Usefulness of Serial B-type Natriuretic Peptide Assessment in Asymptomatic Aortic Stenosis

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B-type natriuretic peptide (BNP) level may be a useful prognostic marker for the management of asymptomatic patients with aortic stenosis (AS). The aim of this study was to identify the echocardiographic determinants of BNP changes during follow-up in AS. We studied 61 asymptomatic patients with greater than moderate AS and preserved left ventricular (LV) ejection fraction who underwent rest and exercise Doppler echocardiography with concomitant BNP level measurement at baseline. BNP measurement was repeated after inclusion every 6 months. Patients were divided into 2 groups according to the median of BNP changes during follow-up. According to parameters at rest, patients in the high BNP changes group had significantly higher E/e′ ratio. Statistically significant correlations were found between BNP changes and E/e′ ratio and indexed left atrial area. According to exercise parameters, patients in the high BNP changes group had significantly lower exercise-induced increase in LV ejection fraction. Statistically significant correlations were found between BNP changes and exercise-induced changes in LV ejection fraction. After adjustment for age, mean aortic pressure gradient, and BNP level at baseline, multivariate analysis identified indexed left atrial area, E/e′ at rest, and exercise-induced increase in ejection fraction as independent determinants of BNP changes during follow-up. In conclusion, this study shows that, in asymptomatic patients with preserved LV function and moderate AS, serial BNP measurements may widely vary. Subclinical LV diastolic and systolic dysfunctions are frequently present in patients with higher serial BNP changes. **© 2014 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2014;114:441−448)**

Aortic stenosis (AS) is the most common valvular heart disease.[1] Risk stratification of asymptomatic patients with AS and preserved left ventricular ejection fraction (LVEF) remains challenging. In clinical practice, the risk-benefit ratio of early surgery should be carefully evaluated, and aortic valve replacement might be discussed in asymptomatic patients considered at high risk.[2,3] Exercise echocardiography has been shown to provide incremental prognostic information beyond echocardiography at rest or exercise testing alone, even in patients with moderate AS.[4] B-type natriuretic peptide (BNP) is probably the biomarker most frequently measured in AS; it is predominantly secreted by ventricular cardiac myocytes in response to increased wall stress.[5] Recent European Society of Cardiology guidelines have suggested elective BNP level measurement for individual risk stratification in asymptomatic AS.[6] Of note, interest has recently grown in terms of serial BNP measurements for better prediction of outcome in patients with valvular heart disease, with a more accurate predictive power than elective measurements.[7,8] However, in AS, little is known about longitudinal changes in BNP levels during serial assessments. The aims of the present study were (1) to prospectively describe the individual changes in BNP levels during longitudinal follow-up of asymptomatic patients with AS and preserved LVEF and (2) to identify whether these changes were related to the presence of baseline left ventricular (LV) systolic and/or diastolic dysfunction.

Methods

We prospectively screened 162 consecutive asymptomatic patients with at least moderate AS (aortic valve area <1.5 cm^2) and preserved LVEF (i.e., $>50\%$) who were referred to our Heart Valve Clinic to perform both resting and exercise Doppler echocardiography with concomitant BNP level measurement (Figure 1). Sixty-one patients met the inclusion criteria and had a BNP measurement repeated after at least 6 months of follow-up and then after each 6 or 12 months, according to the individual management. A careful history evaluation and exercise testing confirmed asymptomatic status. The following clinical characteristics were collected: age, body surface area, gender, dyslipidemia (cholesterol-lowering medications or low-density lipoprotein cholesterol >115 mg/dl), systemic arterial hypertension

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See page 447 for disclosure information.

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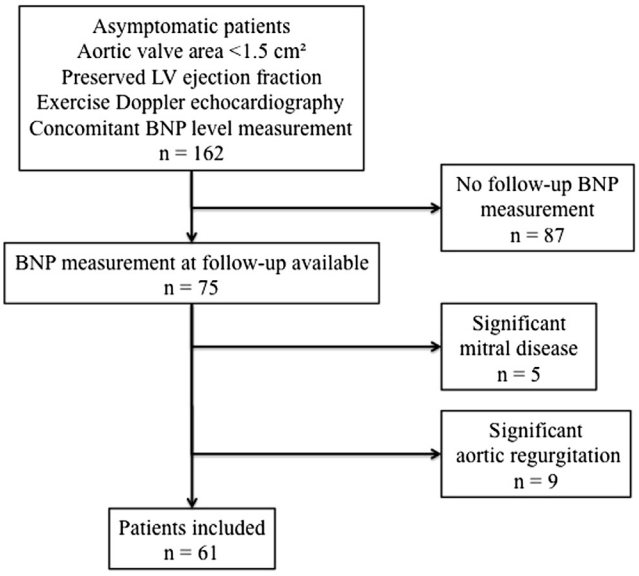

Figure 1. Flowchart of the inclusion and exclusion criteria.

(antihypertensive medications or blood pressure >140/90 mm Hg), diabetes mellitus (oral hypoglycemic medications, insulin, or glycemia >126 mg/dl), current smoking, coronary artery disease (history of myocardial infarction or documented coronary artery stenosis), atrial fibrillation, and chronic renal insufficiency. The relevant institutional review boards approved the protocol, and all patients gave written informed consent.

Before the exercise test, comprehensive transthoracic Doppler echocardiographic examination at rest was performed with a General Electric Vingmed Vivid 9 ultrasound system (Horten, Norway). The acquisitions were stored on a dedicated workstation for subsequent off-line analysis (EchoPAC; General Electric Healthcare, Little Chalfont, United Kingdom). LV stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity-time integral measured by pulse-wave Doppler. LV end-diastolic and end-systolic volumes, as well as ejection fraction, were measured by the biapical Simpson disk method. Intraobserver and interobserver variabilities, in our echocardiography laboratory, for exercise-induced changes in LVEF using Simpson's biplane method were previously assessed and reported.[9] The peak E-wave and A-wave velocities of the mitral inflow were measured using pulse-wave Doppler. Tissue Doppler imaging with pulse-wave Doppler at the level of septal and lateral mitral annulus was used to measure e′. The average of septal and lateral mitral annulus e′ peak velocity was used to calculate the E/e′ ratio. AS severity was evaluated using continuous-wave Doppler to measure the aortic transvalvular maximal velocities, and subsequent peak and mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation.[10] Left atrial area was obtained by planimetry of an end-systolic frame from the apical 4-chamber view. All measures were indexed to body surface area.

A symptom-limited graded bicycle exercise test was performed with an initial workload of 25W and an increase of 25W every 2 minutes in a semisupine position using a tilt table. A 12-lead electrocardiography was monitored continuously, and blood pressure was measured at rest and every 2 minutes during exercise. The test result was considered abnormal if the patient presented one of the following criteria: limiting dyspnea at low workload (i.e., during the 2 first steps of exercise), angina, syncope or near-syncope, increase in blood pressure of <20 mm Hg, ≥2 mm ST-segment depression, or complex ventricular arrhythmias. By design, none of the patients studied presented a positive stress test. At peak exercise, the following echocardiographic parameters were measured: AS severity (peak velocity, mean pressure, and indexed valve area), LV systolic (indexed stoke volume and ejection fraction) and diastolic function (E/e′ ratio) parameters.

Venous blood samples for BNP level measurement were drawn at rest before echocardiography. Chilled ethylenediaminetetraacetic acid–treated tubes were centrifuged immediately at 4,000 rpm (4°C) for 15 minutes. Separated plasma samples were processed by immunofluorescence assay (Biosite, Beckman Coulter, San Diego, California). The inter- and intra-assay variations were 5% and 4%, respectively. The assay detection limit was 1 pg/ml. BNP changes were calculated as the difference between the last BNP measurement obtained during the follow-up and the baseline BNP measurement at inclusion:

$$\text{BNP changes (pg/ml)} = \text{Last BNP at follow-up} - \text{Baseline BNP at inclusion}$$

Annualized BNP changes were calculated as the BNP changes divided by the time between baseline measurement and last follow-up measurement:

$$\text{Annualized BNP changes (pg/ml/year)} = \frac{(\text{Last BNP at follow-up} - \text{Baseline BNP at inclusion})}{\text{Time of follow-up}}$$

Patients were divided into 2 groups according to the median of serial BNP changes (+29 pg/ml). For continuous variables, data are expressed as mean ± SD, and group comparisons were obtained with student *t* test. For categorical variables, data are summarized as percentages, and group comparisons were obtained with chi-square test. Normality distribution was tested with the Kolmogorov-Smirnov test. Relation between serial BNP changes and continuous parameters were analyzed with Spearman correlation coefficient. To identify independent predictors of serial BNP changes, we used a multiple linear regression

Table 1
Demographic and clinical characteristics according to serial B-type natriuretic peptide changes

Variable	Whole Cohort (n = 61)	B-Type Natriuretic Peptide Changes		p-Value
		Low (n = 31)	High (n = 30)	
Age (years)	70 ± 13	68 ± 12	71 ± 13	0.364
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.483
Male gender	39 (64%)	21 (68%)	18 (60%)	0.529
Hypertension	34 (56%)	19 (61%)	15 (50%)	0.375
Diabetes mellitus	12 (20%)	6 (19%)	6 (20%)	0.949
Dyslipidemia	36 (59%)	16 (52%)	20 (67%)	0.232
Current smoker	18 (30%)	8 (26%)	10 (33%)	0.519
Coronary artery disease	14 (23%)	6 (19%)	8 (27%)	0.497
Atrial fibrillation	6 (10%)	2 (6%)	4 (13%)	0.367
Chronic renal insufficiency	4 (7%)	2 (6%)	2 (7%)	0.973
BNP at baseline (pg/mL)	104 ± 142	77 ± 116	132 ± 162	0.135
Heart rate (bpm)	71 ± 11	71 ± 10	70 ± 12	0.545
Systolic blood pressure (mm Hg)	146 ± 20	146 ± 20	147 ± 21	0.904
Diastolic blood pressure (mm Hg)	79 ± 12	80 ± 13	78 ± 12	0.453
Exercise heart rate (bpm)	111 ± 17	114 ± 17	108 ± 18	0.260
Exercise systolic blood pressure (mm Hg)	176 ± 23	180 ± 23	173 ± 23	0.324
Exercise diastolic blood pressure (mm Hg)	87 ± 16	88 ± 15	85 ± 18	0.562
Exercise capacity (Watts)	74 ± 34	83 ± 33	63 ± 31	0.052

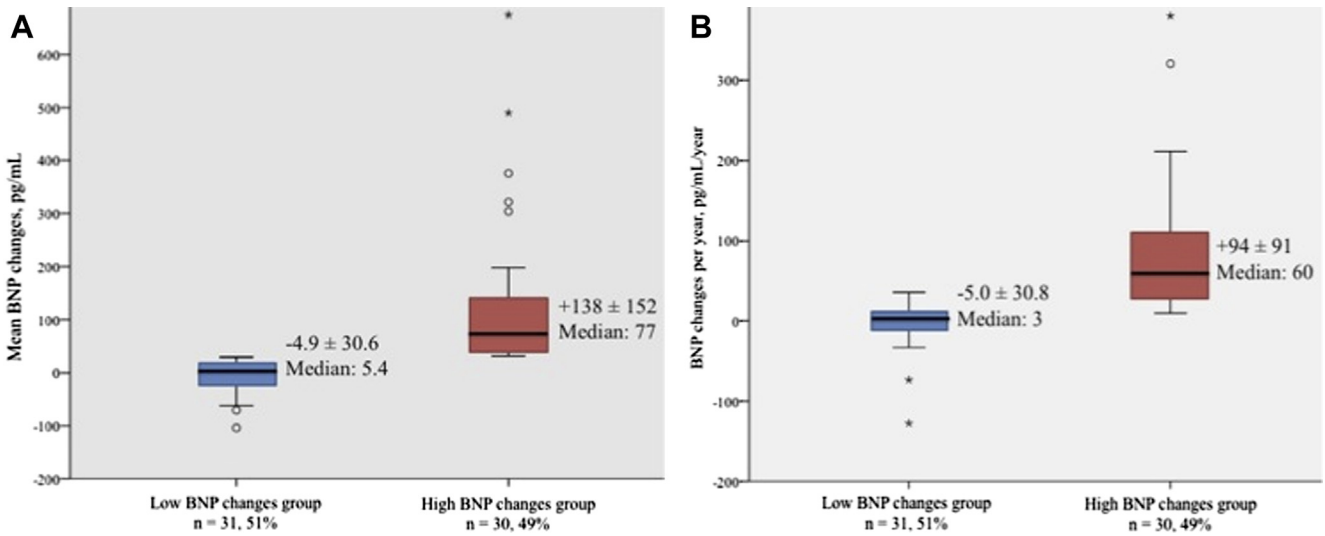

Figure 2. Mean BNP changes *(A)* and annualized BNP changes *(B)* according to BNP changes group (median). The *open circles* represent outliers and the *asterisk* represent extreme outliers.

analysis. Variables with a p value of <0.05 in univariate analysis were automatically included in the multivariable model. In addition, age, mean aortic pressure gradient, and BNP at baseline were forced in the multivariable model because of their well-established impact on the outcome. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 21 (IBM corp., Armonk).

Results

There were no significant differences in demographic and clinical characteristics and BNP level at baseline according to serial BNP changes. A trend for a lower exercise capacity in the high serial BNP changes group was observed (Table 1). Mean BNP at baseline was 104 ± 142 pg/ml (median 66, range 5 to 700) and significantly increased during the follow-up (last measurement: mean = 169 ± 224 pg/ml, median 98, range 8 to 1,380, p <0.001). Mean BNP change at follow-up was +65 ± 130 pg/ml; median +29, range −104 to +675 (Figure 2, panel A). BNP level increased in 48 patients (79%), multiplied by 2 in 16 (26%) and by 3 in 8 (13%) patients. Duration of follow-up between the baseline and the last measurement was 22 ± 12.5 months (median 20, range 7 to 47). More than 1/2 of the patients (62%, n = 38) had >3 measurements. Mean annualized BNP change was +44 ± 84 pg/ml/year (median +20, range: −128 to +380; Figure 2, panel B). At the last BNP measurement, 13 patients had

Table 2
Echocardiographic data according to serial B-type natriuretic peptide changes

Variable	Whole Cohort (n = 61)	B-Type Natriuretic Peptide Changes		p-Value
		Low (n = 31)	High (n = 30)	
Resting parameters				
AS severity				
Peak aortic velocity (m/s)	3.7 ± 0.7	3.7 ± 0.6	3.8 ± 0.7	0.469
Mean aortic pressure gradient (mm Hg)	37 ± 14	35 ± 13	39 ± 16	0.319
Indexed valve area (cm^2/m^2)	0.53 ± 0.13	0.55 ± 0.11	0.51 ± 0.15	0.193
LV geometry and function				
Indexed mass (g/m^2)	88 ± 26	83 ± 26	93 ± 25	0.139
Indexed end-diastolic volume (mL/m^2)	44 ± 12	44 ± 12	44 ± 12	0.942
Indexed end-systolic volume (mL/m^2)	14 ± 6	14 ± 6	14 ± 5	0.744
Indexed stroke volume (mL/m^2)	45 ± 9	45 ± 8	44 ± 10	0.707
LV ejection fraction (%)	69 ± 7	68 ± 6	69 ± 7	0.574
E/e′ ratio	11 ± 4	9 ± 3	12 ± 5	0.022
Indexed left atrial area (cm^2/m^2)	9.6 ± 2.4	9.2 ± 2.2	10.1 ± 2.6	0.167
Exercise parameters				
AS severity				
Peak aortic velocity (m/s)	4.2 ± 0.8	4.1 ± 0.8	4.3 ± 0.8	0.424
Mean aortic pressure gradient (mm Hg)	48 ± 20	47 ± 19	49 ± 23	0.703
Indexed valve area (cm^2/m^2)	0.57 ± 0.13	0.58 ± 0.11	0.55 ± 0.14	0.572
LV geometry and function				
Indexed stroke volume (mL/m^2)	48 ± 12	47 ± 8	49 ± 15	0.604
LV ejection fraction (%)	72 ± 6	73 ± 5	72 ± 8	0.364
E/e′ ratio	12 ± 4	11 ± 3	13 ± 5	0.068
Exercise-induced changes				
Mean aortic pressure gradient (mm Hg)	+11 ± 11	+12 ± 10	+10 ± 13	0.567
LV ejection fraction (%)	+4.0 ± 4.3	+5.2 ± 4.5	+2.5 ± 3.7	0.026
LV ejection fraction by ≥4%	30 (49%)	20 (65%)	10 (33%)	0.047
E/e′ ratio	+1.2 ± 2.7	+1.2 ± 2.6	+1.1 ± 3.0	0.877

AS = aortic stenosis; LV = left ventricular.

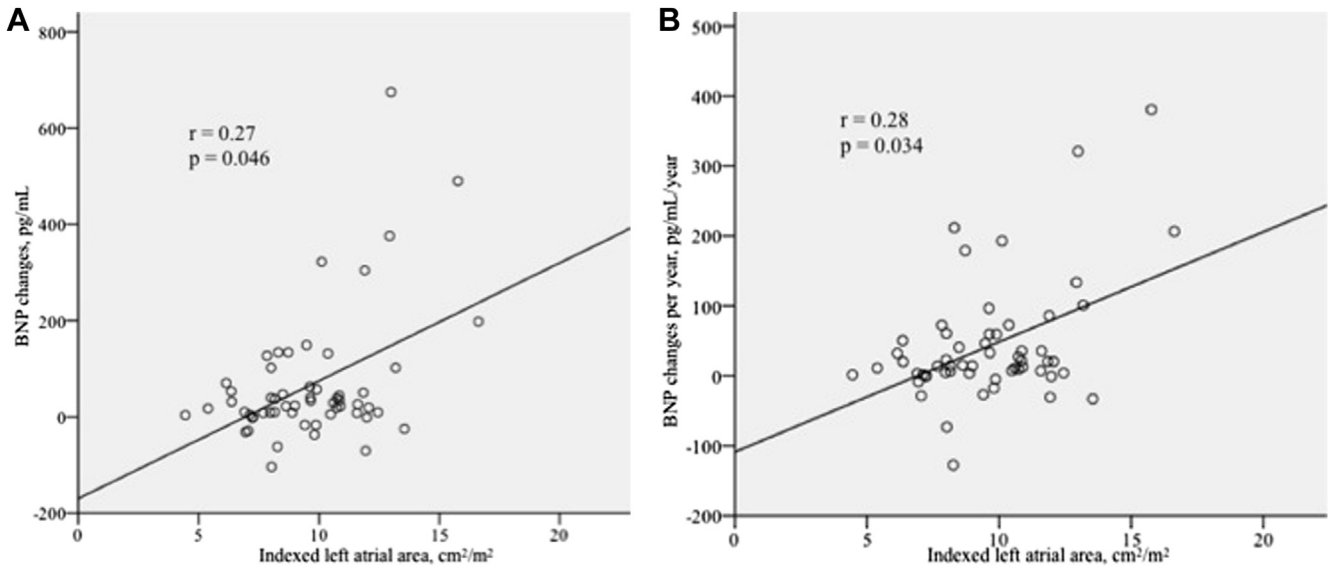

Figure 3. Relation between indexed left atrial area and *(A)* serial BNP changes and *(B)* annualized BNP changes.

symptoms. A trend was observed for a greater increase in annualized BNP in those patients (+92 ± 120 vs +31 ± 66 pg/ml/year, p = 0.09).

By definition, all patients presented a moderate-to-severe AS and a preserved LVEF. Patients with greater increases in BNP during follow-up had higher E/e′ ratio at baseline. There were no significant differences in AS severity, left atrial area, LV mass, and LV volumes and function between groups (Table 2). Statistically significant correlations were found between BNP changes and indexed left atrial area (Figure 3,

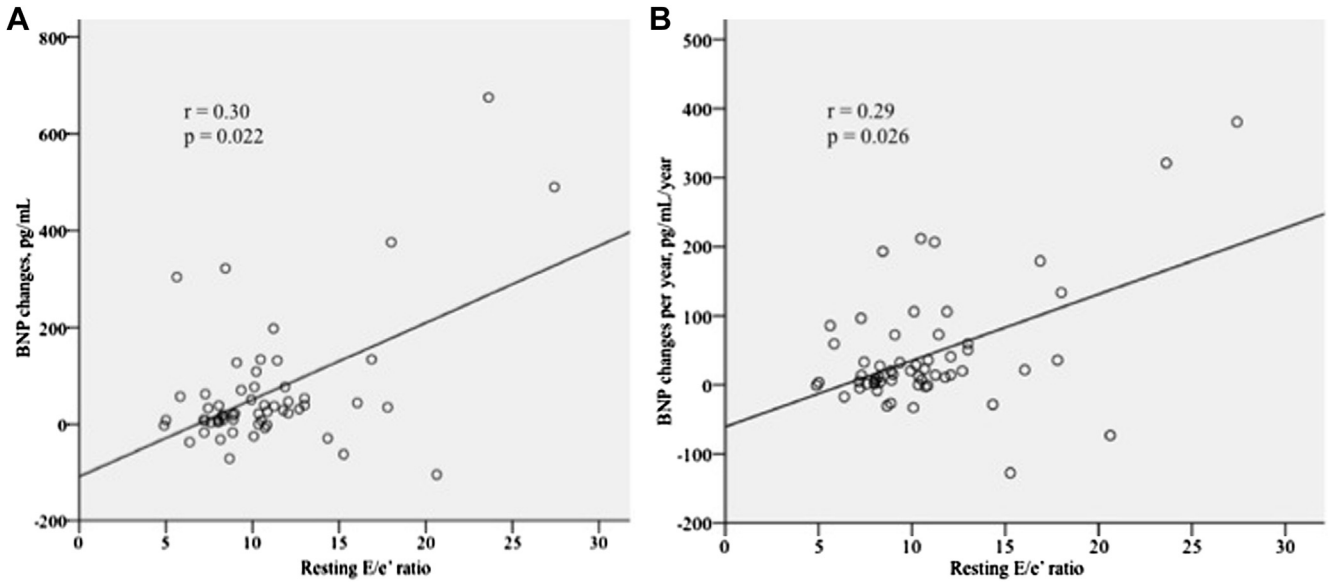

Figure 4. Relation between E/e′ ratio at rest and *(A)* serial BNP changes and *(B)* annualized BNP changes.

Table 3
Correlation between serial B-type natriuretic peptide changes and echocardiographic parameters

Variable	r	p-Value
BNP at baseline	0.24	0.066
Resting parameters		
AS severity		
Peak velocity	0.15	0.248
Mean pressure gradient	0.20	0.126
Indexed valve area	−0.18	0.159
LV geometry and function		
Indexed mass	0.25	0.067
Indexed end-diastolic volume	0.04	0.764
Indexed end-systolic volume	−0.02	0.909
Indexed stroke volume	0.05	0.686
LV ejection fraction	0.10	0.490
E/e′ ratio	0.30	0.022
Indexed left atrial area	0.27	0.046
Exercise parameters		
AS severity		
Peak velocity	0.14	0.299
Mean pressure gradient	0.15	0.270
Indexed valve area	−0.13	0.378
LV geometry and function		
Indexed stroke volume	0.04	0.783
LV ejection fraction	−0.01	0.957
E/e′ ratio	0.20	0.154
Exercise-induced changes		
Mean aortic pressure gradient	−0.03	0.840
LV ejection fraction	−0.33	0.019
E/e′ ratio	0.05	0.974

AS = aortic stenosis; LV = left ventricular.

panel A) and E/e′ ratio (Figure 4, panel A; Table 3). Similarly, statistically significant correlations were found between annualized BNP changes and indexed left atrial area (Figure 3, panel B) and E/e′ ratio (Figure 4, panel B).

Patients with greater increases in BNP during follow-up had lower exercise-induced increases in LVEF. A trend in favor of higher exercise E/e′ ratio was also observed in these patients. There were no significant differences in exercise AS severity parameters and exercise LVEF between groups (Table 2). Statistically significant correlation was found between BNP changes and exercise-induced changes in LVEF (Figure 5, panel A; Table 3). Similarly, annualized BNP changes were correlated with exercise-induced changes in LVEF (Figure 5, panel B). Patients with exercise-induced increase in LVEF (≥4%) had significant lower BNP changes during follow-up (Figure 6).

After adjustment for age, mean aortic pressure gradient at rest, and BNP level at baseline, multivariate analysis identified indexed left atrial area, E/e′ at rest, and exercise-induced increase in ejection fraction as independent determinants of serial BNP changes during follow-up (Table 4). Moreover, after adjustment for age, E/e′ at rest, and BNP level at baseline, indexed left atrial area ($\beta = 12.3 \pm 4.1$, $p = 0.004$), mean aortic pressure at rest ($\beta = 2.0 \pm 0.7$, $p = 0.005$), and exercise-induced increase in ejection fraction ($\beta = -6.0 \pm 2.4$, $p = 0.016$) emerged as independent determinants of annualized BNP changes.

Discussion

The main findings of the present study show that, in asymptomatic patients with preserved LVEF and moderate-to-severe AS, (1) wide individual BNP variations can be observed during regular monitoring; (2) increases in serial BNP levels are related to the severity of diastolic burden as evaluated by higher E/e′—an estimate of LV filling pressure—and indexed left atrial area; and (3) limited contractile reserve as manifested by lower exercise changes in LVEF—latent LV systolic dysfunction—also significantly contributes to higher changes in BNP level during follow-up.

In AS, the single measurement of BNP level correlates with valve area, diastolic function, functional status, and symptomatic deterioration and may improve risk stratification.[11–13] Currently, little is known about serial changes

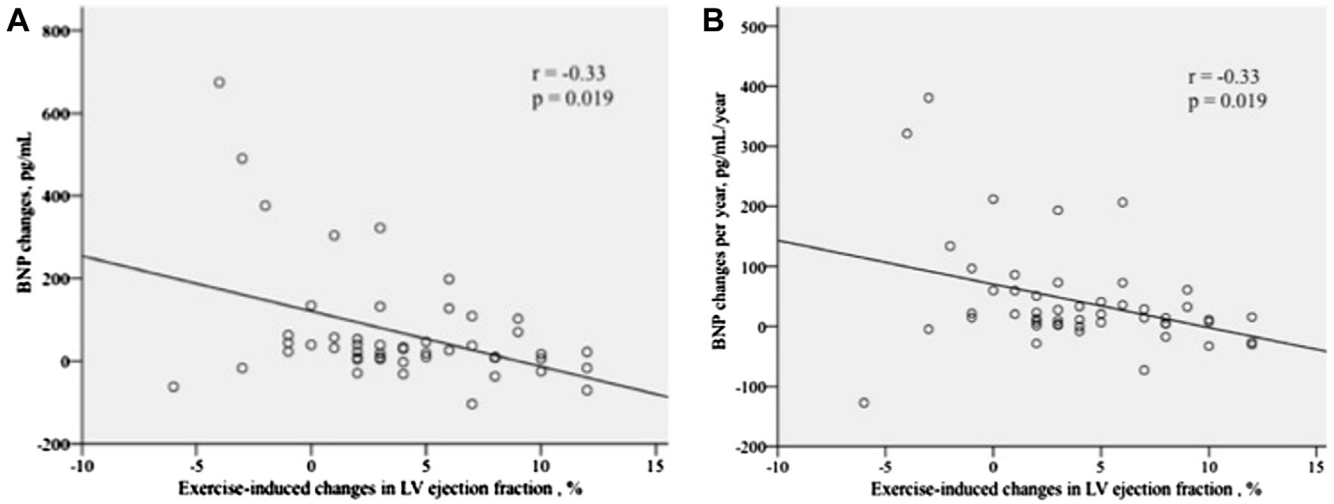

Figure 5. Relation between exercise-induced changes in LVEF and *(A)* serial BNP changes and *(B)* annualized BNP changes.

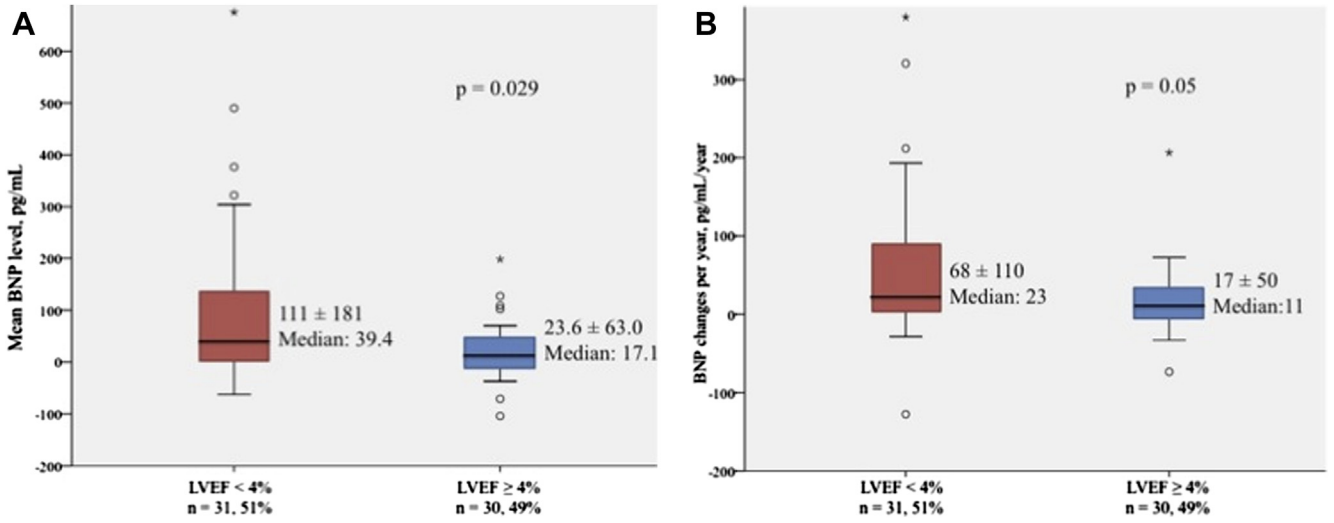

Figure 6. Mean BNP changes *(A)* and annualized BNP changes *(B)* according to exercise-induced changes in LVEF.

Table 4
Determinants of serial B-type natriuretic peptide changes: multiple linear regressions

Variables	Univariable	Multivariable		
	p	β	SE	p
Age	0.146	1.08	1.40	0.446
BNP at baseline	0.066	0.04	0.15	0.806
Mean aortic pressure gradient	0.126	1.94	1.18	0.107
Indexed left atrial area	0.046	20.1	6.8	0.005
Resting E/e′ ratio	0.022	10.0	4.2	0.020
Exercise changes in LV ejection fraction	0.019	−8.5	4.1	0.044

LV = left ventricular.

in BNP levels in asymptomatic patients with AS and preserved LVEF. A small study including 29 asymptomatic patients with moderate-to-severe AS demonstrated that the average rate of increase in N-terminal fragment of prohormone BNP in patients who developed symptoms was higher compared with those who remained asymptomatic (+26 vs +7.2 pmol/L, p = 0.014).[14] Similarly, in a group of 43 initially asymptomatic patients, an increase in BNP was noticed in 14 patients developing symptoms, whereas no change was observed in those remaining stable.[11] Unfortunately, in both studies, cofactors associated with changes in serial BNP levels were not assessed.

In our cohort of asymptomatic patients with AS and preserved LVEF, we demonstrated for the first time that serial BNP changes during follow-up were associated with subclinical LV dysfunction. Patients with higher BNP increases were those with larger left atrial size and higher E/e′, 2 surrogate markers of LV diastolic burden, which has been associated with a poor prognosis.[12] Therefore, assessing the changes in BNP levels may unmask a subgroup of asymptomatic AS with a higher degree of LV diastolic dysfunction, which may precede symptom development.[15]

In addition, we showed that limited contractile reserve—smaller exercise-induced increase in LVEF—was also an independent predictor of BNP changes during follow-up. In

AS, LVEF at rest, which often remains normal for long, may underestimate the extent of intrinsic myocardial impairment.[16] Recently, it has been shown that limited contractile reserve may identify a subset of patients who are at increased risk of abnormal response to exercise and cardiovascular events.[17–19] The limited contractile reserve is thus intimately related to latent myocardial dysfunction, which could be easily detected by a significant increase in serial BNP levels. In a way, these data are similar to what has been observed in patients with degenerative mitral regurgitation.[20,21]

The initial management of patients with AS is frequently conservative because most of them are asymptomatic. However, additional tests to improve risk stratification are required as the individual outcomes are highly variable depending on the degree of LV structural impairments, even with moderate AS.[4] BNP is the most commonly used biomarker in AS. Although BNP carries reasonable prognostic information, it lacks specificity when measured at a given time of the evolution. Conversely, its regular monitoring can identify patients with more advanced disease process who tend to develop symptoms during follow-up.[11,14] Indeed, a significant increase in BNP during follow-up identifies patients with latent LV systolic dysfunction and higher degree of LV diastolic dysfunction. Monitoring changes in BNP level might thus help to define the best timing of aortic valve replacement. In practice, we suggest measuring BNP level at the initial examination of AS and at regular intervals—every 6 to 12 months—during follow-up. An increase in serial BNP level should lead to closer follow-up with a careful search for unrevealed symptoms and repeat echocardiographic evaluation. However, whether these serial BNP changes might be used to predict the individual outcomes need to be addressed.

Some limitations need to be acknowledged. The duration of follow-up and the interval between BNP measurements were not standardized. We tried to counteract this limitation using annualized BNP changes. Even if all patients were followed up in our Heart Valve Clinic and received standard clinical management, we cannot exclude that other factors, such as medical therapy, changes in renal function, or stress related to exercise testing, might have influenced the BNP changes. Furthermore, because we used a tilt table to perform exercise echocardiography, the continuous-wave Doppler recordings were made almost only from the apical position. This may have resulted in underestimation of peak velocity in some patients.

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Disclosures

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