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The Effect of Aortic Valve Replacement on N-Terminal Natriuretic Propeptides in Patients with Aortic Stenosis

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Summary

Background: Increased plasma concentrations of natriuretic peptides have been demonstrated to be associated with increased intracardiac pressure and left ventricular (LV) hypertrophy. After aortic valve replacement (AVR) in aortic stenosis patients, there is a relief of the left outflow obstruction with a substantial hemodynamic improvement. This is followed by a gradual regression of the LV hypertrophy.

Hypothesis: After AVR, reduction in LV filling pressure is expected to occur rapidly, while regression of LV hypertrophy will take place over a longer time period. On this basis we hypothesized that the plasma levels of N-terminal proatrial natriuretic peptide (NT-proANP) would be reduced early in the postoperative period, while N-terminal probrain natriuretic peptide (NT-proBNP), through its closer reflection of LV hypertrophy, would be sustained for a longer period.

Methods: Two groups of patients with aortic stenosis undergoing AVR were followed for 4 and 12 months, respectively. Plasma concentrations of NT-proANP and NT-proBNP were measured before and after AVR and related to preoperative findings and changes in the aortic valve area index.

Results: Before AVR, the patients had significantly increased plasma levels of NT-proANP and NT-proBNP. After AVR, NT- proANP was decreased at 4 and 12 months but remained elevated compared with controls. N-terminal-proBNP tended to decrease, but did not change significantly. When the patients were followed for 12 months, only those with elevated preoperative pulmonary capillary wedge pressure had decreased peptide levels (NT-proANP: $p = 0.017$, NT-proBNP: $p = 0.058$). There was no regression of LV hypertrophy. The patients with the largest postoperative valve area index [1.27 (1.10–1.55) cm^2/m^2] had the largest reduction of NT-proBNP (47%). Those with the smallest valve area index [0.67 (0.54–0.73) cm^2/m^2] had no decrease in NT-proBNP.

Conclusions: Our study suggests that a reduction in left atrial pressure is the main factor causing the change of NT-proANP level after AVR. A small prosthetic valve orifice area with a high aortic valve gradient might prevent regression of LV hypertrophy, thus representing a stimulus for increased cardiac secretion of NT-proBNP.

Key words: aortic stenosis, aortic valve area, atrial natriuretic factor, atrial pressure, brain natriuretic peptide, left ventricular hypertrophy

Introduction

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are cardiac peptides sharing a high degree of sequence and function similarity. The intracardiac distribution of BNP differs from ANP in that upregulation takes place not only in atrial but to a larger extent also in ventricular tissue. Many studies have demonstrated that both peptide plasma levels are increased in states associated with increased intracardiac pressure and left ventricular (LV) hypertrophy.[1] Atrial natriuretic peptide and BNP have been shown in vitro to have the effect of inhibiting the synthesis of collagen by cardiac fibroblasts.[2] This function may play a protective role against compliance changes during LV hypertrophy. Furthermore, it is reported that a decrease in BNP plasma concentrations correlates with the regression of LV hypertrophy in hypertensive patients secondary to treatment by angiotensin-converting enzyme inhibitor.[3]

N-terminal proANP (NT-proANP), the amino terminal part of ANP prohormone, which is supposed to be biologically inactive, has a longer half life and better in vitro stability than ANP.[4,5] Therefore, NT-proANP is regarded as a more reliable

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marker of cardiac function than ANP. N-terminal proBNP (NT-proBNP), the amino terminal part of BNP prohormone, has recently been identified in plasma. Its plasma levels correlate closely with those of BNP.[6] Compared with NT-proANP, the properties of NT-proBNP remain less well characterized.

In aortic stenosis (AS), the obstruction to LV outflow results in proportionate LV hypertrophy as an adaptive response to the increased afterload. Later in the course of the disease, the pulmonary capillary wedge pressure increases as heart failure develops. After aortic valve replacement (AVR), there is immediate relief of the left outflow obstruction with substantial clinical and hemodynamic improvement. This is followed by a gradual regression of LV hypertrophy.[7]

In a recent study of patients with AS, the relationship between aortic root plasma levels of NT-proANP and NT-proBNP with respect to parameters of cardiac function and LV hypertrophy was examined.[8] Presently, we report a comparison of plasma levels of the two N-terminal propeptides at different sites in the circulation of patients with AS. Furthermore, we examined the changes in plasma levels of NT-proANP and NT-proBNP 4 and 12 months after AVR. Due to the slower regression of LV hypertrophy relative to the reduction in LV filling pressure, we hypothesized that the decrease of NT-proANP might occur earlier than that of NT-proBNP, and that NT-proBNP might reflect residual hypertrophy after AVR.

Materials and Methods

Patients

From June 1995 to September 1996, patients with a confirmed diagnosis of AS before AVR were consecutively enrolled into a study to evaluate the relationship of A-type and B-type natriuretic peptides to hemodynamic parameters and LV hypertrophy. Patients with severe aortic or mitral regurgitation (grade III) or serum creatinine concentration > 150 µmol/l were excluded from the study. We presently report the results of two subprotocols of the main study: (1) As the patients were undergoing diagnostic cardiac catheterization, 51 subjects (22 men, 29 women) with a median age of 73 (70–75) years were studied to assess NT-proANP and NT-proBNP levels from different sampling sites in the vascular system. (2) The effect of replacement of the stenotic valve with a mechanical aortic valve (Sulzer/Carbo Medics, Inc., Austin, Tex., USA) on plasma levels of NT-proANP and NT-proBNP were evaluated. A group of 21 patients with a median age of 73 (65–75) years was reexamined after 4 months (Group A). Another group of 32 patients was studied at 12 months (Group B) after AVR. Thirteen patients were examined at both time points and included in both groups. Two patients were excluded from Group B because of concurrent myocardial infarction during catheterization and tricuspid regurgitation (grade III) after surgery, leaving 30 patients (12 men, 18 women) with a median age of 72 (68–75) years for investigation (Table I). The median interval from baseline blood sampling to AVR was 48 days (range 14–261).

Informed consent was obtained from each patient. The study protocol was approved by the regional ethical committee and was designed in accordance with the Declaration of Helsinki.

Echocardiography

Echocardiography was performed for measurement of aortic valve area, the mean aortic valve gradient, left atrial diameter, and LV shortening fraction and LV mass before and 12 months after AVR (Vingmed CFM 800, Vingmed Sound AS, Horten, Norway). Aortic valve area was calculated by the continuity equation according to Ihlen and Molstad[9] and divided by body surface area to give the aortic valve area index (AVAI). The pressure gradient across the aortic valve was esti-

TABLE I Clinical variables before and after aortic valve replacement (AVR)

	Group A (n = 21)		Group B (n = 30)	
	Before AVR	After AVR	Before AVR	After AVR
Age (years)	73 (65–75)		72 (68–75)	
Sex (M/F)	7/14		12/18	
Systolic blood pressure (mmHg)	150 (135–170)	160 (130–185)	140 (130–160)	150 (140–170)
Diastolic blood pressure (mmHg)	80 (80–90)	80 (75–90)	90 (80–90)	88 (80–90)
Serum creatinine (µmol/l)	84 (79–109)	83 (78–99)	85 (82–99)	83 (79–97)
Left atrial diameter (cm)	3.9 (3.1–5.3)	—	3.9 (3.1–4.6)	3.9 (3.3–4.4)
Aortic valve area index (cm^2/m^2)	0.37 (0.30–0.44)	—	0.32 (0.28–0.40)	0.91 (0.79–1.16) [a]
Mean aortic valve gradient (mmHg)	54 (43–67)	—	54 (45–63)	11 (8–13) [a]
Left ventricular shortening fraction (%)	34 (23–40)	—	35 (30–41)	37 (32–41)
Left ventricular mass index (g/m^2)	161 (126–183)	—	178 (128–234)	173 (132–204)
Left ventricular dimension (diastole) (cm)	4.9 (4.6–5.3)	—	4.8 (4.5–5.0)	4.8 (4.3–5.2)
Pulmonary capillary wedge pressure (mmHg)	9 (6–11)	—	10 (8–13)	—
Right atrial pressure (mmHg)	2 (2–4)	—	3 (2–4)	—

Values are median (95% confidence interval).
[a] $p < 0.05$ vs. before AVR.

mated by the simplified Bernoulli equation from flow velocity detected by continuous-wave Doppler integrated throughout systole. Left atrial and ventricular measurements including left atrial diameter, interventricular septal thickness at end diastole (IVSTd), posterior wall thickness at end diastole (PWTd), and LV internal dimension at end systole (LVDs) and at end diastole (LVDd) were obtained from M-mode recordings. Left ventricular mass (LVM) was calculated by the equation of Devereux and Reichek:[10] LVM (g) = 1.04 $[(LVDd + IVSTd + PWTd)^3 - LVDd^3] - 14$ and normalized to body surface area (LVMI). Left ventricular shortening factor was calculated as (LVDd – LVDs)/LVDd. Mitral and aortic regurgitation was evaluated by Doppler color-flow mapping.

Cardiac Catheterization

Before AVR, cardiac catheterization was performed to measure pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and systemic arterial pressure using the fourth intercostal space in the anterior axillary line as zero reference level.

Measurement of N-Terminal Natriuretic Propeptides

Whole blood (10 ml) was sampled from the pulmonary artery, aortic root, and superior caval vein during catheterization and from a cubital vein at follow-up. The blood samples were transferred into prechilled ethylene diamine tetraacetic acid (EDTA) vacutainers which were placed on ice and centrifuged at 4˚C before plasma aliquots were frozen at −70˚C for later analysis.

The plasma NT-proANP (irANP 1-98) concentration was measured in unextracted plasma according to Sundsfjord *et al.*[11] The detection limit for NT-proANP was 185 pmol/l and the between and within assay coefficients of variation were 4.1 and 6.3%, respectively. Recovery was 85% (n = 10).

The plasma NT-proBNP concentration was measured by an in-house developed radioimmunoassay directly in plasma using polyclonal antiserum harvested in a rabbit immunized with N-terminal proBNP (1-21) (Peninsula Laboratories Inc., San Carlos, Calif., USA) as antigen. The detection limit was 9.7 pmol/l and the between and within assay coefficients of variation were 9.0 and 7.3%, respectively. Recovery was 82% (n = 10). Of the 30 patients in Group B, 25 had plasma NT-proBNP measurement.

For control, the plasma concentrations of NT-proANP and NT-proBNP were measured in 19 volunteers (9 men and 10 women) with a median age of 64 (range 54–83) years who had no history of cardiac, renal, or liver disease. These subjects had a median NT-proANP of 619 (296–915) pmol/l and NT-proBNP of 37 (31–52) pmol/l.

Statistical Analysis

Continuous variables were presented by median with 95% confidence interval. The natriuretic peptide data were transformed by natural logarithms to fit the normal distribution. Paired *t*-test with Bonferroni adjustment when appropriate was performed to examine for peptide levels between different sampling sites and the differences of variables before and after AVR. Two-sample *t*-test was performed to compare peptide levels between patients with AS and control. Pearson correlation was used to examine the relation between continuous variables. A probability value of $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS statistical analysis package (version 8.0, SPSS) (SPSS Inc., Chicago, Ill., USA).

Results

Regional Plasma Levels of NT-proANP and NT-proBNP before Aortic Valve Replacement

As shown in Figure 1, there was no significant concentration gradient for NT-proANP from the pulmonary artery to the aortic root [1083 (920–1348) vs. 1024 (940–1036) pmol/l, p = NS], from the aortic root to the superior caval vein [1024

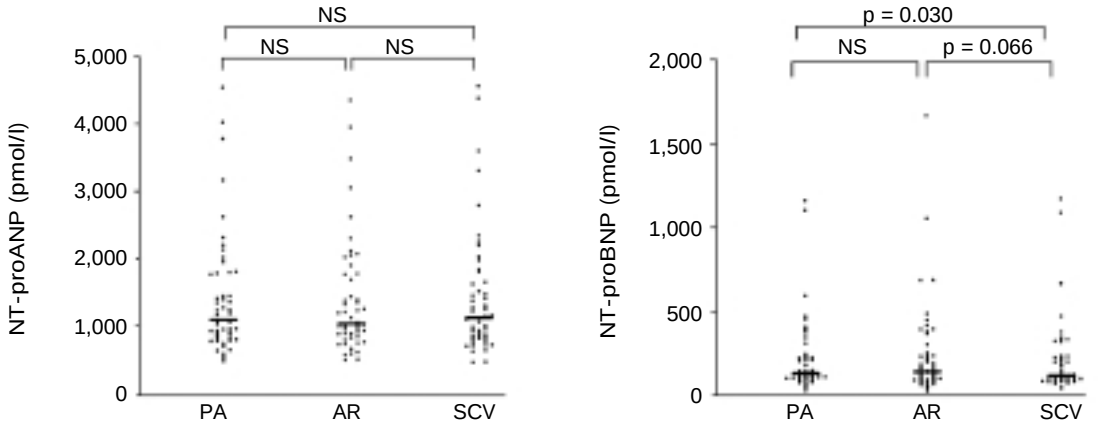

FIG. 1 N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminal probrain natriuretic peptide (NT-proBNP) plasma levels sampled from pulmonary artery (PA), aortic root (AR), and superior caval vein (SCV) in 51 patients with aortic stenosis. NS = not significant.

TABLE II Cardiovascular medication before and after aortic valve replacement

	Group A (n = 21)		Group B (n = 30)	
	Before AVR	After AVR	Before AVR	After AVR
Digitalis	3	2	4	7
Diuretics	8	8	11	10
ACE inhibitors	2	3	2	4
Beta blockers	2	2	6	2

Abbreviations: AVR = aortic valve replacement, ACE = angiotensin-converting enzyme.

(940–1036) vs. 1108 (914–1358) pmol/l, p = NS], or from the superior caval vein to the pulmonary artery [1108 (914–1358) vs. 1083 (920–1348) pmol/l, p = NS]. For NT-proBNP, there was no gradient between the pulmonary artery and the aortic root [133 (110–206) vs. 140 (111–198) pmol/l, p = NS]. The difference between the aortic root to the superior caval vein was of borderline significance [140 (111–198) vs. 114 (104–196) pmol/l, p = 0.066], and a small step-up was demonstrated from the superior caval vein to the pulmonary artery [114 (104–196) vs. 133 (110–206) pmol/l, p = 0.030].

Clinical Characteristics of Patients before and after Aortic Valve Replacement

The baseline variables (before AVR) for Groups A and B are shown in Table I. There were 10 patients in Group A and 19 patients in Group B with mild or moderate mitral regurgitation. Blood pressures, creatinine, and medication remained unchanged from baseline to follow-up in both groups (Table I and Table II). In Group B, the calculated AVAI increased from 0.32 (0.28–0.40) (range 0.12–0.47) cm^2/m^2 before AVR to 0.91 (0.79–1.16) (range 0.54–1.63) cm^2/m^2 after AVR, and the aortic valve gradient decreased from 54 (45–63) (range 27–111) to 11 (8–13) (range 0–30) mmHg (each p < 0.001). Aortic valve size corresponded to calculated AVA (r = 0.55, p = 0.002) but with large scatter. There was no change in LVMI 12 months after AVR.

Changes in Peptide Levels after Aortic Valve Replacement

Before AVR, the plasma levels of NT-proANP and NT-proBNP, which were sampled at the aortic root, were elevated compared with controls (Fig. 2). Aortic valve replacement reduced overall NT-proANP by 25% in Group A (4 months) and by 16% in Group B (12 months) relative to the values before operation (Fig. 2). Nevertheless, NT-proANP remained higher than in controls at 4 (Group A) (p = 0.008) and 12 (Group B) (p = 0.019) months. Overall NT-proBNP tended to decrease slightly but was not significantly different from preoperative values.

Changes in Peptide Levels According to Baseline Pulmonary Capillary Wedge Pressure

Eleven patients in Group B had elevated preoperative PCWP (> 12 mmHg). In this subgroup, NT-proANP was decreased significantly from 2102 (983–3043) to 985 (778–1759) pmol/l (p = 0.017) 12 months after AVR, while among those with normal preoperative PCWP (< 12 mmHg, n = 19), NT-proANP did not change [761 (588–1338) vs. 788 (627–1186) pmol/l, p = NS], although the AVAI in the latter patients increased from 0.32 (0.28–0.41) to 1.01 (0.73–1.23) cm^2/m^2 (p = 0.001) (Fig. 3). Even in patients with normal PCWP, NT-proANP were slightly higher than in control before as well as after AVR (p = 0.031 and p = 0.049). N-terminal-proBNP showed a borderline decrease in patients with elevated PCWP [230 (76–447) vs. 137 (71–189) pmol/l, p = 0.058] and remained unchanged in those with normal PCWP [92 (34–160) vs. 83 (51–144) pmol/l, p = NS] (Fig. 3).

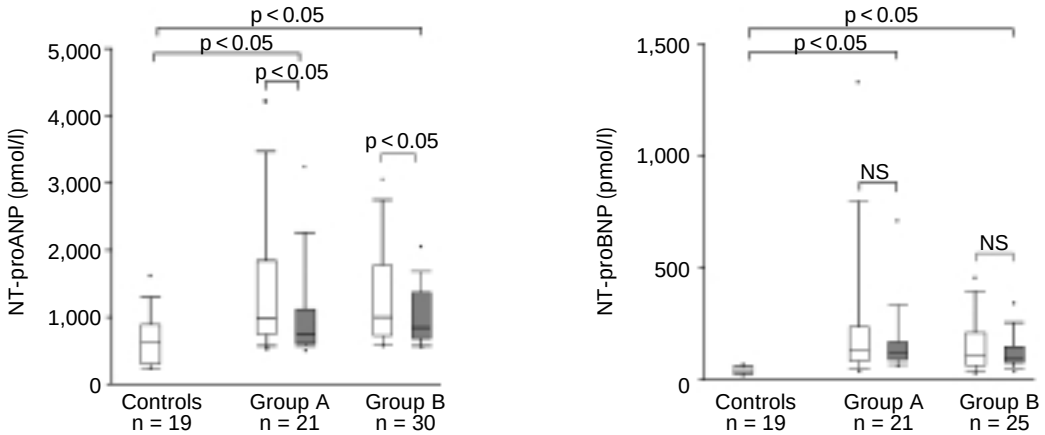

FIG. 2 N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminal probrain natriuretic peptide (NT-proBNP) plasma levels in controls and in patients followed for 4 and 12 months after aortic valve replacement (AVR). Data are median with 25th and 75th percentiles (boundary of the box), 10th and 90th percentiles (whiskers above and below the box), and single outliers (•). NS = not significant. □ = Before AVR, ■ = after AVR.

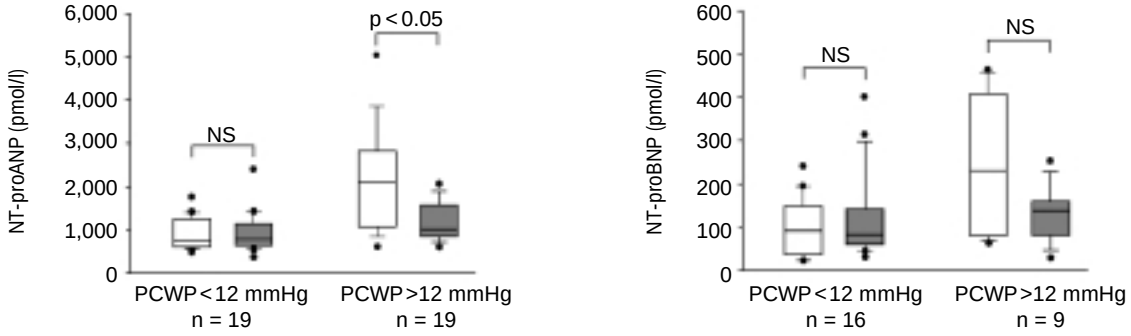

FIG. 3 Changes in N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminal probrain natriuretic peptide (NT-proBNP) plasma levels according to baseline pulmonary capillary wedge pressure (PCWP) in Group B patients. Data are median with 25th and 75th percentiles (boundary of the box), 10th and 90th percentiles (whiskers above and below the box), and single outliers (•). □ = Before AVR, ■ = after AVR (AVR = aortic valve replacement).

Peptides and Postoperative Aortic Valve Area Index

A negative correlation was observed between the plasma levels of NT-propeptides and AVAI before AVR (NT-proANP: $r = -0.49$, $p = 0.023$; NT-proBNP: $r = -0.46$, $p = 0.037$). The slopes and intercepts of regression lines for the NT-propeptides versus AVAI were not significantly decreased 12 months after AVR (p = NS), but the regression lines were shifted to the right (Fig. 4). Patients with a small postoperative AVAI tended to maintain higher levels of peptides than control. This was especially the case for NT-proBNP.

When the patients were categorized according to tertiles of postoperative AVAI [0.67 (0.54–0.73), 0.93 (0.84–1.06), and 1.27 (1.15–1.55) cm^2/m^2], the corresponding median aortic valve gradient was 14, 10, and 10 mmHg, respectively. In these three patient categories, AVR resulted in comparable reductions in the median levels of NT-proANP by 7, 5, and 4%, respectively. In contrast, in the group of patients with the smallest postoperative AVAI, NT-proBNP tended to increase, while it tended to decrease in the larger postoperative AVAI (Fig. 5).

Discussion

It has been recognized that various organs, including the lungs, liver, kidneys, and limbs, are able to clear mature ANP and BNP from the circulation.[12, 13] Two pathways are known to be involved in the clearance for ANP and BNP: binding to natriuretic peptide receptor-C (NPR-C) and degradation by neutral endopeptidase.[14] The regional clearances of N-terminal propeptides of ANP and BNP have not been clarified. In our study, NT-proANP plasma levels showed no detectable differences between the sampling sites. In a study of humans with various cardiac diseases, Hunt *et al.* showed that NT-proBNP had a similar extraction across the kidney and the lower limb as BNP and was an equally good marker of cardiac dysfunction.[15] We observed only a borderline step-down in plasma concentrations of NT-proBNP across the upper body, which might suggest that NT-proBNP is extracted by the upper body to a smaller extent than in the kidney. The step-up of NT-proBNP levels from the superior caval vein to the pulmonary artery may reflect the release of this natriuret-

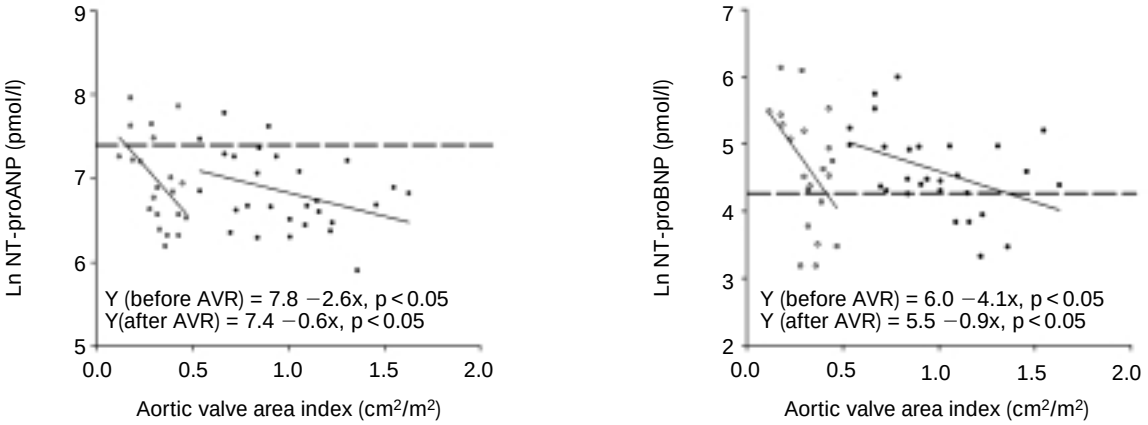

FIG. 4 Correlations between N-terminal proatrial natriuretic peptide (NT-proANP), N-terminal probrain natriuretic peptide (NT-proBNP) (log scale), and aortic valve area index before and 12 months after aortic valve replacement. Dot lines denote 97.5 percentile of control value. • = AVR 12 months, ◦ = before AVR (AVR = aortic valve replacement).

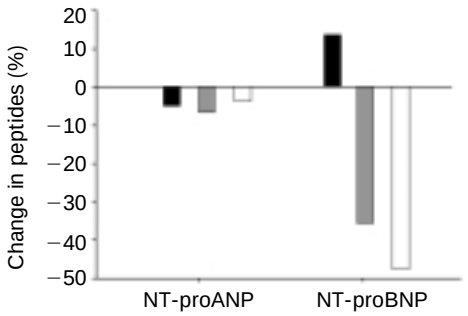

FIG. 5 Changes in N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminal probrain natriuretic peptide (NT-proBNP) 12 months after surgery according to tertiles of postoperative aortic valve area index (AVAI). ■= AVAI 0.67 cm^2/m^2,▩ = AVAI 0.93 cm^2/m^2, □ = AVAI 1.27 cm^2/m^2.

ic peptide from the coronary sinus. There was no decrease in NT-proBNP levels from the pulmonary artery to the aortic root. This does not exclude the possibility that some peptide may be cleared in the pulmonary vascular bed since some natriuretic peptides may be released directly to the cavity of the left atrium through the cardiac veins of Thebesius.[16, 17]

In the present study, NT-proANP and NT-proBNP plasma levels showed no significant differences between the aortic root and the superior caval vein at baseline. Because of the lack of baseline cubital vein samples, aortic root samples were used as a reference for overall natriuretic peptide changes after AVR.

The patients in our study had severe outflow obstruction with a large range of AVAI (0.12–0.47 cm^2/m^2) before AVR. This was reflected in an increased LVMI in more than 90% of the patients. Only 30% had increased PCWP (> 12 mmHg). The prevalence of LV hypertrophy compared with that of atrial pressure increase might explain the relatively higher increases in NT-proBNP compared with NT-proANP (3.6 fold vs.1.9 fold) before AVR relative to controls.

Atrial valve replacement resulted in a significant decrease from baseline of NT-proANP levels after 4 (Group A) and 12 (Group B) months, and most patients attained an NT-proANP level below the 97.5 percentile of control subjects. The NT-proANP reduction was most pronounced in Group A, and this may be explained by the higher PCWP in this group. N-terminal-proBNP changed inconsistently with a small trend for decrease, but the majority of values remained elevated above the 97.5 percentile of controls.

Earlier studies have demonstrated that there is a correlation between natriuretic peptides and parameters of cardiac function and LV hypertrophy. Hemodynamic improvement and the regression of the LV loading conditions after AVR were anticipated to reduce the levels of natriuretic peptides. After valve replacement, the afterload of the left ventricle is immediately reduced, which leads to a reduction of LV ejection time, LV volume, and consequently the load of left atrium.[18] In contrast, the regression of LV hypertrophy takes years after correction of the primary hemodynamic abnormality.[19,20] Within the 4-month follow-up, NT-proANP levels had reached a lower level, which may reflect the effect of increased valve area on left atrial pressure. Furthermore, the reduction of NT-proANP was observed almost exclusively among the patients with elevated preoperative PCWP, supporting the view that the change in atrial pressure is an important factor causing the change of this peptide. The level of NT-proANP attained after 4 months was within values for controls even for the smaller valve sizes. Nevertheless, continued hypertrophy of cardiac myocytes and irreversible deposition of the collagen matrix with retained diastolic dysfunction may explain the negative correlation between NT-proANP and AVAI after surgery and the fact that some patients had residual elevation in plasma levels of NT-proANP. A similar mechanism may explain the finding that even patients with a PCWP < 12 mmHg before AVR had a mean NT-proANP that was significantly higher than that in controls.

Aortic valve area index is a measure of effective orifice area. The regression of hypertrophy is highly dependent on valve size.[21] All artificial valves have some degree of valve prosthesis-patient mismatch, which means that the effective prosthetic valve area after implantation is less than the effective orifice area of a normal aortic valve.[22] The present results demonstrated the association between prosthetic valve size and the calculated aortic valve area. The negative regression between the aortic valve area and the peptide concentrations were maintained and shifted to the right 12 months after surgery. This strongly suggests an influence of valve size on LV hypertrophy and peptide release.

A small effective AVAI after AVR tended to increase NT-proBNP, which explains why overall levels did not change. It is unlikely that the small residual transvalvular pressure gradient by itself can induce hypertrophy. However, it may prevent regression of such hypertrophy and represent a continued stimulus to BNP (and NT-proBNP) expression. In our patients, there were no changes in blood pressures, serum creatinine, and cardiovascular medication, which could explain the maintained elevation of peptide levels. The regressions between AVAI and peptide levels after AVR indicated continued dependence of the valve area, suggesting suboptimal effects of small aortic valves on LV hypertrophy.

Conclusion

Our study suggests that a reduction in left atrial pressure is the main factor causing the change of NT-proANP level after AVR. A small prosthetic valve orifice area with a high aortic valve gradient contributed to a sustained hypertrophy of the left ventricle. The importance of maintained expression and release of NT-proBNP after AVR, and the relation between the levels of natriuretic peptides and the regression of LV hypertrophy need to be evaluated in further long-term studies.

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