



Editorial

Role of BNP in patients with severe asymptomatic aortic stenosis

Devang N. Patel, Steven R. Bailey*

University of Texas Medical Center, Floyd Curl Dr, San Antonio, TX, USA

This editorial refers to “Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide”[†] by P. Lim et al. on page 2048

Senile degenerative valvular aortic stenosis affects approximately 2% of the population over the age of 65. Aortic stenosis impedes left ventricular emptying and increases left ventricular wall stress, which leads to elevation of brain natriuretic peptide (BNP) levels. Aortic stenosis progresses slowly, allowing the left ventricle to develop concentric hypertrophy, which normalizes wall stress. These compensatory mechanisms maintain cardiac output for several years, during which time the patient remains asymptomatic. Development of haemodynamically significant aortic stenosis (aortic valve area <1.0 cm²) is associated with symptoms of exercise-induced angina, syncope and dyspnoea. Lim et al.,¹ in this issue of the *Journal*, provide insight into the possible use of BNP as a screening tool to stratify symptomatic and asymptomatic patients with isolated aortic stenosis at risk for future events (death or aortic valve replacement).

Natural history studies have demonstrated that the onset of symptoms is associated with limited survival (average of 2–3 years). However, surgical replacement of the aortic valve is also associated with significant morbidity and mortality. Randomized trials comparing surgery versus continuing medical therapy are lacking but observational studies have demonstrated that aortic valve replacement at the onset of symptoms is associated with improved symptoms and prolonged survival.

A major problem with the reliance on symptoms alone is that it is based upon the patient's ability to exercise, or

the physician's willingness to exercise a patient, who may have critical aortic stenosis. If a patient is unable to exercise because of non-cardiac disease such as obesity, lung disease, arthritis, peripheral vascular disease, etc., the patient may never develop the classic symptoms of aortic stenosis and determining the timing of aortic valve replacement becomes difficult. There are a significant number of patients with severe but asymptomatic aortic stenosis that do not meet the accepted indications for surgery such as an aortic valve area less than 0.6 cm², left ventricular systolic dysfunction, marked left ventricular hypertrophy, ventricular tachycardia or atrial fibrillation.

One solution to this problem, as advanced by Lim and colleagues, would be to use cardiac biomarkers that could potentially identify asymptomatic as well as symptomatic patients who are likely to benefit from aortic valve replacement. Biomarkers would have to reflect the state of left ventricular wall stress and predict clinical and echocardiographic progression of the disease. Several biomarkers have been studied for this purpose, and they include: brain natriuretic peptide (BNP), NT-BNP (N-terminal part of BNP), N-terminal proBNP (NT-proBNP, the amino terminal part of the BNP prohormone), cardiotrophin-1, tumor necrosis factor- α (TNF- α) and TNF receptors 1 and 2.

Brain natriuretic peptide is an endogenous cardiac hormone, initially isolated in the porcine brain; and is synthesised and secreted predominantly from the left ventricle in response to increased wall stress. It is elevated in patients with symptomatic and asymptomatic left ventricular dysfunction; as well as other states associated with elevated left ventricular filling pressure, such as myocardial infarction and left ventricular hypertrophy. While elevated BNP levels are detected in patients with hypertension, myocardial infarction, angina, dilated cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease and atrial fibrillation, the highest levels are seen in patients with hypertrophic cardiomyopathy and correlate with left ventricular mass irrespective of aetiology.²

* Correspondence to: Dr. Steven R. Bailey, University of Texas Medical Center, Mail Code 7872, 7703 Floyd Curl Dr, San Antonio, TX 78229-3901, USA. Tel.: +1 210 5674601; fax: +1 210 5676960.

E-mail address: baileys@uthscsa.edu (S.R. Bailey).

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BNP levels correlate with severity of left ventricular outflow obstruction both in valvular aortic stenosis and hypertrophic cardiomyopathy.^{3,4} In patients with aortic stenosis, plasma BNP levels have been demonstrated to be highly correlated with left ventricular end-systolic wall stress and reflect onset of symptoms.^{5,6} NT-proBNP levels are elevated in patients with aortic stenosis, even in the presence of mild left ventricular hypertrophy. They are correlated with left ventricular mass index and aortic valve area index, and have been suggested as a marker to predict the need for aortic valve replacement.^{7,8} Following aortic valve replacement, BNP and NT-proBNP levels fall in some patients but remain unchanged in others. This may be due to either persistent left ventricular dysfunction or a persistent left ventricular outflow gradient from the presence of a prosthetic valve.^{9,10}

Prior studies of aortic stenosis and plasma BNP have either been retrospective or cross-sectional in design. The study by Lim et al., is the first to prospectively assess clinical outcomes in patients with echocardiographically defined severe aortic stenosis based on baseline BNP levels, and further supports the role of BNP in identifying asymptomatic patients with severe aortic stenosis likely to benefit from aortic valve replacement. In their study of 70 patients, the median BNP level was 132 pg/ml in symptomatic patients compared to 39 pg/ml in asymptomatic patients, and correlated with NYHA functional class. Using a cut-off value of 66 pg/ml, plasma BNP had a sensitivity of 84%, specificity of 82% and AUC of 0.86 for the detection of symptoms. This is similar to the study by Gerber et al., which demonstrated a sensitivity of 76%, specificity of 76% and AUC of 0.84 at a BNP cut-off value of 14 pmol/L. Patients in the study by Lim et al., were only followed for an average 4.6 months for adverse outcomes (death or aortic valve replacement), however it is surprising to see clinical changes occurring in such a short time span. In multivariate analysis, BNP level was significantly associated with mortality, with no death occurring at the BNP level of <74 pg/ml, whilst survival was significantly reduced at BNP level of >97 pg/ml.

One limitation of the analysis was the failure to include sex in the multivariate analysis. Since women have higher BNP levels, the higher percentage of women in the symptomatic group (47% vs. 23%) might have accounted for the higher BNP level in that group as well as in patients with events.

Another limitation is the lack of general applicability of the results. BNP levels are not only elevated in congestive heart failure and aortic stenosis, but in a wide variety of other conditions which accompany senile degenerative aortic stenosis such as aortic insufficiency, mitral insufficiency, atrial fibrillation, coronary artery disease, cor pulmonale and possibly renal failure. In a study of patients with moderate-severe aortic stenosis by Otto et al.¹¹ co-existing aortic insufficiency was present in 78% of patients (73% mild, 5% moderate or severe) and mitral insufficiency was present in 90% (89% mild and 1% moderate). In addition atrial fibrillation was present in 4%, ejection fraction was <50% in 7%, and regional wall motion abnormalities (implying coronary artery disease) were seen in 14% of the patients. Studies of aortic

stenosis and BNP, have appropriately excluded patients with some or all of the above confounding variables. However, this restricts the clinical applicability of BNP as a marker of outcomes to patients with pure aortic stenosis. Whether the BNP level remains useful in patients with aortic stenosis and other cardiac diseases associated with elevated BNP levels, remains unanswered.

Finally, the authors imply operating on asymptomatic patients with severe aortic stenosis and elevated BNP levels to reduce the risk of sudden death. However, the risk of sudden death in *truly* asymptomatic patients is relatively low (0.3–0.4% per year) compared to the risk of surgery (3–4%) and the risk of death from aortic valve prosthesis (1% per year). Risk of death and therefore the benefit of aortic valve replacement does not become apparent until patients become symptomatic.

Sedentary, asymptomatic patients with aortic stenosis should be first evaluated with exercise testing at a low work load to assess symptom status and haemodynamic response. If patients are unable to exercise because of non-cardiac disease then measurement of plasma BNP level in patients with isolated severe aortic stenosis would be useful as a surrogate marker of symptom status and therefore the need for aortic valve replacement. In conclusion, we still do not know how to screen the majority of patients with senile degenerative aortic stenosis and multi-valvar lesions or concomitant complicating medical illnesses.

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