Usefulness of B-Type Natriuretic Peptide Assay in the Assessment of Symptomatic State in Hypertrophic Cardiomyopathy

Barry J. Maron, MD; Venkatakshra N. Tholakanahalli, MD; Andrey G. Zenovich, MSc; Susan A. Casey, RN; Daniel Duprez, MD; Dorothee M. Aeppli, PhD; Jay N. Cohn, MD

Background—Hypertrophic cardiomyopathy (HCM) has a diverse clinical spectrum that often includes progressive heart failure symptoms and disability. Assessment of symptom severity may be highly subjective, encumbered by the heterogeneous clinical presentation. Plasma B-type natriuretic peptide (BNP) has been used widely as an objective marker for heart failure severity and outcome, predominantly in coronary heart disease with ventricular dilatation and systolic dysfunction.

Methods and Results—We prospectively assessed plasma BNP as a quantitative clinical marker of heart failure severity in 107 consecutive HCM patients. BNP showed a statistically significant relationship to magnitude of functional limitation, assessed by New York Heart Association (NYHA) functional class: I, 136±159 pg/mL; II, 338±439 pg/mL; and III/IV, 481±334 pg/mL (P<0.001). Multivariable analysis showed that BNP was independently related to NYHA class as well as age and left ventricular wall thickness (each with a value of P=0.0001). BNP ≥200 pg/mL was the most reliable predictor of heart failure symptoms, with positive and negative predictive values of 63% and 79%, respectively. BNP power in distinguishing patients with or without heart failure symptoms was less than that for differentiating between no (or only mild) and severe symptoms (area under receiver operating characteristic curve=0.75 and 0.83, respectively).

Conclusions—Plasma BNP is independently related to the presence and magnitude of heart failure symptoms in patients with HCM. As a clinical marker for heart failure, BNP is limited by considerable overlap in values between categories of heart failure severity as well as confounding variables of left ventricular wall thickness and age. (Circulation. 2004;109:984-989.)

Key Words: cardiomyopathy ▪ hypertrophy ▪ heart failure ▪ plasma

B -type natriuretic peptide (BNP) is the product of neurohormonal activation that is manufactured and secreted almost exclusively by ventricular myocardial cells, presumably in response to elevations in end-diastolic pressure and volume. BNP blood levels serve as a means for detecting cardiac pathogenesis of symptoms in emergency settings and quantifying severity of heart failure disability in chronic cardiac disease, predominantly coronary heart disease and dilated cardiomyopathy.1-10

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease that, in addition to conveying risk for sudden death in young people, is also an important cause of heart failure–related disability and death.11-20 Limiting symptoms of exertional dyspnea typically occur in the presence of a nondilated left ventricle (LV) with preserved or even hyperdynamic contractile function, often as a result of diastolic dysfunction.14-20 This circumstance in HCM contrasts with the more common clinical scenario of congestive heart failure secondary to coronary heart disease, often associated with ventricular dilatation and systolic dysfunction.1 The usefulness of BNP for screening HCM patients and in monitoring the severity of symptoms has not been established.

Methods

Selection of Patients
A blood sample was collected for the measurement of plasma BNP from 107 patients with HCM evaluated consecutively between June 2001 and February 2003 at the Minneapolis Heart Institute (n=103) and the University of Minnesota Cardiovascular Center (n=4). Each study patient met diagnostic criteria for HCM, with a hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.1,21 In HCM, heart failure is defined by exertional dyspnea and functional limitation (with or without chest pain or orthopnea), independent of whether episodes of impaired consciousness (eg, syncope, near-syncope, or presyncope) have occurred.11-19

At the outpatient visit during which blood was drawn for BNP measurements, clinical status and functional capacity were assessed according to the New York Heart Association (NYHA) classification by one investigator (B.J.M.) without knowledge of the laboratory measurements, clinical status and functional capacity were assessed according to the New York Heart Association (NYHA) classification by one investigator (B.J.M.) without knowledge of the laboratory measurements, clinical status and functional capacity were assessed according to the New York Heart Association (NYHA) classification by one investigator (B.J.M.) without knowledge of the laboratory.
results. No study patient had significant co-morbid cardiovascular, pulmonary, or renal conditions.

Patients were 9 to 87 years of age (mean, 41±19 years); 82 (80%) were male, and all were white. Maximum LV wall thicknesses were 12 to 45 mm (mean, 23±7 mm) and were ≥30 mm in 21 patients (20%). Basal LV outflow tract obstruction (gradient ≥30 mm Hg) was present in 28 patients (26%). LV end-diastolic cavity dimensions were 26 to 61 mm (mean, 44±7 mm). Five patients had systolic dysfunction with reduced ejection fraction to <50% (mean, 37±6%) and were regarded to be in the end-stage phase.19

Measurement of BNP

Blood samples were collected by venipuncture and placed in tubes containing EDTA. BNP was measured with the Triage BNP assay (Biosite Diagnostics), which is a fluorescence immunoassay for BNP in whole-blood specimens. Precision and analytical sensitivity of the system have been reported.1

Echocardiography

Echocardiographic studies were performed with commercially available Hewlett-Packard instruments at the time of BNP determination. LV hypertrophy was assessed with 2D echocardiography according to published criteria.21 The greatest thickness measured at any site in the LV wall was considered to represent maximal LV wall thickness.22 Peak instantaneous LV outflow gradient was estimated under basal conditions with continuous-wave Doppller.13

Statistical Analysis

Data are expressed as mean±SD or percentages for categorical variables. Relevant relationships were tested by χ² analysis for proportions and unpaired Student’s t test for continuous variables. The statistical relationship between BNP and other relevant demographic and clinical variables such as age and maximum LV wall thickness was first examined by Pearson’s correlation, whereas LV wall thickness and LV ejection fraction were assessed by the Mantel-Haenszel method.

To determine whether age, gender, maximum LV wall thickness, outflow gradient, atrial fibrillation, and NYHA functional class were significant independent predictors of BNP, a multivariable regression analysis was performed. For multi-invariate regression, clinical variables were selected stepwise to reduce the model to only statistically significant parameters. Selection was terminated when none of the remaining variables were significant at the 0.05 level or when the addition of any remaining variable would have reduced the residual error by at least 2%. Trends across subgroups were assessed by the Mantel-Haenszel method.

Sensitivity, specificity, and predictive values for the observed prevalence rates were calculated and reported for cut-points of selected BNP concentrations. Receiver operating characteristic (ROC) curves were used to evaluate the usefulness of BNP as a marker for heart failure symptoms. Area under the curve and probability values were obtained by logistic regression. The 95% confidence limits were based on the F distribution.

All probability values were for 2-tailed tests. A value of P<0.05 was considered indicative of a statistically significant result. The statistical software SAS version 8 was used for all calculations.

Results

Relation of BNP to Functional Class

Group Analysis

For the overall study group, plasma BNP ranged from 0 to 3330 pg/mL (mean, 263±418 pg/mL). BNP values were significantly greater with respect to progressive severity of heart failure symptoms, as judged by NYHA functional classification (P<0.001) (Figure 1 and Table 1). BNP was 136±159 pg/mL in asymptomatic class I patients, 338±439 pg/mL in asymptomatic patients with preserved LV systolic function (1108±1144 versus 377±380 pg/mL, respectively; P=0.02). Patients with moderate to severe mitral regurgitation (n=23) had higher BNP values than those with no or only mild regurgitation (n=84), 410±381 versus 191±254 pg/mL, respectively; P<0.001. Positive and negative predictive values of BNP ≥200 pg/mL for moderate to severe mitral regurgitation were 40% and 89%, respectively. BNP was also greater in the 6 patients with systolic LV dysfunction and ejection fraction <50% than in the 34 symptomatic patients with preserved LV systolic function (1108±1144 versus 377±380 pg/mL, respectively; P=0.02). Patients with moderate to severe mitral regurgitation (n=23) had higher BNP values than those with no or only mild regurgitation (n=84), 410±381 versus 191±254 pg/mL, respectively; P<0.001. Positive and negative predictive values of BNP ≥200 pg/mL for moderate to severe mitral regurgitation were 40% and 89%, respectively. BNP was also greater in the 6 patients with systolic LV dysfunction and ejection fraction <50% than in the 34 symptomatic patients with preserved LV systolic function (1108±1144 versus 377±380 pg/mL, respectively; P=0.02). Patients with moderate to severe mitral regurgitation (n=23) had higher BNP values than those with no or only mild regurgitation (n=84), 410±381 versus 191±254 pg/mL, respectively; P<0.001. Positive and negative predictive values of BNP ≥200 pg/mL for moderate to severe mitral regurgitation were 40% and 89%, respectively. BNP was also
greater in the 66 study patients taking cardioactive medications (most commonly β-blockers or verapamil) than those 31 patients without medications (368 ± 500 versus 134 ± 224 pg/mL, respectively; \( P = 0.001 \)). A BNP value ≥200 pg/mL was the most reliable predictor of heart failure symptoms: sensitivity 65%, specificity 78%, positive predictive value 63%, and negative predictive value 79% (Table 2). Overall, BNP ≥200 pg/mL was also the best discriminator between severely symptomatic HCM patients (classes III/IV) and the other patients: sensitivity 81%, specificity 72%, positive predictive value 42%, and negative predictive value 94%.

The ability of BNP to detect symptoms of heart failure (and symptom magnitude) was also assessed with ROC curve analysis (Figure 4). In this regard, BNP was moderately accurate in discriminating between those patients with and those without heart failure symptoms (area under the ROC curve = 0.75; \( P < 0.001 \)), with 78% sensitivity at the customary BNP cutoff of 100 pg/mL. BNP showed greater power in distinguishing HCM patients with no or only mild symptoms (NYHA classes I and II) from those with marked symptoms (classes III and IV), with the area under the ROC curve = 0.83 (95% CI, 0.49, 1.0; \( P < 0.001 \)) and 91%, sensitivity at the BNP cutoff of 100 pg/mL.

### Multivariable Analysis

BNP was associated with NYHA functional class, even after adjustment for other demographic or HCM-related clinical variables in the multivariable analysis (Table 3). Age and LV wall thickness (Figure 2) were also independently associated with BNP (Table 3). End-stage phase in 6 patients (ejection fraction <50%) did not influence the relation between BNP and NYHA class in the multivariable analysis. Using the significant clinical and demographic variables in the multivariable analysis, multiple \( R \) was 0.45, suggesting that 45% of variability in BNP was explained by these parameters.

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**TABLE 1.** Comparison of Clinical and Demographic Parameters With Symptomatic State in 107 Patients With HCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>I</th>
<th>II</th>
<th>III/VI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>67</td>
<td>19</td>
<td>21</td>
<td>...</td>
</tr>
<tr>
<td>Age (at BNP)</td>
<td>38 ± 17</td>
<td>42 ± 24</td>
<td>51 ± 16</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender</td>
<td>57 (85)</td>
<td>14 (74)</td>
<td>11 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>136 ± 159 (0–755)</td>
<td>338 ± 439 (4–1570)</td>
<td>481 ± 334 (71–3330)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;100</td>
<td>36 (54)</td>
<td>7 (37)</td>
<td>2 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥100</td>
<td>31 (46)</td>
<td>12 (63)</td>
<td>19 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥200</td>
<td>15 (22)</td>
<td>9 (47)</td>
<td>17 (81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥250</td>
<td>13 (20)</td>
<td>7 (37)</td>
<td>17 (81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum LV thickness, mm</td>
<td>22.7 ± 6.8 (12–40)</td>
<td>21.9 ± 5.9 (15–35)</td>
<td>24.5 ± 7.7 (17–45)</td>
<td>NS</td>
</tr>
<tr>
<td>LV outflow gradient ≥30 mm Hg</td>
<td>10 (15)</td>
<td>8 (42)</td>
<td>10 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (7)</td>
<td>3 (16)</td>
<td>5 (24)</td>
<td>0.04</td>
</tr>
<tr>
<td>Left atrium, mm</td>
<td>41 ± 7 (28–59)</td>
<td>45 ± 10 (25–63)</td>
<td>48 ± 10 (34–79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>66 ± 7</td>
<td>65 ± 8</td>
<td>61 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction &lt;50%</td>
<td>0</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>0.002</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>45 ± 8 (26–60)</td>
<td>45 ± 8 (29–61)</td>
<td>44 ± 4 (38–54)</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Any cardioactive drugs | 28 (42) | 19 (74) | 19 (90) | <0.001 |
| β-Blocker | 20 (30) | 12 (63) | 13 (62) | ... |
| Verapamil | 9 (13) | 4 (21) | 7 (33) | ... |
| Disopyramide | 1 (1) | 0 | 1 (5) | ... |
| Diuretics | 2 (3) | 0 | 7 (33) | ... |

*Values are given as mean ± SD or n (%); ranges are also shown in parentheses.*

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**Figure 2.** Proportion of HCM patients in each NYHA functional class with BNP ≥100 pg/mL, <100 pg/mL, and ≥250 pg/mL. Relationships between symptom levels and BNP values were each \( P < 0.001 \).
Discussion

The present findings in a cohort of patients with HCM show a relationship between blood BNP levels and severity of symptoms related to heart failure. BNP, which is secreted from the ventricles in response to myocardial overload, has been shown previously to be a marker for the more common form of congestive heart failure in patients with coronary heart disease (or dilated cardiomyopathy), usually associated with ventricular chamber dilatation and LV dysfunction.1–10 In the present investigation, BNP level also bore a significant relationship to the presence and magnitude of heart failure in HCM. This is notable, given that disabling symptoms in HCM typically occur in the absence of LV cavity volume expansion and systolic dysfunction usually caused by impaired LV diastolic filling and elevated end-diastolic pressure11–20 or LV outflow tract obstruction.13 Mean BNP values of 413 pg/mL for symptomatic and 136 pg/mL for asymptomatic HCM patients are similar to those reported for acquired heart disease.1

Therefore, our findings in HCM generally serve to validate BNP as a quantitative blood marker for heart failure and extend this principle into more diverse cardiac populations than previously reported. Available BNP data in patients with HCM have been quite limited and confined to relatively small patient populations; 2 studies suggest a relationship of BNP only to LV outflow obstruction23,24 (not confirmed here), and another group reported BNP as a marker for silent myocardial ischemia.25

Our aspiration in analyzing BNP in the present study was to formulate a reliable and more accurate adjunct diagnostic tool for heart failure in HCM, given the ambiguity often encountered in assessing symptom magnitude in such patients by personal history or even with exercise testing.17 This has particular clinical relevance because pharmacological agents represent the initial treatment modality for heart failure symptoms in HCM.11–13 Therefore, it would be advantageous to develop tools for objectively and independently assessing the level of heart failure to aid in clinical decisions related to the administration of drugs. Furthermore, in patients with obstructive HCM,18 it is crucial to reliably monitor the magnitude and progression of heart failure symptoms to ascertain when major interventions such as septal myectomy (or possibly alcohol septal ablation) are advisable.11–13

Nevertheless, BNP has certain limitations as a clinically useful addition to the diagnostic armamentarium of HCM. For example, we observed considerable overlap in BNP levels and age, maximum LV thickness, left atrial (LA) size, and LV end-diastolic dimension in patients with HCM.

Figure 3. Association between BNP levels and age, maximum LV thickness, left atrial (LA) size, and LV end-diastolic dimension in patients with HCM.

| TABLE 2. Sensitivity, Specificity, and Predictive Values for BNP in Predicting the Presence of Heart Failure Symptoms (NYHA Classes II–IV) in 107 Patients With HCM* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| BNP Level, pg/mL | Sensitivity, %  | Specificity, %  | Positive Predictive Value, % | Negative Predictive Value, % | Accuracy, % |
| ≤50             | 85 (70–94)      | 42 (30–54)      | 47 (35–59)      | 82 (65–93)      | 58 (42–61)     |
| ≥100            | 78 (62–89)      | 54 (41–66)      | 50 (37–63)      | 80 (65–90)      | 63 (53–72)     |
| ≥150            | 73 (56–85)      | 70 (58–81)      | 59 (44–73)      | 81 (69–90)      | 71 (61–79)     |
| ≥200            | 65 (48–79)      | 78 (66–87)      | 63 (47–78)      | 79 (67–88)      | 73 (63–81)     |
| ≥250            | 58 (41–73)      | 79 (67–88)      | 62 (45–78)      | 76 (65–84)      | 71 (61–79)     |

*95% confidence limits are shown in parentheses.
concentrations between categories of heart failure severity (ie, NYHA classes I versus II versus III/IV) in patients with HCM, consistent with previous studies in patients with acquired heart diseases and heart failure. Indeed, almost 50% of our HCM patients who were asymptomatic nevertheless showed elevated BNP values exceeding the generally recommended cutoff value for normality of 100 pg/mL. Although the significance of such elevated plasma BNP levels in the absence of symptoms is uncertain, it is possible that they represent a preclinical prognostic marker for impending heart failure and clinical decompensation or even a useful (albeit insensitive) test for detecting HCM in phenotype-negative family members who carry a mutant gene for the disease. However, we have used a cross-sectional study design, and therefore, predictions of clinical outcome over time with serial BNP measurements are beyond the scope of this investigation. It should be underscored, however, that clinical progression of heart failure in HCM is often much slower than in coronary artery disease, and future longitudinal studies would require substantial follow-up periods.

The power of BNP in distinguishing patients with heart failure symptoms from those without such symptoms proved to be substantially less in HCM (area under the ROC curve = 0.75) that previously reported for discriminating heart failure symptoms from those without such symptoms. AUC indicates area under ROC curve. BNP values shown on curves are pg/mL.

Figure 4. ROC curve of BNP for discriminating HCM patients with heart failure symptoms (NYHA classes II–IV) from those without symptoms (class I), as well as between patients with severe symptoms vs those with no (or mild) symptoms. AUC indicates area under ROC curve. BNP values shown on curves are pg/mL.

Table 3. Univariate and Multivariable Regression Analysis for BNP With Regard to Clinical Variables in 107 HCM Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate P</th>
<th>Multivariate, Coefficient ± SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.002</td>
<td>0.03 (0.007)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.007</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NYHA class (I vs II vs III/IV)</td>
<td>0.0001</td>
<td>0.60 (0.14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maximum LV wall thickness, mm</td>
<td>0.0001</td>
<td>0.11 (0.02)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV outflow obstruction*</td>
<td>0.0006</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.014</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*Gradient <30 mm Hg vs ≥30 mm Hg.

between patients with and those without congestive heart failure caused primarily by coronary artery disease (area under the ROC curve = 0.90),

but was greater than in differentiating between non-HCM congestive heart failure with systolic versus diastolic dysfunction (area under the ROC curve = 0.66) (Figure 4). Conversely, BNP showed substantial power in differentiating HCM patients with marked heart failure symptoms from those with no or only mild symptoms (area under the ROC curve = 0.83).

More than 90% of our patients who experienced severe symptoms and functional disability (ie, NYHA classes III/IV) did in fact show greatly elevated BNP values (mean, 481 pg/mL), with a range to >3000 pg/mL. Conversely, the finding that BNP levels were within the normal range in a minority of HCM patients with severe heart failure is similar to recent observations in congestive heart failure caused by coronary artery disease. This observation may be explained by episodic BNP secretion but also raises the possibility that such normal BNP values ultimately imply better prognosis.

In congestive heart failure unrelated to HCM, BNP values in patients with systolic dysfunction and ventricular dilatation are approximately 2-fold those of patients with pure diastolic dysfunction and nondilated ventricles, suggesting that BNP secretion is strongly volume dependent. Although symptoms of heart failure in HCM are usually related to LV diastolic dysfunction, the present study also included a small subset of patients with predominantly systolic dysfunction and dilated ventricles typical of the “end-stage” phase. Indeed, our HCM patients with LV systolic dysfunction had BNP values that were 3-fold those of symptomatic patients with preserved systolic function.

The important observation in HCM that LV wall thickness is a strong independent predictor of BNP level (and therefore a confounding variable) suggests that myocardial mass is an important element in determining BNP and must be taken into consideration when interpreting the test values in individual patients. This relationship is consistent with the recognition that LV wall thickness (and mass) in HCM is unique and far exceeds that in any other cardiac disease, particularly when compared with heart failure caused by coronary artery disease. Also, we recognize that using NYHA functional class as the “gold standard” for comparison with BNP is limited by the subjectivity implicit in assessing symptom level with this model.

In conclusion, our data support a potential clinical role for BNP as an adjunctive test for clarifying the uncertainty that often arises in assessing functional disability in HCM patients. However, considerable variability in BNP values among patients with different symptom magnitude, and the independent impact of confounding variables such as LV wall thickness (and age), substantially restrict the practical clinical usefulness of BNP as a blood test marker for heart failure in HCM.

References


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