Is Elevated Plasma B-Natriuretic Peptide in Amyloidosis Simply a Function of the Presence of Heart Failure?

Melanie Nordlinger, MD[a], Barbarajean Magnani, PhD, MD[b], Martha Skinner, MD[a,c], and Rodney H. Falk, MD[a,d,*]

This study sought to determine plasma levels of B-natriuretic peptide (BNP) in patients with light-chain–associated amyloidosis and correlate them with the presence or absence of heart failure (HF) and the presence or absence of echocardiographic abnormalities. Patients with normal echocardiographic results had significantly lower BNP levels than those with echocardiographic features of cardiac amyloidosis, whereas BNP levels in the group with HF did not differ from those in patients with asymptomatic cardiac amyloidosis. This observation supports previous observations, suggesting that the elevation of BNP in cardiac amyloidosis may be due not only to elevated ventricular filling pressure but also to direct myocyte damage due to extracellular deposits of amyloid. **(Am J Cardiol 2005;96:982–984)**

The quantitative measurement of B-natriuretic peptide (BNP) is a sensitive tool for the diagnosis of heart failure (HF).[1] The hormone is expressed predominately in the ventricles as pro-BNP, which is cleaved into 2 fragments, BNP and the inactive N-terminal (NT)–pro-BNP. In patients with light-chain–associated (AL) amyloidosis, Palladini et al[2] found that the level of NT–pro-BNP was a prognostic indicator of survival. When defining cardiac involvement, the investigators of that study did not distinguish among patients with echocardiographic abnormalities with and without HF or with simply isolated abnormal electrocardiographic results. Therefore, the relation between the presence of HF due to amyloidosis and pro-BNP levels cannot be accurately determined. BNP is currently the more commonly assayed peptide in the United States, and BNP levels and NT–pro-BNP levels are closely linked. Immunohistochemistry of the myocardium in cardiac amyloidosis suggests that BNP expression may be greater in myocytes that are subject to deformation by adjacent amyloid deposits.[3] Thus, it has been postulated that in addition to the well-recognized stimulus of elevated intracardiac pressure for the expression of BNP, patients with cardiac amyloid may have an additional mechanism of regional mechanical stress caused by the extracellular amyloid deposits. If HF is the predominant mechanism of BNP elevation in amyloidosis, clinical features of HF should be associated with a higher level of BNP than would be present in patients with amyloidosis and normal echocardiographic results or in those with earlier disease characterized by abnormal echocardiographic results but no evidence of HF.[4] In contrast, if myocardial amyloid infiltration also resulted in the expression of BNP by a local effect of amyloid deposits on myocytes, then the ability to distinguish symptomatic and asymptomatic patients with cardiac amyloidosis by the level of BNP may be more difficult. We therefore sought to examine the relation of BNP levels to the presence of cardiac amyloidosis with and without associated HF.

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Sixty-five patients with biopsy-proved systemic AL amyloidosis were prospectively evaluated with the approval of the institutional review board of Boston University Medical Center. Patients who were receiving dialysis, had a history of heart transplantation, or a history of hypertension were excluded. All patients underwent a medical history, physical examinations, chest x-rays, electrocardiograms, echocardiograms, and routine blood examinations, including assays of BNP. All patients were evaluated clinically by a cardiologist, who also reviewed their echocardiograms, to determine the presence of cardiac amyloidosis and HF. The cardiologist had no knowledge of the results of the BNP assays. Cardiac amyloidosis was considered present when the echocardiogram showed increased wall thickness in the absence of hypertension, valvular disease, or any other condition known to cause true left ventricular hypertrophy. HF was defined as dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnea unexplained by pulmonary disease, with a chest radiographic appearance of HF, and/or the presence of elevated jugular venous pressure.

The concentration of BNP was measured on the Bayer ADVIA Centaur (Bayer Diagnostics, Tarrytown, New York). This is a fully automated 2-site sandwich assay using direct

[a]Amyloidosis Treatment and Research Program and Sections of [c]Arthritis and [d]Cardiology, Department of Medicine, Boston University School of Medicine; and [b]Department of Laboratory Medicine, Boston Medical Center, Boston, Massachusetts. Manuscript received March 8, 2005; revised manuscript received and accepted May 13, 2005.

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* Corresponding author: Tel: 617-421-6050; fax: 617-421-6083.

E-mail address: rfalk@partners.org (R.H. Falk).

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Table 1
Clinical and echocardiographic features of patients in relation to BNP levels

Variable	Group I Amyloidosis With Normal Echocardiogram (n = 35)	Group II Cardiac Amyloidosis Without HF (n = 10)	Group III Cardiac Amyloidosis With HF (n = 17)
Age (yrs) (mean ± SEM), M/F	58.3 ± 2, 27/11	57.9 ± 3, 7/3	63.2 ± 2, 8/9
LVEF (%)	62 ± 4‡	57 ± 8	48.5 ± 13
Septal thickness (mm)	10.6 ± 1.2*	14.8 ± 2.0	14.8 ± 2.4
BNP >100 pg/ml	8	9	15
Mean BNP (pg/ml) ± SEM	72† ± 17.1	557 ± 187.7	583 ± 83.5

* $p < 0.01$ compared with groups II and III; † $p < 0.001$ compared with groups II and III; ‡ $p < 0.001$ compared with group III.
There were no differences in septal thickness, left ventricular ejection fraction (LVEF), or BNP between groups II and III.

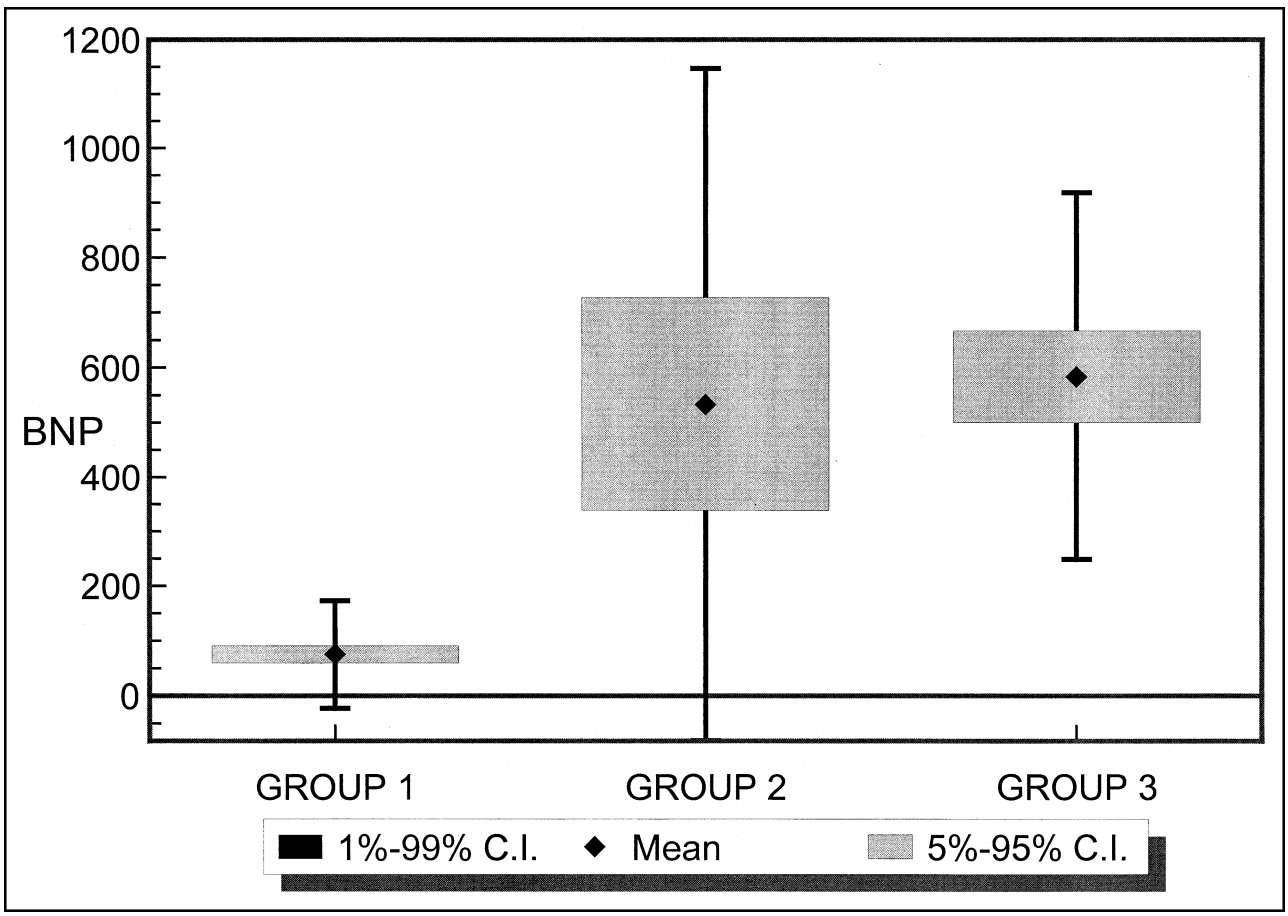

Figure 1. Mean values of BNP *(diamonds)* with 95% confidence intervals (CIs) *(boxes)* and 99% CIs *(lines)*. Although patients in groups II and III had similar mean levels of BNP, the CIs were much larger in group II, representing a larger range of values in this group without clinical evidence of HF.

chemiluminescent technology that measures only the physiologically active BNP molecule in ethylenediaminetetraacetic acid plasma. Although the concentration of BNP increases with age, the following guidelines are used with this assay to determine HF: for patients without HF, 100 pg/ml is used as a decision threshold, with a clinical specificity of 97.4%. In clinically confirmed HF, 72.6% of patients had BNP concentrations >100 pg/ml.

Patients were divided into 3 categories on the basis of the presence or absence of echocardiographic abnormalities and the presence of HF. Group I (n = 38) had no echocardiographic evidence of cardiac amyloidosis, group II (n = 10) met echocardiographic criteria for cardiac amyloidosis but did not have congestive HF, and group III (n = 17) met criteria for cardiac amyloidosis with associated congestive HF. The proportion of patients in each group reflects the anticipated proportions of patients with and without cardiac involvement in AL amyloidosis. Statistical analysis among groups was performed by analysis of variance using the Kruskal-Wallis nonparametric test.

The results are listed in Table 1 and Figure 1. As anticipated, BNP levels between group I and group II or group III revealed a statistically significant difference ($p < 0.001$). However, the mean BNP levels did not differ between group II and group III, despite the presence of clinical HF in the latter group. Eight of the patients in group I (no echocardiographic abnormalities) had BNP levels >100 pg/ml. Review of the 12-lead electrocardiograms in these patients revealed that 7 of those patients had abnormal electrocardiographic results, with low voltage in 4. Of the remaining 31 patients in group I with normal BNP levels, 10 had abnormal electrocardiographic results, with low voltage present in 3. The finding of abnormal electrocardiographic results in group I patients was associated with elevated BNP levels despite normal echocardiographic results ($p = 0.005$, Fisher's exact test).

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This study demonstrates that BNP levels are elevated in cardiac amyloidosis, regardless of the presence or absence of clinical evidence of HF. Although the numbers were relatively small in group II, we think it unlikely that underpowering can account for the lack of difference between this group and group III, because the mean BNP values were so close in the 2 groups. The observation that mean BNP level was similar in groups II and III (those without and with clinical evidence of HF) could be interpreted as an indicator that cardiac dysfunction is difficult to determine by history and clinical examination. However, we do not believe this to be the case for a number of reasons. Cardiac amyloidosis is a biventricular disease, and the elevation of left ventricular pressure is usually accompanied by elevation in right-sided cardiac pressures, with associated elevation in jugular venous pressure. Because all patients were evaluated by the same experienced cardiologist with specific expertise in cardiac amyloidosis, it is unlikely that the clinical evaluations would have been incorrect. Furthermore, we have previously used this clinical classification when evaluating pulsed tissue Doppler and strain and strain rate echocardiography[5,6] and have demonstrated that the 3 groups differ from 1 another in indexes of longitudinal function, even when fractional shortening is preserved. This underscores the validity of the separation of the groups by clinical evaluation in the present study.

An alternative explanation is that the similar values of BNP reflect the peptide's expression as a direct result of the effects of amyloid deposits on the cardiac myocytes. In their immunohistochemical study of endomyocardial biopsies in cardiac amyloidosis, Takemura et al[3] demonstrated that BNP expression was augmented compared with controls and observed that the myocytes adjacent to amyloid deposits tended to show more intense staining for BNP than those that were not abutting extracellular amyloid. They concluded that amyloid deposits may cause regional myocardial stress in addition to the hemodynamic stress caused by diastolic dysfunction and that such regional stress would contribute to BNP expression. In our study, groups II and III had similar ventricular septal thicknesses, suggesting a similar degree of myocardial infiltration despite differences in congestive HF. This would be compatible with the concept that the degree of myocardial infiltration rather than exclusively the cardiac filling pressure plays a role in BNP elevation in cardiac amyloidosis.

A further observation in our study that underscores the hypothesis that regional myocardial stress from amyloid deposits may result in BNP expression is that BNP elevation >100 pg/ml was present in 21% of patients without echocardiographic evidence of cardiac amyloidosis. Although this may represent undiagnosed heart disease, this was apparent neither clinically nor echocardiographically, and the finding that a significantly greater proportion of these patients had low voltage on their electrocardiograms suggests that subclinical cardiac amyloid infiltration may produce elevated BNP despite the appearance of normal 2-dimensional echocardiographic results.

In summary, in patients with systemic amyloidosis and cardiac involvement of a degree sufficient to cause typical echocardiographic changes, plasma BNP is frequently elevated. The previous report, postulating that regional myocardial stress in addition to elevated ventricular filling pressures is responsible for BNP elevation in amyloidosis[3] is supported by our finding that mean BNP elevation was as great in patients without HF as in those with HF and by the observation of elevated BNP in some amyloid patients with normal echocardiographic results but abnormal electrocardiographic results suggestive of very early cardiac infiltration.

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