Clinical research

Relation of N-terminal pro B-type natriuretic peptide to progression of aortic valve disease

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Aims Recently an elevation of B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) in patients with aortic stenosis (AS) and aortic regurgitation (AR) has been described. The objective of this study was to evaluate the relation of NT-proBNP values to the progression of aortic valve disease.

Methods and results One hundred and sixty-eight patients were included. NT-proBNP was elevated in patients with AS (n = 109) and AR (n = 37) linked to disease severity. Values for NT-proBNP, pressure gradient, and left ventricular mass were identical in patients (n = 22) after previous valve replacement and in those patients with mild AS. NT-proBNP levels decreased in 86 patients after valve replacement (2292 ± 353 vs. 785 ± 101 pg/ml; P < 0.01) but increased in 82 patients who were treated conservatively (616 ± 120 vs. 1155 ± 432 pg/mL; P = 0.029), related to the progression of disease.

Conclusion NT-proBNP is elevated in patients with aortic valve disease linked to disease severity and decreases after successful surgical therapy but increases in conservatively treated patients. These data underline the consistent relation of NT-proBNP to severity of aortic valve disease. Therefore, NT-proBNP should be considered as a biomarker for the monitoring of disease during follow-up, but further studies are warranted.

KEYWORDS
Natriuretic peptide; B-type natriuretic peptide; Aortic valve disease; Aortic valve replacement

Introduction

Aortic valve diseases, namely aortic stenosis (AS) and aortic regurgitation (AR), are common in developed countries, with AS being the most common valvular heart disease.1,2 Echocardiography is the most important examination to confirm the diagnosis, to assess the severity, and to monitor the progression of AS and AR. To date, no biochemical markers are available for the diagnostic work up in patients with aortic valve disease with therapeutic implications.

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are neurohormones synthesized and secreted mainly from ventricular myocardium. Stimulus for their release is an increase in ventricular wall stress.3

In patients with AS, BNP and NT-proBNP are elevated with a correlation to severity,4–7 providing prognostic information for symptom-free survival and post-operative outcome.8 There are only little data available on BNP and NT-proBNP in patients with chronic AR showing an association of both markers to symptoms, left ventricular function, and left ventricular mass (LVM).9,10 The only published data on changes in natriuretic peptides in the course of surgically treated patients with AS originate from a study by Qi et al.11 They could show a trend towards a decrease of NT-proBNP in 31 patients 12 months after valve replacement. No data exist on BNP or NT-proBNP in patients with AR with
respect to therapy and nothing is known about the diagnostic utility of these markers for the detection of disease progression.

Therefore, we hypothesized that changes of NT-proBNP reflect changes in myocardial stress of patients with aortic valve disease with an increase in patients who are treated conservatively and a decrease in patients who are undergoing valve replacement. Thus, we conducted a prospective observational longitudinal study to analyse changes of NT-proBNP with respect to the therapeutic strategy and clinical success.

Methods

Patients

This study originally included 249 patients who were referred for further evaluation of aortic valve disease. Eighty-one (33%) patients were excluded from the analysis because they did not attend the follow-up. The remaining 168 patients, of whom complete follow-up data were available, were included in the analysis. AS was present in 109 patients and chronic AR in 37 patients. To compare the effect of surgical therapy on NT-proBNP, 22 patients who underwent aortic valve replacement at least 12 months previous to inclusion (previous AVR) were included. Because it is established that values for BNP and NT-proBNP are elevated in patients with reduced left ventricular function and an ejection fraction (EF) < 45%, only patients with an EF > 45% documented by echocardiography were included. Functional status was assessed and graded according to the New York Heart Association (NYHA) classification by physicians blinded to NT-proBNP values. The medical history was assessed as the patients reported it or, if available, on the basis of their medical records. The indication for valve surgery was left to the discretion of the treating physician, who was blinded to NT-proBNP values. A follow-up visit took place 335 days (median) (interquartile range: 251–349 days) after study entry. At follow-up, medical history and functional status were assessed. Echocardiography and blood sampling for NT-proBNP analysis were performed at baseline and at follow-up.

Echocardiography

A comprehensive transthoracic echocardiography study was performed with an Agilent Sonos 1.75–3.5 MHz scanner (Phillips Medical Ultrasound) with the use of harmonic imaging at study entry and at follow-up. All examinations were done by an experienced echocardiographer, blinded to NT-proBNP measurements. Left ventricular diameter was assessed by M-mode in the left parasternal view. EF was visually assessed. For quantification of left ventricular function, the shortening fraction and the EF according to Teichholz14,15 were calculated based on M-mode measurements. The maximal and mean aortic velocities were assessed by continuous-wave Doppler echocardiography from the apical or right parasternal view. In sinus rhythm, transaortic velocity was averaged over three cycles and in patients with atrial fibrillation over seven cycles. Maximum and mean pressure gradients were calculated using the built-in software. Severity of AS was graded according to the mean transvalvular pressure gradient (TPG) obtained echocardiographically. A mean TPG below 30 mmHg was considered mild AS (AS I), from 30 and 50 mmHg moderate AS (AS II), and above 50 mmHg severe AS (AS III). Severity of AR was assessed by colour Doppler echocardiography using the width of the regurgitation jet as previously described16 and graded into mild AR I (< 5 mm), moderate AR II (5–10 mm), and severe AR III (> 10 mm). LVM was calculated using the formula of Devereux and Reichek.17

NT-proBNP measurement

From all patients, blood samples were taken at study entry and at follow-up from an antecubital vein in gel-filled tubes. The specimens were centrifuged within 1 h and serum was frozen at –80°C until analysis. NT-proBNP was measured by an electrochemiluminescence-immunoassay (Elecys proBNP, Roche Diagnostics, Mannheim, Germany).

Statistics

Values for NT-proBNP are given as mean (AM) ± SEM. For group-wise statistical comparison of NT-proBNP values the Mann-Whitney test (two groups), the Kruskal-Wallis test (n groups), and the Wilcoxon rank (paired variables) test were used. For the analysis of the baseline characteristics of the patients, the t-test (two groups) or ANOVA (n groups) were used for continuous variables and the χ² test for categorial variables. Subgroup analysis of baseline characteristics (age, creatinine, body mass index (BMI), LVM, left ventricular end-diastolic diameter (LVM), and TPG) have been formally assessed by the use of Bonferroni’s test for multiple comparisons and by the use of the χ² test for the categorial variables frequency of atrial fibrillation and coronary artery disease (CAD). The correlation analysis of NT-proBNP to clinical parameters was performed by the use of the Spearman correlation coefficient. For all statistical analysis, the statistical software SPSS 10.0 for windows was used.

Results

A total of 168 patients were included: 109 patients with AS, 37 patients with AR, and 22 patients after previous AVR at least 12 months before inclusion. According to the definition, earlier mentioned 17 patients were classified as mild AS, 17 patients as moderate AS, and 75 patients as severe AS. AR was classified as mild AR in 20 patients, as moderate AR in 12 patients, and as severe AR in five patients. The detailed baseline characteristics of the patients are shown in Table 1. Patients were distributed equally with respect to gender. Patients with AS and after previous AVR (69 ± 10 and 69 ± 8 years, respectively; P = 0.98) were older as patients with AR (61 ± 12 years; AS vs. AR P = 0.002 and AR vs. AR P = 0.02), but there were no differences of age within the group of patients with AS of various degrees and within the group of patients with AR of various degrees. There was no difference in creatinine, BMI, and frequency of atrial fibrillation between the different subgroups. CAD, either a history of coronary artery bypass grafting (CABG), percutaneous intervention, acute myocardial infarction, or presence of relevant coronary artery stenosis at angiography was present in 49 patients. The frequency of CAD was not different in patients with AS or AR, but a history of CABG was more often present in patients after previous AVR.

LVM was increased in association to severity in AS and in AR, whereas LVDD was related to severity only in patients with AR, but not in patients with AS. There was no difference in mean TPG, LVM, and LVDD.
<table>
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<tr>
<th></th>
<th>AS I</th>
<th>AS II</th>
<th>AS III</th>
<th>AR I</th>
<th>AR II</th>
<th>AR III</th>
<th>Previous AVR</th>
<th>P-value</th>
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<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>17</td>
<td>75</td>
<td>20</td>
<td>12</td>
<td>5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Gender male, n (%)</td>
<td>11 (65)</td>
<td>9 (53)</td>
<td>39 (52)</td>
<td>11 (55)</td>
<td>8 (67)</td>
<td>4 (80)</td>
<td>5 (23)</td>
<td>0.38</td>
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<td>Surgical treatment, n (%)</td>
<td>0</td>
<td>8 (47)</td>
<td>64 (85)</td>
<td>1 (5)</td>
<td>8 (67)</td>
<td>5 (100)</td>
<td>0</td>
<td>&lt;0.01</td>
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<td>Age (years)</td>
<td>67.4 ± 10.9</td>
<td>69.8 ± 8.8</td>
<td>69.5 ± 10.7</td>
<td>61.1 ± 12.0</td>
<td>59.8 ± 12.5</td>
<td>65.0 ± 12.3</td>
<td>68.5 ± 8.3</td>
<td>0.01</td>
</tr>
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<td>Creatinine (mg/dL)</td>
<td>1.02 ± 0.21</td>
<td>0.99 ± 0.13</td>
<td>0.89 ± 0.21</td>
<td>0.86 ± 0.14</td>
<td>0.86 ± 0.24</td>
<td>0.91 ± 0.24</td>
<td>0.99 ± 0.27</td>
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<td>BMI (m²/kg)</td>
<td>28.7 ± 2.7</td>
<td>27.8 ± 3.2</td>
<td>27.3 ± 3.5</td>
<td>27.3 ± 3.5</td>
<td>24.7 ± 2.9</td>
<td>26.3 ± 2.4</td>
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<td>6 (8)</td>
<td>1 (5)</td>
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<td>0.23</td>
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<td>5</td>
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<td>11</td>
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<td>1</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>3</td>
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<td>5</td>
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<td>1</td>
<td>0.36</td>
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<td>LVM (g)</td>
<td>198 ± 50</td>
<td>230 ± 75</td>
<td>264 ± 71</td>
<td>224 ± 51</td>
<td>265 ± 93</td>
<td>349 ± 92</td>
<td>213 ± 80</td>
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<td>LVDD (mm)</td>
<td>50 ± 6</td>
<td>48 ± 6</td>
<td>50 ± 7</td>
<td>51 ± 5</td>
<td>53 ± 8</td>
<td>61 ± 6</td>
<td>49 ± 6</td>
<td>&lt;0.01</td>
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<td>TPG (mmHg)</td>
<td>17 ± 5</td>
<td>38 ± 6</td>
<td>62 ± 16</td>
<td>34 ± 8</td>
<td>29 ± 6</td>
<td>29 ± 10</td>
<td>31 ± 7</td>
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<td>Shortening fraction (%)</td>
<td>58 ± 13</td>
<td>58 ± 17</td>
<td>57 ± 13</td>
<td>62 ± 11</td>
<td>56 ± 9</td>
<td>54 ± 14</td>
<td>58 ± 10</td>
<td>0.834</td>
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<td>EF (%)</td>
<td>414 ± 127</td>
<td>1561 ± 636</td>
<td>2400 ± 382</td>
<td>186 ± 40</td>
<td>628 ± 301</td>
<td>2111 ± 1212</td>
<td>562 ± 190</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD. Frequencies are shown as absolute numbers and relative numbers in parenthesis. P-value is given for the comparison of all subgroups (n-independent samples).
between patients with mild AS and patients after previous AVR.

Out of 249 patients with baseline data, 168 patients personally attended the follow-up examination. From the 81 remaining patients, eight patients died during the follow-up period. For the remaining 73 patients, the reasons for not attending the follow-up visit are unknown. There were no differences between patients with and without follow-up regarding age (67 ± 11 vs. 68 ± 13 years, P = 0.607), creatinine (0.92 ± 0.21 vs. 0.94 ± 0.25 mg/dL, P = 0.504), left ventricular EF (57 ± 8 vs. 57 ± 7%, P = 0.691), LVM (246 ± 77 vs. 236 ± 75 g, P = 0.332), gender distribution (41 vs. 53% female, χ² = 3.19, P = 0.074), diagnosis (AS 65 vs. 62%; AR 22 vs. 25%; and previous AVR 13 vs. 14%; χ² = 0.351, P = 0.839), and NT-proBNP at baseline (1469 ± 199 vs. 1749 ± 391 pg/mL, P = 0.187).

**NT-proBNP at baseline**

In patients with AS and in patients with AR, NT-proBNP at baseline was elevated in all subgroups with an association to the degree of severity (Table 1) and to functional status (NYHA I 592 ± 133 pg/mL, NYHA II 888 ± 184 pg/mL, NYHA III 2245 ± 546 pg/mL, NYHA IV 4394 ± 199 pg/mL; P < 0.01). There was no difference of NT-proBNP in patients with mild AS and those after previous AVR (414 ± 127 vs. 562 ± 190 pg/mL, P = 0.46) (Figure 1). NT-proBNP was significantly higher in females (1926 ± 440 vs. 1147 ± 186 pg/mL, P = 0.03) and in patients with atrial fibrillation (4103 ± 1244 vs. 1283 ± 188 pg/mL, P < 0.01) and was positively correlated to age (ρ = 0.44, P < 0.01). No significant correlation of NT-proBNP to creatinine and BMI was found.

A total of 49 patients were asymptomatic (NYHA I). In this subgroup, patients with NT-proBNP values above the 75th percentile (617 pg/mL) had a higher LVM (283 ± 25 vs. 223 ± 12 g, P = 0.029) and tended to have a higher mean TPG (36 ± 6 vs. 27 ± 4 mmHg, P = 0.10).

Eighty-two patients were treated conservatively. NT-proBNP levels at baseline were lower in those patients when compared with 86 patients who were treated surgically (616 ± 120 vs. 2292 ± 353 pg/mL, P < 0.01).

**Change of NT-proBNP in association to treatment and clinical outcome**

In the total study group, a decrease of NT-proBNP from baseline to follow-up was present in 95 patients and in 73 patients NT-proBNP increased. The number of patients with a fall in NT-proBNP levels was significantly higher in surgically treated patients (65 vs. 21, χ² < 0.01) and accordingly the number of patients with an increase was higher among those who were treated conservatively (52 vs. 30, χ² < 0.01) (Figure 2A and B).

Mean values of NT-proBNP and LVM increased in conservatively treated patients but decreased in surgically treated patients (Table 2). Changes of NT-proBNP were related to clinical improvement as assessed by a change in functional class (NYHA-class) in surgically treated patients. Surgically treated patients, who did not improve clinically, had lower NT-proBNP levels at baseline without a change at follow up, whereas patients who improved clinically after surgery had higher initial NT-proBNP values with a significant decrease at follow-up (Figure 3). In 58 of the 82 conservatively treated patients, a progression of aortic valve disease, either an increase in NYHA-class, pressure gradient in AS patients or left ventricular diameter in AR patients, was detectable. NT-proBNP values increased in patients with progression (673 ± 151 pg/mL at baseline vs. 1449 ± 607 pg/mL at follow-up, P = 0.018) but remained unchanged in patients without progression.

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![Figure 1](image-url)  
**Figure 1** NT-proBNP at study entry (baseline) in patients with aortic valve disease in relation to disease severity. Values are shown as mean ± SEM.
In the subgroup of patients with AS, valve replacement had been performed in 72 patients and 37 patients had been treated conservatively. There was no significant change of NT-proBNP and the mean TPG, but a significant increase in L VM from baseline to follow-up in conservatively treated patients. In surgically treated patients, NT-proBNP, TPG mean, and L VM decreased significantly (Table 2). However, in a subgroup of patients (n = 19) without improvement in clinical symptoms after surgery, changes in NT-proBNP and L VM did not reach statistical significance even though TPG mean decreased significantly (NT-proBNP 1086 ± 204 pg/mL vs. 964 ± 186 pg/mL, \( P = 0.29 \); LVM 251 ± 17 vs. 231 ± 18 g, \( P = 0.22 \); TPG mean 58 ± 4 vs. 18 ± 2 mmHg, \( P < 0.01 \)). Changes in NT-proBNP, logarithmically transformed, were positively correlated to changes in mean TPG \( (r = 0.44, P < 0.01) \) (Figure 4) and were correlated to changes in LVM \( (r = 0.27, P = 0.017, n = 80) \).

For surgically treated patients, the 90th percentile for NT-proBNP at baseline was 7100 pg/mL. If those patients \( (n = 8) \) with NT-proBNP values >7100 pg/mL were excluded from the analysis, there was still a significant drop in NT-proBNP from baseline to follow-up from 1445 ± 189 to 715 ± 110 pg/mL, \( P < 0.001 \). Patients with NT-proBNP values above the 90th percentile tended to be more often female (six females, \( \chi^2 = 3.3, P = 0.079 \)).

### Table 2  NT-proBNP, LVM, TPG mean, and LVDD with respect to treatment

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Surgical</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>All patients</td>
<td>n</td>
<td>82</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>616 ± 120</td>
<td>1155 ± 432</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>219 ± 8</td>
<td>249 ± 8</td>
</tr>
<tr>
<td>Patients with AS</td>
<td>n</td>
<td>37</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>937 ± 237</td>
<td>1125 ± 234</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>216 ± 11</td>
<td>260 ± 14</td>
</tr>
<tr>
<td>TPG mean (mmHg)</td>
<td>33 ± 3</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>Patients with AR</td>
<td>n</td>
<td>23</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>188 ± 36</td>
<td>319 ± 113</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>230 ± 13</td>
<td>239 ± 13</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>52 ± 1</td>
<td>53 ± 1</td>
</tr>
</tbody>
</table>

Figure 2  NT-proBNP at study entry (baseline) and at follow-up in patients with aortic valve disease (A) who were treated conservatively and (B) who were treated surgically.
P = 0.07) and had a trend towards higher values for creatinine (1.07 ± 0.25 vs. 0.89 ± 0.19 mg/dL, P = 0.064) and a lower EF (53 ± 8 vs. 57 ± 6%, P = 0.08).

Twenty-three patients with AR were treated conservatively and 14 patients underwent surgery. In conservatively treated patients, there was no significant change of NT-proBNP, LVM, and LVDD, even though a tendency towards an increase in NT-proBNP was present. In contrast, NT-proBNP, LVM, and LVDD decreased significantly after surgery (Table 2).

There was no change of the mean TPG (17 ± 1 mmHg at baseline vs. 18 ± 1 mmHg at follow-up) and of NT-proBNP (562 ± 190 pg/mL at baseline vs. 558 ± 138 pg/mL at follow-up, P = 0.106) during the follow-up period in patients after previous AVR.

**Association of NT-proBNP to size and type of valve prosthesis**

In 86 patients, valve replacement was performed. A bioprosthesis was implanted in 49 patients and a mechanical prosthesis in 37 patients. There was no difference in size between the two different types of valve prosthesis, but age, mean TPG, and NT-proBNP were higher in patients with a bioprosthesis (Table 3). However, if we corrected for age by excluding young patients from the mechanical valve group and old patients from the bioprosthesis group, there was no significant difference in NT-proBNP values (bioprosthesis 477 ± 191 pg/mL vs. mechanical valve 460 ± 169 pg/mL, P = 0.902) of the remaining 24 patients in each group (bioprosthesis 69 ± 6 years vs. mechanical valve 66 ± 4 years, P = 0.146). The implanted prosthetic heart valves had a size ranging from 21 to 29 mm with a median of 23 mm. Dividing the patients according to median of the prosthetic valve size, patients with smaller sized valves had a higher mean TPG and a trend towards higher NT-proBNP values (Table 3).

**Discussion**

The main determinant for severity of aortic valve disease is the presence of clinical symptoms in combination with echocardiographic or angiographic findings. At present, biomarkers are not routinely used for diagnosis and evaluation of patients with aortic valve disease. The data of the present study demonstrates that NT-proBNP, a biomarker indicating neurohormonal activation, is elevated in patients with aortic valve disease linked to severity of disease and to clinical symptoms. Furthermore, we could show that NT-proBNP is related...
to disease progression in conservatively treated patients and to clinical success of surgical therapy.

These findings are in accordance with the results of previously published studies showing a correlation of either BNP or NT-proBNP to the aortic valve area,\(^5\) the mean TPG,\(^4,19\) and functional status in patients with AS,\(^6,20\) and to functional status in patients with AR.\(^9\) The consistent findings of these studies, in addition to the data of the present study, underline the usefulness of NT-proBNP as a biochemical marker for the severity of aortic valve disease.

Values for NT-proBNP, mean TPG, and LVM in patients after previous AVR were lower as those for patients with severe aortic valve disease, but identical to values of patients with mild AS, suggesting that a fall of NT-proBNP levels has occurred after valve replacement. Furthermore and even more importantly, we assessed longitudinal data demonstrating a significant drop of NT-proBNP levels in patients with severe AS and with severe AR after valve replacement. The decrease of NT-proBNP in surgically treated patients was linked to an improvement in clinical symptoms. In contrast, the majority of conservatively treated patients had an increase of NT-proBNP at follow-up, which was related to a progression of valve disease.

In two recently published studies, an independent predictive value of BNP and NT-proBNP for prognosis of patients with severe AS undergoing valve replacement has been reported, raising the question whether neurohormones might be helpful for risk stratification and deciding on the optimal timing for valve replacement.\(^8,20\) The data of our study adds important information to this question, because this is the first longitudinal study showing a relation of NT-proBNP to disease progression. Therefore, our data suggest that serial assessment of NT-proBNP could contribute to therapeutical decision making. However, the exact diagnostic role of NT-proBNP and the clinical cut-off level should be elucidated in further studies. The question of an optimal decision limit for NT-proBNP and what constitutes a meaningful change of NT-proBNP in serial testing remains an open issue.

The results of elevated NT-proBNP depending on disease severity and changes of NT-proBNP depending on the kind of therapy were found to be similar in patients with AS and with AR. Either type of valve disease leads to an enhancement of left ventricular wall stress caused by either pressure overload in AS or volume overload in AR.

Differences with regard to the TPG and haemodynamic performance between various types of prosthetic heart valves and of valves with different size are described in the literature.\(^21,22\) In accordance with these previous reports we found higher pressure gradients in patients with a smaller sized prosthetic valve and in patients with a bioprosthesis. Even though NT-proBNP levels were higher in patients with bioprostheses, this effect may be explained by the higher age of these patients and cannot be correlated to haemodynamic differences of the valve types. However, there was a trend towards higher NT-proBNP values in patients with smaller sized mechanical valves, which was independent of age.

Patients who did not have a clinical benefit from surgery were in lower NYHA-class at baseline and had a tendency towards lower levels of NT-proBNP at study entry. This observation suggests that valve replacement in patients with low NT-proBNP might not be indicated, especially if patients are only mildly symptomatic. These findings raise the question whether NT-proBNP could be a useful biochemical marker for the indication of aortic valve surgery in addition to clinical assessment and echocardiography. However, further studies are warranted to confirm present data and particularly to assess the prognostic value of BNPs in patients with aortic valve disease.

**Conclusions**

NT-proBNP is elevated in patients with aortic valve disease (AS and AR) and decreases after successful surgical treatment linked to an improvement in clinical symptoms, but increases in conservatively treated patients related to disease progression. This supports the value...
of NT-proBNP as a biochemical marker assessing myocardial stress due to aortic valve disease. Accordingly, NT-proBNP seems to be a suitable biomarker for the evaluation and monitoring of patients with aortic valve disease in addition to clinical and echocardiographic findings.

Limitations

Even though this investigation included a relatively large number of patients when compared with previously published studies, it was of an exploratory nature without any pre-fixed hypotheses on the predictive value of NT-proBNP to be proved or disapproved. The prognostic value of NT-proBNP has to be confirmed in a separate trial. We need to acknowledge that the follow-up rate of 67% (168 out of 249 patients) in this study was low, because we included only patients who personally attended a follow-up examination. This fact might account for a selection bias. However, clinical characteristics and NT-proBNP values of patients with and without follow-up were not different. The functional status was assessed by experienced cardiologists according to the NYHA classification, but we did not incorporate a more objective method for the assessment of cardiopulmonary exercise capacity such as ergospirometry. Even though this would have been desirable, assessment of NYHA class reflects daily routine and is the basis for the indication of valve replacement. Assessment of NT-proBNP at baseline and at follow-up was under the standard medication of the patients, including beta-blocker, ACE-inhibitors, and diuretics. For all of these drugs, an influence on natriuretic peptide levels is known and an impact of NT-proBNP in the present study has to be considered.

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References