Increased Plasma Natriuretic Peptide Levels Reflect Symptom Onset in Aortic Stenosis

Ivor L. Gerber, MB, ChB; Ralph A.H. Stewart, MD; Malcolm E. Legget, MB, ChB; Teena M. West, MSc; Renelle L. French; Timothy M. Sutton, MB, ChB; Timothy G. Yandle, PhD; John K. French, MB, PhD; A. Mark Richards, MD, DSc; Harvey D. White, MB, DSc

Background—The onset of symptoms is a critical point in the natural history of aortic stenosis and the cardinal indication for valve replacement. This study assessed the associations between natriuretic peptide levels, disease severity, and cardiac symptoms in aortic stenosis.

Methods and Results—Seventy-four patients with isolated aortic stenosis underwent independent assessment of symptoms, transthoracic echocardiography, and measurement of plasma levels of atrial natriuretic peptide, brain natriuretic peptide (BNP), and N-BNP. Natriuretic peptide levels were also measured in 100 clinically normal control subjects. The aortic valve area was smaller in symptomatic patients (n=45) than in asymptomatic patients (n=29; mean, 0.71±0.23 cm² and 0.99±0.31 cm², respectively; P<0.0001). Plasma natriuretic peptide levels were higher in symptomatic patients than in asymptomatic patients (for N-BNP: median, 112 versus 33 pmol/L; interquartile range, 70 to 193 versus 16 to 58 pmol/L, respectively; P=0.0002). After adjustment for age, sex, serum creatinine, aortic valve area, and left ventricular ejection fraction, N-BNP levels were 1.74 times higher (95% confidence interval, 1.12 to 2.69) for symptomatic than asymptomatic patients with aortic stenosis (P=0.014). Natriuretic peptide levels increased with the New York Heart Association class (for N-BNP median values were 13, 34, 105, and 202 pmol/L for normal control subjects, class I, class II, and class III/IV patients, respectively; interquartile ranges for the same patients were 8 to 21, 16 to 58, 57 to 159, and 87 to 394 pmol/L; P<0.0001). Similar associations were observed for BNP and atrial natriuretic peptide.

Conclusions—Plasma natriuretic peptide levels are elevated in symptomatic patients with aortic stenosis. Measurement of natriuretic peptides may complement clinical and echocardiographic evaluation of patients with aortic stenosis. (Circulation. 2003;107:1884-1890.)

Key Words: atrial natriuretic factor • echocardiography • natriuretic peptides • stenosis • valves

The natural history of aortic stenosis in adults includes a prolonged asymptomatic period during which morbidity and mortality are very low.1,2 Symptom onset signals a dramatic change in outlook and, after the development of angina, syncope, or heart failure, average survival with medical therapy is <3 years.3,4 Although the clinical outcome is different in symptomatic compared with asymptomatic patients, there are wide overlaps in hemodynamic and echocardiographic measures of severity between these patient groups.5 According to current American College of Cardiology/American Heart Association guidelines, no single clinical, hemodynamic, or echocardiographic measure has been adopted as a class I recommendation for valve replacement in the absence of symptoms in patients with isolated aortic stenosis.6

In many patients, the development of symptoms is clear, but in others, symptoms are difficult to assess because of inactivity or under-reporting. In some patients, it may also be unclear whether symptoms are related to the aortic stenosis. A noninvasive marker of early cardiac decompensation would therefore be helpful in monitoring disease progression in patients with aortic stenosis.

The natriuretic peptides are endogenous cardiac hormones that include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and its aminoterminal portion, N-BNP.7–9 Natriuretic peptide levels correlate with the New York Heart Association (NYHA) symptom class and left ventricular (LV) function, are independently prognostic of cardiovascular outcomes,10 and are strong, independent predictors of sudden death in patients with cardiac failure.11 Furthermore, they aid in discriminating between cardiac and noncardiac dyspnea leading to hospital admission.12 Although plasma natriuretic peptide levels have been shown to be related to disease severity in aortic stenosis,13–15 previous studies have not evaluated the association between natriuretic peptide levels and symptoms in aortic stenosis. In the present study, we
evaluated natriuretic peptide levels in patients with aortic stenosis as a potential marker of disease severity and the presence of symptoms.

**Methods**

**Patients**

Seventy-four patients who had isolated aortic stenosis assessed at Green Lane Hospital (Auckland, New Zealand) between January 2001 and November 2001 and with a peak aortic velocity of ≥2.5 m/s were enrolled in the study. The exclusion criteria included myocardial infarction within 6 months, regional wall motion abnormalities on echocardiography, prior cardiac surgery, more than mild mitral valve disease or aortic regurgitation, a plasma creatinine level >0.16 mmol/L, and known severe respiratory disease (forced expiratory volume in 1 s <1 L). The study protocol was approved by the regional ethics committees, and all patients gave written informed consent.

**Clinical Assessment**

The presence or absence of symptoms was assessed by 2 independent cardiology specialists blinded to the patients’ natriuretic peptide levels and echocardiographic results. Patients were judged symptomatic if they had a history of symptoms of heart failure (NYHA class ≥II) and/or angina (Canadian Cardiovascular Society class ≥1) and/or exertional presyncope or syncope considered due to aortic stenosis.

**Echocardiographic Data**

Echocardiographic data were obtained with the use of a Hewlett Packard 5500 Sonos ultrasound system. All patients underwent comprehensive examination including M-mode, 2D, and Doppler echocardiography. Analysis was performed off-line by a single experienced echocardiographer blinded to the patients’ symptom status, previous echocardiographic results, and natriuretic peptide levels. Measurements were made according to American Society of Echocardiography guidelines16 and averaged from 3 to 5 cardiac cycles. The peak aortic velocity was recorded using continuous-wave Doppler from the window yielding the highest-velocity signal. The mean aortic valve gradient was obtained by tracing the continuous Doppler from the window yielding the highest-velocity signal. The peak aortic velocity was measured in patients with color Doppler evidence of tricuspid regurgitation, and right ventricular systolic pressure was calculated as follows:

\[
\text{Systolic Pressure} = 4 \times \text{Peak Aortic Velocity}^2 + C
\]

**Measurement of Natriuretic Peptide Levels**

Venous blood samples were taken with the patient resting quietly while semirecumbent. Samples were taken into chilled EDTA tubes, placed immediately on ice, and centrifuged within 20 minutes at −4°C. The plasma was stored at −80°C before being assayed for N-BNP, BNP, and ANP using established radioimmunoassays.17 The within-assay coefficients of variation for the natriuretic peptides were 2% for ANP, 5.2% for BNP, and 3.5% for N-BNP >200 pmol/L, 3.9% for N-BNP 50 to 200 pmol/L, and 11.6% for N-BNP <50 pmol/L.

**Statistical Analysis**

When the results for N-BNP, BNP, and ANP were similar, the results for N-BNP only are given to simplify presentation. Comparisons between groups for continuous variables were made using t tests or one-way ANOVA where appropriate, and the \( \chi^2 \) test was used for categorical variables. Pearson’s correlation coefficient was used to assess the association between natriuretic peptide levels and echocardiographic variables. Two-way ANOVA was used to compare the mean natriuretic peptide levels within each NYHA class. Analyses of covariance were used to assess natriuretic peptide levels in symptomatic and asymptomatic patients after adjustment for the confounders. The homogeneity of slopes was assessed by fitting an interaction term. Because the distribution of the natriuretic peptide levels was positively skewed, the natural log transformation was used, and all analyses used log-transformed levels unless otherwise specified. The areas under the receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of natriuretic peptide and echocardiographic variables. The cutoffs were chosen when the sensitivity and specificity were maximized. Linear regression models were fit to the control data to provide normal natriuretic peptide ranges for a given sex and age. Model fits for the natural log-transformed levels were assessed by plotting residuals. The 95% confidence intervals (CI) for the ratio of the geometric means between the groups (symptomatic/asymptomatic) are reported for each peptide. A Stata 6.0 statistical software package was used for ROC analysis, and SAS release 8.0 software was used for the remaining analyses.

**Results**

**Baseline Characteristics of the Patients**

Of the 74 patients with aortic stenosis, 41 (55%) were male and 33 (45%) were female; they had a mean age of 69.2 ± 12.5 years. There were 100 normal control subjects, of whom 41 were male and 59 were female (mean age, 55 ± 11 years). The cause of the aortic stenosis was rheumatic in one, bicuspid valve in 15, and degenerative calcification in 58 patients. The cardiac rhythm was sinus in 69, atrial fibrillation in 4, and paced in one patient. Twenty-nine patients (39%) were asymptomatic and 45 (61%) were symptomatic.

**Association With Echocardiographic Measures**

Log-transformed BNP, N-BNP, and ANP correlated with the aortic valve area (correlation coefficient \( r = -0.55, -0.57, \) and \(-0.55\) respectively), peak aortic velocity (\( r = 0.33, 0.35, \) and \(0.38\) respectively), mean aortic gradient (\( r = 0.36, 0.37, \) and \(0.38\) respectively), LV mass index (\( r = 0.62, 0.59, \) and \(0.46\) respectively), LV end-diastolic volume index (\( r = 0.51, 0.41, \) and \(0.47\) respectively), LV end-systolic volume index (\( r = 0.54, 0.45, \) and \(0.48\) respectively), LV ejection fraction (\( r = -0.48, -0.42, \) and \(-0.39\) respectively), LV systolic circumferential wall stress (\( r = 0.29, 0.26, \) and \(0.37\) respectively), right ventricular systolic pressure (\( r = 0.60, 0.59, \) and \(0.63\) respectively), left atrial diameter (\( r = 0.30, 0.34, \) and \(0.35\) respectively) and LV end-diastolic posterior wall thickness (\( r = 0.37, 0.38, \) and \(0.29\) respectively; \( P < 0.05 \) for all comparisons).

Natriuretic peptide levels were similar in patients with normal diastolic function (\( n = 24; \) N-BNP: median, 59 pmol/L; interquartile range, 24 to 136 pmol/L), an impaired relaxation pattern (\( n = 31; \) N-BNP: median, 58 pmol/L; interquartile range, 35 to 97 pmol/L) or a pseudonormal pattern (\( n = 5; \) N-BNP: median, 70 pmol/L; interquartile range, 22 to 150 pmol/L). Natriuretic peptide levels were higher in the 4 patients (all symptomatic) with restrictive diastolic dysfunction (median, 243 pmol/L; interquartile range, 198 to 348 pmol/L). Three of these patients also had a LV ejection fraction <50%.
Comparison Between Symptomatic and Asymptomatic Patients

The symptomatic patients were older (72±10 versus 65±15 years; P=0.035) and had a higher serum creatinine (0.10±0.02 versus 0.09±0.02 mmol/L; P=0.01), but there was no difference between these two groups with respect to sex, history of hypertension, diabetes mellitus, smoking, or the use of any cardiovascular medication.

The natriuretic peptide levels and echocardiographic measures of asymptomatic and symptomatic patients are compared in Table 1. N-BNP, BNP, and ANP levels were higher in symptomatic patients than in asymptomatic patients. After adjustment for age, sex, serum creatinine, aortic valve area, and LV ejection fraction, the natriuretic peptide levels remained higher in symptomatic patients than in asymptomatic patients (for N-BNP: geometric mean 1.74 times higher [95% CI, 1.12 to 2.69], P=0.014; for BNP: 1.51 times higher [95% CI, 1.03 to 2.23], P=0.036; and for ANP: 1.27 times higher [95% CI, 0.95 to 1.69]; P=0.10, respectively).

Natriuretic peptide levels increased as the aortic valve area decreased, as illustrated for N-BNP in Figure 1. The median N-BNP levels in the control subjects and in the 4 groups of patients categorized by aortic valve area, symptom status, and LV systolic function are shown in Figure 2. There was a significant increase in N-BNP levels as the severity of aortic stenosis increased (P<0.0001). In a subanalysis of patients with an aortic valve area ≤1.0 cm² (n=59), the aortic valve area was similar in symptomatic (n=43; mean aortic valve area, 0.68±0.19 cm²) and asymptomatic patients (n=16; mean aortic valve area, 0.76±0.12 cm²; P=0.18), but the natriuretic peptides were higher in symptomatic (N-BNP: median, 142 pmol/L; interquartile range, 73 to 210 pmol/L) compared with asymptomatic patients (N-BNP: median, 53 pmol/L; interquartile range, 28 to 91 pmol/L; P=0.0007). The difference remained significant after adjusting for age, sex, serum creatinine, and ejection fraction (P=0.01). Similar results were obtained for BNP and ANP.

Natriuretic Peptide Levels by NYHA Class, Angina, and Syncope

N-BNP, BNP, and ANP levels all increased with increasing NYHA class (Table 2). Within each NYHA class, natriuretic

![Figure 1. Association between N-BNP levels and aortic valve area in patients with aortic stenosis. The line drawn at the N-BNP level of 60 pmol/L indicates the cutpoint of maximum sensitivity and specificity for the presence of symptoms.](image-url)
peptide levels were not higher in patients with angina, presyncope, or syncope than in those without these symptoms. Coronary angiography was only performed in patients scheduled for aortic valve surgery (n=42; 57%). There was a significant association between the presence of at least one ≥50% angiographic coronary artery stenosis and angina (P=0.0095).

**Sensitivity and Specificity for the Presence of Symptoms**
The sensitivity and specificity of natriuretic peptide levels and echocardiographic measures for the presence of symptoms are shown in Table 3. Natriuretic peptide levels, aortic valve area, and peak aortic velocity were stronger predictors of symptoms than measures of LV volume, mass, ejection fraction, systolic circumferential wall stress, posterior wall thickness, or diastolic function. A ROC curve showing the sensitivity and specificity of N-BNP and aortic valve area for the presence of symptoms is shown in Figure 3.

**Age and Sex**
The level of each natriuretic peptide increased with age in normal subjects (P<0.0001), as illustrated for N-BNP in Figure 4. For an increase in age of 10 years, N-BNP on average increased 1.40 times (95% CI, 1.25 to 1.57), BNP increased 1.25 times (95% CI, 1.16 to 1.36), and ANP increased 1.30 times (95% CI, 1.21 to 1.38). Plasma levels of natriuretic peptides were higher in women than in men after adjustment for age (N-BNP, 1.70 times higher [95% CI, 1.33 to 2.18]; BNP, 1.33 times higher [95% CI, 1.13 to 1.57]; and ANP, 1.31 times higher [95% CI, 1.13 to 1.50]; P<0.001 for all). There was no significant interaction between age and sex. The use of an age- and sex-adjusted normal range did not improve the predictive value of natriuretic peptide levels for symptoms.

**Discussion**
The importance of early and accurate recognition of symptoms in patients with aortic stenosis is emphasized by the risk of rapid deterioration and sudden death after symptom onset in some patients.19,20 An additional reason for identifying early symptoms is that surgery can be performed with low operative mortality compared with the higher surgical risk when symptoms are severe or when surgery is not elective.21 The most common initial symptoms are exertional dyspnea and fatigue.5 These symptoms are nonspecific, subtle at onset, and often difficult to evaluate clinically.

In the present study, there was a strong association between the NYHA class and plasma levels of N-BNP, BNP, and ANP. Importantly, natriuretic peptide levels were higher in patients with NYHA class II symptoms than in those with NYHA class I symptoms or those without symptoms. The sensitivity and specificity of natriuretic peptide levels for the presence of symptoms are shown in Table 3. Natriuretic peptide levels, aortic valve area, and peak aortic velocity were stronger predictors of symptoms than measures of LV volume, mass, ejection fraction, systolic circumferential wall stress, posterior wall thickness, or diastolic function. A ROC curve showing the sensitivity and specificity of N-BNP and aortic valve area for the presence of symptoms is shown in Figure 3.

**TABLE 2. Association Between Natriuretic Peptide Levels and Symptoms**

<table>
<thead>
<tr>
<th>Natriuretic Peptide</th>
<th>NYHA Class I</th>
<th>NYHA Class II</th>
<th>NYHA Class III/IV</th>
<th>F Statistic</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n=74)</td>
<td>(n=30)</td>
<td>(n=28)</td>
<td>(n=16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>34 (16–58)</td>
<td>105 (57–159)</td>
<td>202 (87–394)</td>
<td>22.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP</td>
<td>8 (6–14)</td>
<td>25 (13–35)</td>
<td>40 (18–66)</td>
<td>20.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ANP</td>
<td>18 (13–24)</td>
<td>31 (19–40)</td>
<td>47 (24–59)</td>
<td>15.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No angina (n=47)</td>
<td>(n=30)</td>
<td>(n=11)</td>
<td>(n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>34 (16–58)</td>
<td>91 (33–142)</td>
<td>243 (193–298)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Angina (n=27)</td>
<td>(n=0)</td>
<td>(n=17)</td>
<td>(n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>…</td>
<td>106 (72–176)</td>
<td>147 (74–435)</td>
<td>0.64</td>
<td>0.4</td>
</tr>
<tr>
<td>No syncope (n=60)</td>
<td>(n=30)</td>
<td>(n=18)</td>
<td>(n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>34 (16–58)</td>
<td>108 (64–176)</td>
<td>243 (147–394)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Presyncope (n=9)</td>
<td>(n=0)</td>
<td>(n=6)</td>
<td>(n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>…</td>
<td>91 (50–115)</td>
<td>50 (22–514)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Syncope (n=5)</td>
<td>(n=0)</td>
<td>(n=4)</td>
<td>(n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-BNP</td>
<td>…</td>
<td>101 (64–201)</td>
<td>85</td>
<td>2.30</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range) and in pmol/L. The results for patients with and without angina, presyncope, and syncope had similar patterns for BNP and ANP.

*P values were generated from ANOVA on natural logarithm–transformed peptide levels.
class I symptoms, suggesting that natriuretic peptide levels can be used to discriminate between early symptoms of heart failure and normal effort tolerance. After adjustment for NYHA class, there was no association between natriuretic peptide levels and syncope or the presence or absence of angina. This suggests that the stimulus for increased secretion of natriuretic peptides by cardiac myocytes is associated with the clinical manifestation and exertional dyspnea. However, angina and syncope have different pathophysiologies in patients with aortic stenosis and are not associated with increased secretion of natriuretic peptides.

The compensatory response of the left ventricle to the chronic and gradually progressive pressure overload of aortic stenosis is concentric hypertrophy. Typically, the ejection fraction is preserved until late in the course of the disease. However, there may be significant myocyte dysfunction even when the ejection fraction is normal in the presence of concentric LV hypertrophy. In the present study, there was a progressive increase in natriuretic peptide levels with decreasing aortic valve area, but a large increase in natriuretic peptide levels in patients with an ejection of <50%, emphasizing the important association between LV systolic function and natriuretic peptide levels. Increased LV wall stress has been proposed as a stimulus for the release of natriuretic peptides in aortic stenosis. In this study, there was a weaker but significant correlation between wall stress and natriuretic peptide levels, and wall stress was higher in symptomatic compared with asymptomatic patients. The development of diastolic dysfunction is another plausible explanation for symptom onset. However, the majority of symptomatic patients in this study had normal diastolic function or an impaired relaxation pattern rather than more severe diastolic dysfunction.

The most widely used measures of aortic stenosis severity in clinical practice are the peak aortic velocity and the aortic valve area, as determined by the continuity equation. As in previous studies, these measures were most strongly associated with the presence of symptoms. However, there was a large overlap between symptomatic and asymptomatic patients, consistent with the known heterogeneous response to the pressure load of aortic stenosis. In contrast, there was less overlap in natriuretic peptide levels between symptomatic and asymptomatic patients. Furthermore, the natriuretic peptides, and N-BNP in particular, provided additional predictive value to the aortic valve area and LV ejection fraction for the presence of symptoms.

These findings are consistent with observations from experimental models in which increased synthesis and release
of BNP occurred with the transition from compensated to decompensated LV function. This transition may not be reliably detected by current echocardiographic measures. Although there is increased understanding of the molecular changes that occur during myocardial decompensation, the signaling pathways that lead to increased natriuretic peptide secretion are currently poorly defined.

Whereas echocardiographic assessment of aortic stenosis requires trained and experienced sonographers with meticulous attention to the technical details of imaging and Doppler flow recording, the introduction of automated assays means that measurement of plasma levels of natriuretic peptides is simple, not operator-dependent, relatively inexpensive, and reproducible. Compared with BNP, N-BNP has no specific clearance receptors. As a result, its half-life is longer, it is less influenced by short bursts of secretion. Although N-BNP seemed to have the best discriminatory value for symptoms, the current study did not have sufficient statistical power to distinguish reliably between the different natriuretic peptides. N-ANP has similar biological properties to N-BNP and has been shown to be a more reliable marker than ANP, but it was not measured in this study.

Previous studies have shown that natriuretic peptide levels increase with normal aging and are higher in women than in men with no cardiac disease. Similar age and sex differences were observed in normal control subjects in the current study. These observations suggest that the use of an age- and sex-specific normal range would improve the diagnostic accuracy of natriuretic peptide levels. However, in the current study, the association between natriuretic peptide levels and symptoms did not increase after adjustment for age. A possible explanation is that the increase in natriuretic peptide levels reflects age-related changes in myocardial function that in themselves increase the likelihood of symptoms. In this case, the absolute level of natriuretic peptides rather than the age- and sex-adjusted levels may be most predictive.

The association between natriuretic peptide levels and symptoms was stronger in men than in women. It is not clear whether this sex difference existed because women report symptoms differently or whether there is a sex difference in the response of the left ventricle to the hemodynamic load of aortic stenosis, as other researchers have suggested. In previous studies, women have had greater impairment of functional status and a poorer exercise capacity than men, despite a similar aortic valve area and greater LV fractional shortening.

As in clinical practice, it is likely that some patients’ symptoms were not a consequence of aortic stenosis, whereas others were classified as asymptomatic because they undertook little physical activity or ignored subtle symptoms. Exercise testing has been proposed as a method of identifying patients with aortic stenosis who are at increased risk. Although a lack of increase in systolic blood pressure with exercise predicts a poor outcome, exercise capacity does not, and some patients are unable to exercise. Furthermore, exercise testing needs to be performed with close monitoring and is contraindicated in symptomatic patients; thus, it was not undertaken in this study. Further studies comparing the clinical value of exercise testing and natriuretic peptide levels in apparently asymptomatic patients with aortic stenosis are needed.

In conclusion, plasma natriuretic peptide levels are elevated in symptomatic patients with aortic stenosis. Measurement of natriuretic peptides is likely to complement, but not replace, clinical and echocardiographic evaluation of patients with aortic stenosis. Further large prospective studies are needed to determine whether serial measurements of natriuretic peptide levels can be used to monitor disease progression and predict clinical outcome and whether high natriuretic peptide levels should be an indication for surgery in apparently asymptomatic patients.

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References

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