Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide

Pascal Lima,*, Jean Luc Monin, Mehran Monchi, Jérome Garot, Agnès Pasquet, Luc Hittinger, Jean Louis Vanoverschelde, Alain Carayon, Pascal Gueret

Department of Cardiology, Henri-Mondor Hospital, Créteil, Assistance Publique Hôpitaux de Paris, 51 Avenue De Lattre De Tassigny, 94010 Créteil, France
Department of Intensive Care Medicine, Institut Jacques Cartier, Massy, France
Department of Biochemistry, Pitié Salpetrière Hospital, Paris, France
Department of Cardiology, Saint Luc Hospital, Brussels, Belgium

Received 31 May 2004; revised 28 September 2004; accepted 30 September 2004

Aims B-type Natriuretic Peptide (BNP) is activated in patients with severe, symptomatic aortic stenosis (AS), but the prognostic value of BNP in this setting has not been extensively studied. This study aimed to assess the prognostic value of the BNP level in symptomatic and asymptomatic patients with severe AS.

Methods Seventy consecutive patients referred to our echocardiography laboratory for severe AS with preserved left ventricular function were prospectively enrolled (40 men, median age 74 years [62–82]; aortic valve area 0.7 cm² [0.6–0.8]; transaortic gradient 48 mmHg [38–60], and left ventricular fractional shortening 38% [32–43]). C-terminal BNP serum level at enrolment was evaluated against baseline functional and echocardiographic parameters as well as clinical outcome.

Results BNP level was elevated in the presence of symptoms and increased with NYHA functional class. BNP serum level >66 pg/ml detected symptomatic patients with a sensitivity, specificity and accuracy of 84%, 82% and 84%, respectively. In symptomatic and asymptomatic patients, BNP level was a strong independent predictor for cardiovascular death by multivariable analysis adjusted to age and NYHA functional class.

Conclusions BNP serum level allows to differentiate symptomatic from asymptomatic patients with severe AS. BNP is an independent predictor of outcome in these patients and may be helpful for risk stratification.

Introduction

According to Current Practice Guidelines, timing for valve replacement in severe aortic stenosis (AS) is largely based on the presence of symptoms. Conversely, the truly
asymptomatic status is often difficult to assess in an individual patient. Exercise testing is recommended in case of severe AS with equivocal symptoms, but a recent survey of current practice has demonstrated that this test is rarely performed in the setting of AS. Therefore, new haemodynamic or biological indices are needed to better assess functional status and to predict outcome in patients with severe AS. B-type Natriuretic Peptide (BNP) is secreted predominantly from the cardiac ventricles in response to increased wall stress. BNPs level is elevated in patients with left ventricular dysfunction and correlates to prognosis. Previous reports have shown that BNP levels are correlated to left ventricular mass in AS patients and to end-systolic wall stress or functional class. However, the prognostic value of BNP levels has not been extensively studied in patients with AS. The goal of this prospective study was to assess the prognostic value of BNP serum levels in patients with severe AS and preserved left ventricular systolic function.

Methods

Patients

Between July 2001 and June 2002, 70 consecutive patients referred to our echocardiography laboratory for evaluation of AS were prospectively enrolled. Inclusion criteria were: isolated severe AS (aortic valve area (AVA) <1 cm²) with normal left ventricular systolic function, defined as LV fractional shortening ≥30% without segmental wall motion abnormality. Patients with more than mild aortic regurgitation or other significant valvular lesion were excluded. The protocol was approved by our Institution Review board, and all patients gave informed consent before the investigations.

Doppler echocardiography

A complete Doppler echocardiographic examination was performed with commercially available equipment (Sequoia C 256, Siemens/ Acuson (Mountain view, California)). Analysis was performed online by a single experienced echocardiographer blinded to the patients’ clinical history or natriuretic peptide level. Left ventricular outflow track flow velocity was recorded in the apical view. Stroke volume was calculated according to standard formulae. Transaortic flow was recorded with continuous wave Doppler using a multi-window approach, transaortic gradients were calculated using the simplified Bernoulli equation. AVA was calculated by the continuity equation. For each Doppler measurement, high quality tracings were obtained and three to five cycles were averaged, avoiding post-extrasystolic beats.

Clinical assessment and endpoints

For each patient, clinical information about functional status (NYHA class) and medical history was collected by a standard questionnaire at study entry. Patients were considered as asymptomatic if they were free from shortness of breath, angina and syncope. Information at follow-up was obtained by direct patient interview, or from the referring physician. Therapeutic decision for each patient was taken by the referring physicians, blinded to natriuretic peptide value and according to current practice guidelines. The clinical endpoint for outcome was cardiovascular death defined by sudden death, death from heart failure, or post-operative death.

Natriuretic peptide measurements

Venous blood samples for BNP levels were drawn from an antecubital vein at the first clinical evaluation and after 30 min of supine rest, into chilled EDTA tubes, placed immediately on ice, and centrifuged at 2000g at 4 °C for 15 min. Separated plasma samples were frozen at −20 °C until radioimmunoassay (Shionoria BNP). The inter- and intra-assay variations were 11% and 8%, respectively. The assay detection limit was 1 pg/ml.

Statistical analysis

The sample size was not statistically calculated when the study was designed because no data about the relationship between BNP levels and prognosis in severe AS was published before. Continuous data are presented as median values and corresponding quartiles (25th and 75th percentiles). Dichotomous data are presented as percentages. Spearman’s correlation co-efficient was used to assess the association between BNP levels and continuous echocardiographic continuous variables. For logistic regression and Cox models, the natural logarithm of BNP value was used because its distribution was skewed. Univariate analyses were performed using non-parametric statistical tests. The χ² test or the Fisher’s exact test was applied for dichotomous and categorical data. To compare numerical data between two or several groups, the Mann–Whitney test, the Kruskal–Wallis test or the trend test were used when appropriate. Univariate analysis included the eight variables listed in Table 1. The logistic model was used to predict patients with symptomatic AS. Variables with

| Table 1 | Clinical and echocardiographic characteristics of symptomatic and asymptomatic patients with AS. EDST for end-diastolic septum thickness, others abbreviations as in text |
|----------------------|---------------------|---------------------|---------------------|---------------------|
|                      | All patients (n = 70) | Asymptomatic (n = 17) | Symptomatic (n = 53) | p-Value |
| Age (years)a          | 74 [62–82]          | 74 [63–79]          | 74 [68–82]          | 0.42 |
| Female sex            | 30 (43%)            | 5 (23%)             | 25 (47%)            | 0.2 |
| Mean gradient (mm Hg)a| 48 [38–60]          | 43 [29–55]          | 48 [39–62]          | 0.32 |
| Peak gradient (mm Hg)a| 79 [60–106]         | 70 [47–87]          | 81 [64–109]         | 0.08 |
| AVA (cm²)a            | 0.70 [0.60–0.80]    | 0.90 [0.70–1.0]     | 0.70 [0.60–0.80]    | 0.008 |
| LV fractional shortening (%)a | 38 [32–43] | 37 ± 7 | 39 ± 9 | 0.6 |
| BNP (pg/ml)a          | 74 [66–82]          | 39 [14–63]          | 132 [75–280]        | <0.0001 |

a Values expressed as median [quartiles].
p < 0.1 were entered into multivariable logistic models and were selected by a backward procedure. The receiver-operating characteristic (ROC) curve was determined to evaluate the diagnostic performance of BNP and AVA to detect symptomatic patients. Optimal cut-off points for the diagnosis of symptomatic AS were chosen when the sensitivity and specificity were maximized. Survival curves according to BNP levels were established by the Kaplan–Meier estimation method. Univariate analysis of the predictive factors of cardiovascular death was performed using the log-rank test for qualitative variables and Cox proportional hazards model for quantitative variables. For Cox models, Schoenfeld residuals were used to test for non-proportionality, and non-proportionality was assumed when p < 0.1. For continuous variables, the linearity assumption was assessed by plotting the continuous independent variable against the dependent variable, using the LOWESS smoothing function, with locally weighted least squares. Because of the low event rate in our study, univariate and multivariable analysis of survival included only known risk factor (NYHA functional class, age) and BNP values. Two-tailed p-values < 0.05 were considered statistically significant. Analyses were performed using STATA software (Version 7.0 for windows, Stata Corp., College Station, TX, USA).

Results

Patients

The baseline characteristics of the 70 consecutive patients with severe AS are reported in Table 1. The cause of AS was degenerative in 65 patients, bicuspid aortic valve in four and rheumatic disease in one patient. Associated coronary artery disease, hypertension and diabetes mellitus were present in 6, 31 and 22 patients, respectively. The cardiac rhythm was sinus in 68, atrial fibrillation in 1, and paced in one patient. At study entry, 17/70 (24%) patients were asymptomatic and 53/70 (76%) were symptomatic. Dyspnea was present in 49/70 patients (NYHA class II = 34, III = 15), angina, syncope were associated in five and three patients respectively. Isolated angina was present in four patients.

BNP and functional status

For the population as a whole, BNP serum level was 97 [58–228] pg/ml. The clinical characteristics, BNP levels and echocardiographic data of symptomatic and asymptomatic patients shown in Table 1. Symptomatic patients had significantly lower AVA and higher BNP levels. Other characteristics including age, sex, pressure gradients and LV parameters were comparable. BNP levels increased with NYHA functional class (trend test p < 0.01, Fig. 1). Isolated angina was not associated with elevated BNP level (80 [68–119] pg/ml vs. 109 [55–69] pg/ml in patients without angina, p = 0.41).

The multivariable logistic regression model including BNP levels and AVA revealed that only BNP values were predictive of symptomatic aortic stenosis (OR = 3.4 [1.6–7.3], p < 0.01). Sensitivity and specificity of BNP and AVA for the detection of symptomatic patients was assessed by ROC curve analysis (Fig. 2). Optimal cut-off value of BNP to detect the presence of symptoms was 66 pg/ml with a sensitivity, specificity and accuracy of 84%, 82% and 84%, respectively. Area under the curve (AUC) was 0.86. In contrast, AVA was poorly predictive of symptoms (AUC = 0.28).

BNP and echocardiographic data

There was a weak but significant correlation between BNP and AVA, and between BNP and mean and peak trans-aortic pressure gradients (r = –0.49, p < 0.0001, r = 0.34, p = 0.004 and r = 0.33, p < 0.05, respectively). No correlation was found with LV size or time velocity integral of the outflow tract. BNP levels did not differ according to age, sex and medical history.

BNP and outcome

Follow-up data were available for all patients at a median interval of 308 days [range, 11–472]. Of the 17 asymptomatic patients, four developed symptoms and underwent AVR and one patient with critical AS (AVA...
0.5 cm²) and high BNP level (185 pg/ml) died from sudden death. Among the whole population, AVR was performed in 43 patients because of symptomatic functional status (39 initially symptomatic and four becoming symptomatic during the study).

Ten patients died from cardiovascular death and one because of cancer. Their clinical, echocardiographic characteristics and BNP levels are reported in Table 2. Univariate analysis showed that log BNP and NYHA class III were significantly associated to poor outcome, while age was of borderline significance ($p = 0.1$). By multivariable analysis (including log BNP, age, and NYHA class III), only BNP levels remained significantly associated to mortality (Table 3). Kaplan–Meier survival curves according to BNP levels are shown in Fig. 3.

Discussion

The main findings of this study are: (1) BNP serum levels are highly accurate to separate symptomatic from asymptomatic patients with severe AS, with significant differences among patients according to NYHA class. (2) High BNP levels were significantly associated with poor outcome in asymptomatic and symptomatic AS. By multivariable analysis, BNP serum level was the only independent predictor of cardiovascular death.

Valve replacement in asymptomatic AS

The decision to operate asymptomatic patients with severe AS remains a source of debate. The main reason for this is an operative risk for AVR in the most recent series of 3–4%,3,19 which is higher than the spontaneous risk in truly asymptomatic patients.1 In this setting, exercise testing can yield important information for clinical decision making. However, the results of a recent international Survey of current practice in Europe revealed that less than 6% of patients with asymptomatic AS undergo exercise testing.1 The inter-individual variability of LV adaptation to pressure overload is partly responsible for the poor utility of haemodynamic parameters for therapeutic decision making in asymptomatic patients.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>BNP values, clinical and echocardiographic characteristics of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>AVR</td>
</tr>
<tr>
<td>1</td>
<td>Heart F Comorbidities</td>
</tr>
<tr>
<td>2</td>
<td>Heart F Refused</td>
</tr>
<tr>
<td>3</td>
<td>Heart F Refused</td>
</tr>
<tr>
<td>4</td>
<td>S Death Awaiting AVR</td>
</tr>
<tr>
<td>5</td>
<td>S Death Asymptomatic</td>
</tr>
<tr>
<td>6</td>
<td>S Death Awaiting AVR</td>
</tr>
<tr>
<td>7</td>
<td>Post-Op</td>
</tr>
<tr>
<td>8</td>
<td>Post-Op</td>
</tr>
<tr>
<td>9</td>
<td>Post-Op</td>
</tr>
<tr>
<td>10</td>
<td>Post-Op</td>
</tr>
<tr>
<td>11</td>
<td>Cancer Co-morbidities</td>
</tr>
</tbody>
</table>

Reasons for medical treatment in symptomatic patients were reported in the column AVR (-). Heart F, heart failure; S Death, sudden death; Post-Op, post-operative death. $V_{max}$, maximum trans aortic velocity.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Univariate and multivariable analysis for predictors of survival according to Cox models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
</tr>
<tr>
<td></td>
<td>HR [95% CI]</td>
</tr>
<tr>
<td>Log BNP</td>
<td>2.9 [1.4–6.1]</td>
</tr>
<tr>
<td>NYHA III</td>
<td>4.0 [1.1–13.8]</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 [0.9–1.1]</td>
</tr>
</tbody>
</table>

Fig. 3 Kaplan–Meier survival curves for patients with median BNP value ≤97 (n = 35) and >97 pg/ml (n = 35).
with severe AS. On the other hand, the risk of sudden death and progressive irreversible LV dysfunction exist in asymptomatic patients. Thus, new haemodynamic and/or biological markers of AS severity are needed to predict outcome and risk stratify these patients.

**BNP and functional status**

Our results show that the presence of symptoms is associated with higher BNP levels and lower AVA compared to asymptomatic patients. These data are supported by Gerber et al., who reported an increase in natriuretic peptide levels with NYHA class. We found that AVA was poorly related to the presence of symptoms. In contrast, a BNP serum level >66 pg/ml has an accuracy of 84% to differentiate symptomatic from asymptomatic patients. This cut-off point is lower than the 100 pg/ml value reported by Maisel et al. to identify congestive heart failure as the cause of dyspnoea in an emergency department setting. Two reasons could explain this difference: first, radioimmunoassay provides a lower BNP value compared to immuno-fluorescence assay. Second, patients with isolated angina may have lower BNP values compared to patients with dyspnoea, because of lower LV filling pressures.  

**BNP and outcome**

In experimental and clinical studies, the secretion of BNP is mainly stimulated by LV wall stress and seems to be directly involved in LV remodeling. In the present study, BNP level was higher in asymptomatic with adverse outcome. It can be hypothesised that, either the BNP level better reflects functional status, or that BNP is a more sensitive marker of early LV dysfunction than clinical functional status. In patients with AS, the close correlation between BNP serum level and LV end-systolic wall stress reported by Ikeda et al. is in favour of the second hypothesis. Moreover, among symptomatic and asymptomatic patients, we report that BNP levels are independently associated with mortality. The mortality rate increased in proportion to BNP levels. Thus, this continuous risk measurement provided by BNP reinforces the concept that BNP is a marker of LV dysfunction in the complex adaptative process to AS. As suggested by Berger-Klein et al., serial BNP measurements may be highly informative for identification of patients at risk for serious cardiovascular adverse events. It may also help therapeutic strategy to decide the optimal timing for AVR before the onset of symptoms. This was further supported by Berendes et al. who reported a significant association between survival after cardiac surgery and pre-operative BNP level. Lastly, the occurrence of sudden death without preceding symptoms was rare in our study and was observed in one patient who had critical AS and high serum BNP level.

**Study limitations**

Despite a standard questionnaire, the functional status was not objectively assessed by exercise testing in all patients, mainly because most patients were symptomatic. The impact of associated coronary artery disease was not evaluated because medically treated patients did not undergo systematic coronary angiography. BNP measurements were not systematically repeated during the follow-up period, and therefore the prognostic value of serial BNP changes could not be assessed, particularly in asymptomatic patients. Finally, the prognostic value of BNP has to be confirmed in the asymptomatic subgroup of patients in a larger population.

**Conclusion**

In patients with severe aortic stenosis and preserved left ventricular function, a BNP serum level >66 pg/ml is accurate to differentiate symptomatic from asymptomatic patients. In these patients, BNP serum level is a strong predictor for cardiovascular death. The assessment of BNP serum level is a simple and reproducible test that could be used in complement, or as an alternative to, exercise testing in patients with severe AS and equivocal symptoms. Finally, BNP serum level may be helpful for risk stratification in asymptomatic patients with severe AS.

**References**


