Impact of Serial B-Type Natriuretic Peptide Changes for Predicting Outcome in Asymptomatic Patients With Aortic Stenosis

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ABSTRACT

Background: The aim of this study was to determine the impact on the outcome of serial B-type natriuretic peptide (BNP) changes during follow-up in asymptomatic patients with ≥ moderate aortic stenosis (AS) and preserved left ventricular ejection fraction.

Methods: We prospectively screened 69 patients who underwent comprehensive transthoracic echocardiography, BNP level measurement at baseline and after every 6 or 12 months. Annualized BNP changes were calculated as the difference between the last and baseline BNP measurements divided by the duration of follow-up. The primary endpoint was the occurrence of symptoms, aortic valve replacement, or cardiovascular death.

Results: During a follow-up of 30 ± 19 months, 43 patients experienced a cardiac event. These patients were significantly older (73 ± 9 years) and had a larger aortic valve area compared to the patients who remained asymptomatic. The annualized BNP change was significantly higher in patients who experienced a cardiac event (14.7 ± 14.1 vs. 4.1 ± 3.6 ng/mL, p = 0.003).

Conclusion: The serial changes of BNP measurement can be used as a predictor of outcome in asymptomatic patients with AS and preserved LV ejection fraction.
and symptomatic deterioration. Moreover, recent European Society of Cardiology guidelines have suggested BNP level measurement for risk stratification in asymptomatic AS. Some authors have evaluated serial BNP measurements in patients with valvular heart disease demonstrating a better prediction of outcome compared with single measurements. Accordingly, we previously published a related paper providing interesting insight into the relationship between the increase in serial BNP and the presence of LV systolic and diastolic dysfunction. However, in AS, little is known about prediction of outcome using serial changes in BNP levels. The aim of the present study was to identify whether serial changes in BNP levels during the follow-up of asymptomatic patients with AS and preserved LVEF could predict outcome.

Methods

Study population

Consecutive asymptomatic patients with at least moderate AS (aortic valve area < 1.5 cm²) and preserved LVEF (> 50%) referred for clinical evaluation and Doppler echocardiography to our heart valve clinic were prospectively screened. A careful history and exercise testing confirmed the asymptomatic status. Patients with concomitant > mild mitral valve disease or aortic regurgitation were excluded. Concomitantly, BNP level measurement was performed at baseline and repeated after at least 6 months of follow-up, and then, after every 6 or 12 months, in all 69 included patients. The institutional review boards approved the study and all patients gave written informed consent.

Echocardiographic measurements

Transthoracic Doppler echocardiographic examination was performed with a GE Vingmed VIVID 9 ultrasound system (Horton, Norway). The acquisitions were stored and subsequent off-line analyses were performed using a dedicated workstation (EchoPac, General Electric Healthcare, Little Chalfont, UK). The LV outflow tract area was multiplied by the LV outflow tract velocity time integral measured by pulsed-wave Doppler to calculate the LV stroke volume. The bi-apical Simpson disk method was applied to measure the LV end-diastolic and end-systolic volumes, and ejection fraction. Pulsed-wave Doppler at mitral inflow was used to measure peak E-wave and A-wave velocities and tissue Doppler imaging with pulsed-wave Doppler at the level of septal and lateral mitral annulus for e’ velocities. The E/e’ ratio was calculated using the average of septal and lateral mitral annulus e’ peak velocity. The LV global longitudinal myocardial deformation was evaluated from standard 2D images with adequate frame rate (> 60/s) by speckle tracking analysis. Manual tracing of the endocardial borders on an end-systolic frame was performed, and automatically tracking on subsequent frames was applied. Adequate tracking for each segment was verified and manually corrected, if necessary. The global longitudinal strain was the average of the segment strains from apical 4-, 2-, and 3-chamber views. Peak and mean aortic gradient were calculated using the simplified Bernoulli equation with the aortic transvalvular maximal velocities obtained by continuous-wave Doppler, and the continuity equation was used to calculate the aortic valve area. The left atrial (LA) area was obtained by planimetry in the apical 4-chamber view at end-systole. Systolic pulmonary artery pressure was derived from the tricuspid regurgitant maximal velocity using the modified Bernoulli equation and the addition of estimated right atrial pressure.

Serial BNP measurements

Venous blood samples were drawn at rest with chilled ethylenediaminetetraacetic acid tubes, centrifuged immediately...
at 4000 rpm (4°C) for 15 minutes, and processed by an immunofluorescence assay (Biosite, Beckman Coulter, San Diego, CA). The assay detection was 1 pg/mL, and inter- and intra-assay variations were 5% and 4%, respectively. Annualized BNP changes were calculated as the BNP changes (difference between the last BNP measurement obtained during the follow-up and the baseline BNP measurement at inclusion) divided by the time between baseline measurement and last follow-up measurement:

\[ \text{Annualized BNP changes (pg/mL/y)} = \frac{\text{Last BNP at follow-up} - \text{Baseline BNP at inclusion}}{\text{Time of follow-up}} \]

Cardiac event-free survival

Patient follow-up was individualized and performed according to current guidelines, that is, every 6 or 12 months. Follow-up information was obtained after a complete medical chart review and discussions with the patients and/or general physicians. The follow-up was complete in 66 patients (96%). The primary endpoint was the occurrence of the first composite endpoint defined as the occurrence of symptoms, aortic valve replacement (indicated by symptoms or LV dysfunction according current class I indication), 2,3 or cardiovascular death.

Results

Determinants of annualized BNP changes

Among the 69 included patients, mean BNP at baseline was 96 ± 135 pg/mL (median: 62) and it significantly increased during the follow-up (last measurement: mean 180 ± 233 pg/mL [median 98]; \( P < 0.001 \)). More than half of the patients (61%, \( n = 42 \)) had more than 3 follow-up measurements, and the duration of follow-up between the baseline and the last measurement was 24 ± 17 months. The mean of annualized BNP changes was +59 ± 132 pg/mL/y (median: 20). Statistically significant correlations were found between annualized BNP changes and age \(( r = 0.271; P = 0.024)\), aortic severity parameters (peak aortic velocity: \( r = 0.312; P = 0.009 \)), indexed LA area \(( r = 0.293; P = 0.018)\), and baseline BNP \(( r = 0.275; P = 0.022)\). There was a trend observed between the E/e' ratio \(( r = 0.235; P = 0.057)\) and annualized BNP changes. There were no significant correlations between annualized BNP changes and LV mass \(( P = 0.344)\), volume \(( P = 0.833)\), injection 

\[ \text{Impact of annualized BNP changes on cardiac event-free survival} \]

During a global follow-up (baseline BNP measurement to the last follow-up) of 30 ± 19 months, 43 patients (62%) presented a cardiac event. The duration of follow-up between the last BNP measurement and the last follow-up was 6 ± 11 months. Aortic valve replacement was performed in 37 (54%) patients motivated by the occurrence of symptoms in 27 (39%) patients and by an abnormal exercise test showing symptoms clearly related to AS in 10 (14%) patients. Among the 6 (9%) remaining events, 4 (6%) were related to the development of patient symptoms but were treated medically because of prohibitive high surgical risk and 2 (3%) patients died from a cardiovascular cause. Patients with a cardiovascular event were significantly older, and had more often dyslipidemia, more severe AS, and a larger indexed LA area (Tables 1 and 2). In addition, they had higher BNP at follow-up and annualized BNP changes, but there was no difference according to BNP at baseline. Only those patients experiencing a cardiovascular event had a significant increase in BNP level from baseline to follow-up (Fig. 1).

Cardiac event-free survival was 81% ± 5% and 49% ± 6% at 1 and 3 years, respectively. According to the median of annualized BNP changes, patients with lower annualized BNP changes had a significantly higher cardiac event-free survival (1 year: 97% ± 3% vs 63% ± 8%; 3 years: 68% ± 8% vs 31% ± 8%; \( P < 0.001 \); Fig. 2). Similar results were found according to tertiles of annualized BNP changes: patients in tertile 3 had a significantly reduced 2-year event-free survival compared with tertile 1 (46 ± 11% vs 82 ± 8%; \( P = 0.001 \); Fig. 3). Using the multivariable Cox proportional hazard model, higher annualized BNP changes were independently associated with increased risk of cardiac events after adjustment for sex and baseline BNP; and age, dyslipidemia, and
Pathophysiology of BNP release in AS

In AS, chronic pressure overload imposed on the LV leads to progressive LV hypertrophy, a compensatory mechanism aiming to maintain normal LV wall stress. However, at a later stage, when this compensatory mechanism is overridden, LV wall stress and filling pressure increase triggering BNP activation and release.\(^9\)\(^,\)\(^10\) In symptomatic AS, BNP release has been shown to reflect the elevation in LV filling pressures.\(^20\) In symptomatic or asymptomatic severe AS with structural impairment such as diastolic dysfunction, LA dilatation, LV hypertrophy, and fibrosis, elevated single BNP level measurement is a marker of already elevated LV filling pressures predicting poor short-term outcome.\(^9\)\(^,\)\(^10\)\(^,\)\(^15\) However, in asymptomatic moderate-to-severe AS without significant structural changes, the baseline BNP level is potentially more dependent on the overall patients’ picture (age, gender) rather than on the degree and consequences of AS.\(^18\) This

Table 2. Comparison of echocardiographic data according to adverse cardiac events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole cohort (n = 69)</th>
<th>No events (n = 26, 38%)</th>
<th>Events (n = 43, 62%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS severity</td>
<td>Peak aortic velocity (m/s)</td>
<td>3.8 ± 0.7</td>
<td>3.5 ± 0.6</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Mean aortic pressure gradient (mm Hg)</td>
<td>37 ± 14</td>
<td>29 ± 9</td>
<td>42 ± 14</td>
</tr>
<tr>
<td></td>
<td>Indexed valve area (cm²/m²)</td>
<td>0.53 ± 0.13</td>
<td>0.58 ± 0.13</td>
<td>0.50 ± 0.12</td>
</tr>
<tr>
<td>LV geometry and function</td>
<td>Indexed mass (g/m²)</td>
<td>88 ± 26</td>
<td>85 ± 30</td>
<td>90 ± 23</td>
</tr>
<tr>
<td></td>
<td>Indexed end-diastolic volume (mL/m²)</td>
<td>45 ± 12</td>
<td>45 ± 14</td>
<td>45 ± 12</td>
</tr>
<tr>
<td></td>
<td>Indexed end-systolic volume (mL/m²)</td>
<td>15 ± 5</td>
<td>15 ± 5</td>
<td>14 ± 6</td>
</tr>
<tr>
<td></td>
<td>Indexed stroke volume (mL/m²)</td>
<td>45 ± 10</td>
<td>44 ± 10</td>
<td>46 ± 9</td>
</tr>
<tr>
<td></td>
<td>LV ejection fraction (%)</td>
<td>67 ± 6</td>
<td>66 ± 7</td>
<td>69 ± 6</td>
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<tr>
<td></td>
<td>GLS (%)</td>
<td>−20 ± 3</td>
<td>−20 ± 3</td>
<td>−20 ± 3</td>
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<tr>
<td></td>
<td>E'/e ratio</td>
<td>11 ± 4</td>
<td>10 ± 4</td>
<td>11 ± 4</td>
</tr>
<tr>
<td></td>
<td>Indexed left atrial area (cm²/m²)</td>
<td>9.6 ± 2.4</td>
<td>8.7 ± 1.9</td>
<td>10.2 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>Systolic pulmonary arterial pressure (mm Hg)</td>
<td>36 ± 9</td>
<td>34 ± 7</td>
<td>37 ± 10</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; BNP, B-type natriuretic peptide; GLS, global longitudinal strain; LV, left ventricular.
can explain the discrepant results observed in the present cohort and previous published data, even by our group. Single BNP measurement provides a snapshot of the present clinical situation but not of the evolution of the disease, which is known to be highly individual. In contrast, the progression of AS and its repercussions on LV are prone to affect the BNP release over time with a gradual increase. Higher annualized BNP changes can be the sign of the progressive exhaustion of LV adaptation to the increased afterload, which precedes the occurrence of symptoms. Of note, in our cohort, indexed LA area, a sensitive marker of elevated LV filling pressure, was an independent determinant of annualized BNP changes.

Serial BNP changes and outcome in AS

In patients with AS, the prognostic value of single BNP level measurement has been largely demonstrated. Different cutoff values, ranging from 61 to 130 pg/mL, have been related to the occurrence of symptoms, need for aortic valve replacement, and cardiac-related death. To note, those cutoff values were not adjusted to counteract the interindividual variation of BNP levels related to age and gender. To address this issue, Clavel et al. have shown that BNP normalized to age and sex was also highly predictive of outcomes in a large cohort. However, there are few data regarding serial BNP changes for predicting outcome in asymptomatic patients with AS and preserved LVEF. In a small cohort of 29 asymptomatic patients with moderate-to-severe AS, the average rate of increase in the NT-proBNP level was greater in patients who developed symptoms compared with those who remained asymptomatic (+26 vs +7.2 pmol/L; P = 0.014). Similarly, in a group of 43 initially asymptomatic patients, a mean BNP increase from 188 to 486 pg/mL was noticed in 14 patients developing...
measurements in our cohort. The rate of progression of stenosis was significantly higher in patients who presented cardiac events than those did not. However, AS severity assessment using Doppler echocardiography requires experienced sonographers who are aware of technical pitfalls, compared with BNP level measurement being reproducible, low cost, and not operator dependent. In our cohort, a cutoff value of annualized BNP changes (> 20 pg/mL/y) provided a sensitivity and specificity of 71% and 77%, respectively, to predict the occurrence of events. We believe that serial BNP measurements should be integrated into the AS management algorithm as complement to clinical and echocardiographic evaluation. However, further larger studies addressing mortality reduction after aortic valve replacement guided by serial BNP changes are needed to confirm the benefit of this strategy.

Limitations

The duration of follow-up and the interval between BNP measurements were not standardized in the entire cohort as individual management was left to the discretion of the cardiologist. The use of annualized BNP changes may partially temper such limitation. Furthermore, 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 or changes in renal function, might have influenced the BNP changes. The majority of the reported cardiac events were aortic valve replacement indicated by symptoms for which the evaluation remains subjective. However, the occurrence of symptoms is a current class I indication for surgery and reflects general practice.

Conclusions

In our cohort of asymptomatic patients with AS and preserved LVEF, higher annualized BNP changes (> 20 pg/mL/y) were associated with a significantly lower cardiac event-free survival multiplied by 2.73 the risk of cardiac events. Moreover, compared with patients remaining free from a cardiac event, those experiencing a cardiac event had a progressive increase in BNP level from baseline to follow-up despite the absence of significant differences in BNP at baseline. Consequently, serial BNP changes may be useful to anticipate the development of class I indication for aortic valve replacement and to predict outcome.

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Disclosures

The authors have no conflicts of interest to disclose.

References


