EDITORIAL COMMENT

B-Type Natriuretic Peptide in Aortic Stenosis

New Insight in the Era of Biomarkers?*

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> "...little things are infinitely the most important"
> —Sir Arthur Conan Doyle (1859–1930) (1)

B-type natriuretic peptide (BNP) has been described as a potential indicator of disease severity in aortic stenosis (AS). BNP is released predominantly in the left ventricle (LV), and its level correlates with aortic valve area (AVA), transvalvular gradient, patient functional status, LV diastolic dysfunction, and LV end-systolic wall stress in AS (2–4). Both LV dysfunction and levels of BNP were shown to have prognostic value in asymptomatic AS, defined as a group of particular clinical interest (2). Repeated measurements of plasma BNP can give additional value to clinical and echocardiographic assessment in post-operative follow-up in asymptomatic patients with AS after aortic valve replacement (AVR) (5). However, in contrast to heart failure, biomarkers have not been used in the assessment of diagnostic or prognostic aspects of valvular heart disease (6).

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In this issue of the *Journal*, Clavel et al. (7) report on a prospective observational study in a large number of patients with AS. All patients had clinical evaluation and Doppler echocardiographic assessment simultaneously with BNP measurement. The study has several methodological advantages, including large sample size (n = 1,953), appropriately applied exclusion criteria, high event rate, and hard endpoint. In addition, follow-up time was long (up to 8 years) and time-dependent analysis was used to determine the outcome of AVR.

The authors presented 2 new interesting clinical and laboratory determinants, BNP ratio and BNP clinical

activation, which allowed overcoming the obstacle of different BNP normal ranges related to age, sex, and various assays, thus individualizing BNP values to each patient (7).

BNP level has been previously confirmed as an independent predictor of mortality in patients with AS, but these findings originated from small samples observed in short follow-up periods (4,8). In this study, elevated BNP level was associated with poor prognosis in AS, suggesting that BNP clinical activation independently correlated with long-term survival and should be used as an important parameter in indicating AVR (7). However, the critical view that BNP clinical activation may not be caused by only AS but also by other comorbidities may be correct and should be proved by large clinical trials. Adding BNP clinical activation to other standard parameters used for considering surgery is strengthened by crucial new facts presented in the paper. BNP was nearly independent of AVA (r = −0.10; p < 0.001) and mean gradient (r = 0.12; p < 0.0001) and, in multivariate analysis, was predictive for all measures of AS severity and consequences. This is supported by the fact that in isolated AS, BNP was proved as a major independent determinant of survival after diagnosis and was a useful predictor of the clinical benefit of AVR.

The degree of BNP clinical activation was also associated with mortality in specific group of asymptomatic patients with severe AS, with an adjusted hazard ratio of 7.38 if the BNP ratio was ≥3 (7). Because early AVR in asymptomatic severe AS is controversial, considering the risk of sudden death and progressive LV dysfunction, this fact adds an important clinical aspect to the body of previous knowledge (4,9). Therefore, BNP may be useful as a noninvasive and reproducible tool in screening asymptomatic patients who will benefit from surgery.

The study has the following limitations.

Serial BNP measurements in this study were not performed, and therefore, BNP dynamicity was not followed. Bergler-Klein et al. (3) suggested that serial measurements of BNP are important and may contribute to adequate referral of asymptomatic patients with AS to valve surgery, whereas onset of symptoms indicates short survival. Also, elevated natriuretic peptide levels were predictors for symptom-free survival in AS, and serial plasma levels indicated symptom development and AVR (3).

Survival of the group with asymptomatic severe AS was not separately analyzed regarding treatment. Because hemodynamic parameters are not the best approach to indicate surgery in this group of patients, due to variable adaptation of the LV to pressure overload (4), BNP clinical activation may be a useful additional guide.

The role of BNP in patients with AS may be especially useful in specific subgroups of patients, such as those with low-gradient "severe" AS (AVA <1 cm^2; mean gradient <40 mm Hg) and preserved LV systolic function. These patients represent a subset of approximately 30% of asymptomatic patients with AS, with outcomes comparable to those of moderate AS, and AVR is suggested only in symptomatic

patients (10). Because these facts are based on retrospective analysis without comparison with severe AS, prospective analysis in the future, including BNP measurements, may be a useful option (9,10).

Assessment of patients with AS include both clinical approaches and precise echocardiography measurements (9,11). Integration of BNP measurements into AS management algorithms may have potential advantages in determining survival and indicating surgery in these patients. BNP-guided clinical approaches, based on time-dependent analysis revealing mortality reduction in patients with elevated BNP levels after AVR, may be additionally helpful in decision making for surgical consideration in AS (7). The predictive role of BNP in clinical practice and for consideration of AVR may be promising, but further studies with better risk stratification of patients with AS are needed to get the final answer.

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