortic valve replacement (TAVR). NT-proBNP was assessed preoperatively, postoperatively and 2 months after the intervention in 31 consecutive patients (median age 84) undergoing TAVR and the association with baseline characteristics and outcome was analysed. They concluded that NT-pro-BNP independently predicted regression of LV mass after 2 months and an early decrease of NT-pro-BNP postoperatively indicated improvement of functional capacity at 2 months.

The main limitations of the current study are the small sample size and the relatively short follow up; accordingly, larger studies with longer follow up are needed to confirm the present results. In addition, different etiologies were included, and findings need confirmation in homogenous populations.

We concluded that NT-proBNP levels after mitral, aortic and DVR correlate with changes in NYHA functional class as well as changes in LA size and LVD and function. Thus we can hypothesize that interval measurement of NT-proBNP level at clinic visits can allow early detection of any clinical deterioration as well as assessment of the long term outcome of those patients.

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