Valvular Heart Disease

B-Type Natriuretic Peptide in Organic Mitral Regurgitation: Determinants and Impact on Outcome

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Background—B-type natriuretic peptide (BNP) activation observed in cardiac diseases is a predictor of poor outcome; however, in organic mitral regurgitation (MR), BNP determinants and prognostic value are unknown.

Methods and Results—We prospectively enrolled 124 patients with chronic organic MR (aged 63±15 years, 60% males) in whom we measured BNP level and simultaneously quantified MR degree, left ventricular (LV) remodeling, and left atrial (LA) volumes and analyzed long-term outcome. Baseline BNP level (54±67 pg/mL, median 31 pg/mL) was associated variably with multiple clinical and echocardiographic characteristics, but in multivariate analysis, independent determinants of BNP, beyond age and sex (both P≤0.01), were LV end-systolic volume index, LA volume, atrial fibrillation, and symptoms (all P<0.02). Conversely, MR degree was not independently associated with BNP. During follow-up, patients with high versus low BNP (≥31 versus <31 pg/mL) displayed lower survival rates (at 5 years, 72±10% versus 95±5%, P=0.03) and higher rates of the combined end point of death and heart failure (at 5 years, 42±10% versus 16±7%, P=0.03). In multivariate analysis, with adjustment for age, sex, functional class, MR severity, and ejection fraction, BNP was independently predictive of mortality (hazard ratio per 10 pg/mL, 1.23 [95% CI 1.07 to 1.48], P=0.004) and of death or heart failure (hazard ratio per 10 pg/mL, 1.09 [95% CI 1.001 to 1.19], P=0.04).

Conclusions—BNP activation in organic MR reflects primarily ventricular and atrial consequences rather than degree of MR. Higher BNP level in patients with organic MR independently predicts adverse events under conservative management. Therefore, BNP activation in organic MR is an emerging biomarker of severity of MR consequences and of poor clinical outcome, and its assessment should be considered in the clinical evaluation and risk stratification of patients with MR. (Circulation. 2005;111:2391-2397.)

Key Words: natriuretic peptides ■ echocardiography ■ regurgitation ■ prognosis

Organic mitral regurgitation (MR) is a frequent and progressive valve disease that is difficult to manage clinically because insidious cardiac overload causes hemodynamic, left ventricular (LV), and left atrial (LA) alterations, which lead to poor clinical outcome. Among mechanistic complications, recent reports noted that MR may also cause hormonal activation, with an elevated level of B-type natriuretic peptide (BNP). This observation is important because in various cardiac diseases, BNP activation reflects hemodynamic alterations, detects LV dysfunction, and provides prognostic information and thus was touted as an important clinical tool.

However, in chronic organic MR, BNP physiological determinants and outcome implications are undefined. Indeed, it is unclear whether BNP purely reflects the symptoms or MR severity or whether it is a biomarker of ventricular and atrial alterations due to the MR. Furthermore, no study has yet analyzed BNP implications for subsequent survival and development of heart failure. Such an outcome link would be important, because few markers of high risk under conservative management exist to guide clinical decision making.

Therefore, we prospectively enrolled patients with chronic organic MR, measured BNP levels simultaneous to extensive clinical and Doppler echocardiographic assessment, and analyzed their outcome under medical management. We hypothesized that BNP is essentially determined by the adverse physiological consequences of MR, rather than by its degree, and that BNP is an independent determinant of outcome under medical management. The verification of these hypotheses would pave the way for routine utilization of BNP in the risk stratification and management of patients with MR.

Methods

This study was conducted consecutively and prospectively. Patients were enrolled between 1996 and 1998 if they had chronic, isolated, pure, and organic MR (degenerative lesions, healed endocarditis, or...
chronic rheumatic disease) of mild or larger degree, underwent comprehensive quantitative Doppler echocardiography performed by the authors, and consented to blood draw for BNP measurement. Exclusion criteria were acute MR, previous valve repair or replacement, papillary muscle rupture, ischemic cause of MR, absence of intrinsic mitral disease, and associated aortic or congenital disease. No exclusions were based on sex, age, or treatment received. Clinical evaluation and management of the patients were conducted by their independent physicians with symptom assessment by the New York Heart Association classification and atrial fibrillation (AF) diagnosis by ECG. Doppler echocardiographic recording and blood sampling were collected simultaneously but were processed independently. Follow-up was obtained in 2002 after all baseline clinical, hormonal, and echocardiographic data were processed and entered in a database that was not subsequently altered.

### Doppler Echocardiography

Comprehensive Doppler echocardiography was performed. MR was quantified by 3 methods: quantitative Doppler with mitral and aortic stroke volumes,\textsuperscript{15,16} and the proximal isovelocity surface area method.\textsuperscript{2} These methods were averaged, which allowed calculation of regurgitant volume, regurgitation fraction (RF), and effective regurgitant orifice.\textsuperscript{18} LV end-diastolic and end-systolic volume indexes and ejection fraction were measured by Simpson disk method as recommended.\textsuperscript{19} LA volume was measured by the biplane area-length method with 2 orthogonal apical views at end systole.\textsuperscript{20} Systolic pulmonary artery pressure (SPAP) was measured with tricuspid regurgitant velocity. Cardiac index was calculated with pulse-wave Doppler echocardiography.

### Blood Sampling

Blood sampling was obtained for all patients immediately after enrollment in the echocardiographic laboratory. After patients had been in a supine position for at least 30 minutes, a blood sample was drawn from a peripheral vein, immediately placed on ice, and transferred to the laboratory facilities in the same campus. After plasma extraction, BNP and 3′5′-cGMP were measured by standard radioimmunoassay.\textsuperscript{14,21,22}

### Statistical Analysis

Results are presented as mean±SD or percentages. Group comparisons were performed with ANOVA, \textit{t} test, or \textit{χ}\textsuperscript{2} test as appropriate. Associations of baseline BNP (dependent variable) to independent variables (Table 1) were tested with linear and nonparametric regressions (categorical variables). Analyses were performed overall and stratified by symptoms, RF, and LA volume classes. Multivariate analysis with stepwise multiple linear regression was used to define independent determinants of BNP levels and included adjustment for age and sex. Because pulmonary pressure could not be measured in all patients, initial models did not include it, but the final model was rerun with the addition of this variable to assess its potential additive predictive value. As an adjunctive analysis, BNP was stratified in 4 categories (below BNP median ≤31 pg/mL) and with division of values greater than the median into 3 categories: 31 to 60, 61 to 90, and >90 pg/mL. We then calculated with logistic regression analysis the ORs of an upward category change in BNP according to increments of independent determinants. Outcome after diagnosis was analyzed under conservative management by censoring at death or last follow-up for patients who did not undergo surgery and at surgery for those who did (64 patients ultimately underwent surgery, up to 6 years after diagnosis). Events analyzed were total mortality and the combined end point of mortality or new heart failure with rates estimated by the Kaplan-Meier method and tested by log rank. Evaluation of BNP as a predictor of outcome used the Cox proportional hazards analysis, univariately and after adjustment for age, sex, effective regurgitant orifice, symptoms, and ejection fraction,\textsuperscript{23} with calculation of adjusted hazard ratios (HRs) and 95% CIs. \textit{P}<0.05 was considered significant.
Results

Baseline Characteristics

A total of 124 patients (aged 63±13 years, 60% males) were enrolled in the study and followed up for 4.4±1.4 years. Their baseline characteristics are presented in Table 1. MR cause was degenerative in 116 (with prolapse in 94), chronic rheumatic in 5, and healed endocarditis in 3 patients. Overall, RF was 41±18%, with a wide range: 30% had mild MR (RF <30%), 34% had moderate MR (RF 30% to 49%), and 35% had severe MR (RF ≥50%). SPAP measurable in 113 patients was 38±11 mm Hg. BNP plasma level was 54±67 pg/mL, with a wide range (0.10 to 410 pg/mL, median 31 pg/mL). Overall, BNP level correlated with that of its biological second messenger cGMP (r=0.38, P<0.0001). Higher BNP category (BNP <31, 31 to 60, 61 to 90, or >90 pg/mL) was associated with higher cGMP level (respectively, 2.9±2.2, 4.5±3.2, 4.3±2.8, and 6.3±5.0 pg/mL; P=0.0002).

Determinant of BNP in MR

For display purposes, patients were divided according to BNP median (31 pg/mL). Table 1 summarizes comparisons between groups with high and low BNP and correlations between explanatory variables and BNP. Patients with higher versus lower BNP level (≥31 pg/mL versus <31 pg/mL) were older, more symptomatic, and more often in AF (all P<0.0002) and had higher SPAP and higher LA volume (both P<0.0001), with trends toward more severe MR and larger end-systolic volume index (ESVI). All of these variables (Table 1) showed significant correlations with BNP level (all P≤0.02). Stratified by symptom class (Figure 1) and MR severity (Figure 2), BNP level increased significantly with symptom severity (P<0.0001) and tended to increase with MR severity (P=0.08), but within each class, a wide range of BNP level was observed, with large overlap between consecutive classes.

In multivariate linear regression analysis (Table 2) with adjustment for age and sex, independent predictors of high BNP level were mainly consequences of MR (symptoms, ESVI, LA volume, and AF; P<0.02 for all). Association between BNP level and LA volume (Figure 3) showed an overlap between classes, but BNP levels ≥100 pg/mL were observed almost exclusively in patients with marked LA enlargement. Importantly, MR degree (RF) was univariately but not independently associated with BNP level. When SPAP was added to the model, it was additionally independently associated with BNP level (P<0.0001). These results were not altered after exclusion of endocarditic and rheumatic lesions. Adjusted ORs of higher BNP category (95% CI) for specific increments of ESVI, LA, and presence of AF after multivariate logistic regression analysis are indicated in Table 2. New York Heart Association symptom class was not independently predictive of higher BNP category with logistic analysis.

Outcome Analysis

Under medical management of MR (between diagnosis and last follow-up or surgery), 7 patients died, and 11 patients incurred congestive heart failure. Patients with higher (≥31 pg/mL) compared with lower (<31 pg/mL) levels of BNP experienced lower survival (at 5 years, 72±10% versus 95±5%, P=0.03; Figure 4) with a univariate HR per 10 pg/mL of 1.17 (95% CI 1.06 to 1.28, P=0.003). After adjustment for age, sex, symptoms, ejection fraction, and effective regurgitant orifice, BNP level was independently predictive of survival, with an adjusted HR of 1.23 (95% CI 1.07 to 1.48) per 10 pg/mL (P=0.004).

Combined adverse events (death or heart failure) occurred at higher rates in patients with BNP ≥31 versus <31 pg/mL (at 5 years, 42±10% versus 16±7%, P=0.03; Figure 5), with a univariate HR of 1.12 (95% CI 1.04 to 1.19) per 10 pg/mL (P=0.004). After adjustment for age, sex, symptoms, ejection fraction, and effective regurgitant orifice, BNP independently predicted death or heart failure (adjusted HR 1.09 [95% CI 1.001 to 1.19] per 10 pg/mL, P=0.04). Outcome analyses were unchanged after exclusion of patients with endocarditic and rheumatic lesions.
Discussion

The present study, which to the best of our knowledge is the largest and the first to analyze the association of BNP with clinical outcome in MR, showed that BNP activation is present in chronic organic MR and is biologically active. BNP activation essentially reflects the hemodynamic, ventricular, and atrial consequences of MR, assessed by ESVI, LA volume, and AF, irrespective of MR degree. The functional symptom class only contributes modestly to BNP activation, which is not a mere reflection of symptoms but rather a biomarker that integrates the severity of the MR consequences. Furthermore, elevated BNP levels are independently associated with higher rates of mortality and of the combined end point of death or heart failure. Thus, BNP activation in MR is an emerging biomarker of severe consequences and poor clinical outcome under conservative management; BNP measurement in patients with organic MR is a promising clinical tool for risk stratification, which suggests that large cohorts of patients with organic MR and BNP measurement should be analyzed.

Rationale of the Study

BNP, synthesized and released by overloaded myocardium,\textsuperscript{21,24,25} has natriuretic and vasodilator properties mediated by its second messenger, cGMP.\textsuperscript{13,25} MR causes volume overload with LA enlargement\textsuperscript{26,27} and LV remodeling\textsuperscript{8,28,29} and induces BNP activation.\textsuperscript{9,10} The present study confirms BNP activation in chronic organic MR and shows that it is biologically active, with parallel cGMP elevation.

In heart failure and coronary disease, BNP level reflects the magnitude of hemodynamic and LV alterations and predicts outcome,\textsuperscript{11,14,30} is linked to the presence of functional MR,\textsuperscript{31} and is a major biomarker of risk,\textsuperscript{32,33} so that BNP measurement was recently recommended as integral to clinical management.\textsuperscript{34–36} In organic MR, there is a profound need for such a biomarker, because the identification of high-risk patients is essential for clinical management and to indicate when surgery is necessary.\textsuperscript{1,23} Currently proven risk markers in organic MR, symptoms\textsuperscript{23} and LV dysfunction,\textsuperscript{4,23,29} are observed in a minority of patients and late in the disease course, such that these markers are associated with poor postoperative outcome.\textsuperscript{4,37} MR surgery before such markers are present was proposed, but selection of potential candidates remains controversial,\textsuperscript{23,37,38} requiring new markers of cardiac remodeling and poor outcome under medical management. Demonstration that BNP activation may be such a marker is of considerable importance and may provide substantial help in the clinical management of patients with MR.

### Table 2. Determinants of BNP in MR and Adjusted ORs for Higher BNP Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>BNP, Multivariate Analysis (P)</th>
<th>Adjusted OR of Moving to the Next Highest BNP Level (≤30, 31–60, 61–90, ≥90 pg/mL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume</td>
<td>0.0001</td>
<td>Per 10 mL 1.13 (1.02–1.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>AF</td>
<td>0.006</td>
<td>If present 5.30 (1.32–21.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>ESVI</td>
<td>0.02</td>
<td>Per 10 mL/m 1.58 (1.14–2.21)</td>
<td>0.007</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.01</td>
<td>Per class 1.36 (0.71–2.60)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sex</td>
<td>0.01</td>
<td>If female 5.01 (1.92–13.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.0003</td>
<td>Per year 1.08 (1.04–1.11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association.

### Figures

**Figure 3.** Scatterplots of BNP stratified according to LA volume, classified as <50, 50 to 99, and ≥100 mL; 25th, 50th, and 75th percentile BNP values are shown by bars in each group. Mean±SD by LA class are, respectively, 21±30, 39±49, and 85±63 pg/mL.

**Figure 4.** Survival under conservative management of patients with organic MR stratified according to baseline BNP level higher (dotted line) or lower (continuous line) than 31 pg/mL. Values indicated are mean±SE at 5 years.
observed previously, possibly because of insensitive methods. The ESVI-BNP association in MR was not dependent of known BNP links with age and sex, does not consequences. BNP association with MR consequences, in- concept that BNP level integrates various untoward MR induc- tion. Volume overload induces LV remodeling and dysfunction, which leads to poor outcome. Importantly, a larger ESVI independently determines a higher BNP level. The ESVI-BNP association in MR was not observed previously, possibly because of insensitive methods used to assess LV remodeling (diameter versus volumes). Similarly, MR induces LA overload and enlargement and subsequent AF, which leads to heart failure and poor prognosis. Remarkably, higher BNP independently reflects atrial enlargement and fibrillation, which, in contrast to lone AF, reveals differences in arrhythmia mechanism due to atrial overload in MR. In addition, LA volume measurement better reflects LA overload than a single diameter, revealing strong associations between LA consequences of MR and BNP activation. Finally, the additive association with BNP activation of pulmonary pressures, determined by both reduced LA compliance and degree of MR, furthers the concept that BNP level integrates various untoward MR consequences. BNP association with MR consequences, independent of known BNP links with age and sex, does not merely reflect an association of BNP with degree of MR and may contrast with BNP determinants in heart failure. Furthermore, BNP overlap between MR grades (Figure 2) clearly shows that BNP is not a surrogate for MR degree and cannot be used clinically for this purpose. Therefore, BNP activation is essentially determined by adverse hemodynamic, ventricular, and atrial alterations due to MR and consequently denotes the fact that organic MR is complicated by serious consequences.

**BNP and MR Outcome**

The hypothesis that BNP is a predictor of outcome in patients with MR stems from outcome studies conducted in patients with heart failure or ischemic heart disease that showed BNP as a strong independent predictor of mortality and morbidity. A similar predictive value in chronic MR that allows identification of high-risk patients under medical management is of great interest. Indeed, the only clinical characteristics predictive of outcome under medical management, overt symptoms and LV dysfunction, are observed in a minority of patients and late in the course of the disease. The current high-feasibility, low-risk, and excellent long-term outcome of valve repair suggest that patients at high risk under medical management should be considered for surgery irrespective of symptoms. This seminal study was designed to examine long-term follow-up after diagnosis and 134

**Determinants of BNP Activation**

In previous limited MR series, BNP primarily reflected functional class. Such a conclusion would restrain the use of BNP, because symptoms are readily assessed clinically. The present study reveals BNP activation and physiological significance in organic MR, which reflect combined cardiac alterations due to MR. Indeed, despite MR progression, symptoms may be absent, in contrast to subclinical complications initiated by MR. Volume overload induces LV remodeling and dysfunction, which leads to poor outcome. Importantly, a larger ESVI independently determines a higher BNP level. The ESVI-BNP association in MR was not observed previously, possibly because of insensitive methods used to assess LV remodeling (diameter versus volumes). Similarly, MR induces LA overload and enlargement and subsequent AF, which leads to heart failure and poor prognosis. Remarkably, higher BNP independently reflects atrial enlargement and fibrillation, which, in contrast to lone AF, reveals differences in arrhythmia mechanism due to atrial overload in MR. In addition, LA volume measurement better reflects LA overload than a single diameter, revealing strong associations between LA consequences of MR and BNP activation. Finally, the additive association with BNP activation of pulmonary pressures, determined by both reduced LA compliance and degree of MR, furthers the concept that BNP level integrates various untoward MR consequences. BNP association with MR consequences, independent of known BNP links with age and sex, does not merely reflect an association of BNP with degree of MR and may contrast with BNP determinants in heart failure. Furthermore, BNP overlap between MR grades (Figure 2) clearly shows that BNP is not a surrogate for MR degree and cannot be used clinically for this purpose. Therefore, BNP activation is essentially determined by adverse hemodynamic, ventricular, and atrial alterations due to MR and consequently denotes the fact that organic MR is complicated by serious consequences.

**Clinical Implications**

The findings of the present study, which shows that BNP activation reflects severe consequences of MR and is a marker of poor outcome, suggest that BNP should be added to the clinical armamentarium; however, BNP measurement cannot be substituted for MR quantification, which should follow guidelines of the American Society of Echocardiography. In organic MR, BNP activation reflects serious MR consequences irrespective of its degree. These consequences are measurable by Doppler echocardiography, but such measurements are not performed consistently in routine practice. In this context, BNP activation should direct the attention of clinicians toward more severe LA, LV, and hemodynamic consequences than may appear with a cursory evaluation. Such patients should be evaluated carefully, and additional quantitative and hemodynamic measurements may be indicated.

In view of the association of BNP activation with worse outcome, careful clinical attention should be directed to patients with such activation, and the need for mitral surgery should be considered anew. If prompt mitral surgery does not appear to be in the best interest of patients with MR and BNP activation, they should be monitored closely, with follow-up visits scheduled within a short time frame.

The association of BNP activation with both severe MR consequences and poor outcome suggests that BNP measurement is a promising research tool in the population of patients with MR. Indeed, BNP appears to be a legitimate end point in clinical trials evaluating the medical treatment of MR.

**Study Limitations**

The scope of this study was not to address all points of interest and biological mechanisms with regard to BNP in

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**Figure 5. Incidence of death or new heart failure under conservative management of patients with organic MR stratified according to baseline BNP level higher (dotted line) or lower (continuous line) than 31 pg/mL. Values indicated are mean±SE at 5 years.**
MR. We focused on major consequences and outcome of MR, which provided novel and important information. Cost-benefit and further outcome analyses should be performed, and analysis of BNP activation progression with progression of MR consequences would be useful in confirming causal mechanistic relationships. To address these important questions, very large populations will be required. However, the seminal data presented here pave the way for these analyses to be conducted in various population strata in future large prospective studies. The value of quantitative Doppler echocardiographic methods has been debated; however, LV volumes are reliable with high-resolution imaging. LA volume has been measured to describe LA remodeling, and MR has been quantified by 3 validated methods. 15–17

Conclusions

The present study demonstrates that in organic, chronic MR, BNP activation is present and biologically active and reflects essentially the severe hemodynamic, ventricular, and atrial consequences of MR, irrespective of its degree. Furthermore, elevated levels of BNP are independent predictors of mortality and morbidity under medical management. Thus, BNP emerges as a biomarker of severity of MR consequences and of poor clinical outcome in patients with MR. BNP measurement should be considered in patients with organic MR to support the clinical decision-making process. These promising data pave the way for further analyses of BNP implication in larger series.

References


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