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Determinants and prognostic value of B-type natriuretic peptide in patients with aortic valve stenosis

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ABSTRACT

Background: The prognostic value of N-terminal fragment of pro B-type natriuretic peptide (Nt-proBNP) in aortic stenosis (AS) is still being debated. We sought to evaluate the determinants of Nt-proBNP in AS and its prognostic value in asymptomatic patients.
Methods: Patients with pure isolated at least mild degenerative AS enrolled in our prospective cohort (2006–2013) constituted our population. Clinical and biological measurements as well as echocardiographic evaluations were performed at study entry for all patients. Severe AS was defined by a valve area <1 cm^2. Asymptomatic patients were contacted every six months and seen every year. The occurrence of AS-related events (sudden death, congestive heart failure or new onset of symptoms) within two years was recorded prospectively.
Results: We enrolled 809 patients. Nt-proBNP increased with AS severity ($p < 0.0001$) and symptomatic status ($p < 0.0001$) but there was a wide overlap between groups of AS severity or symptomatic status. Nt-proBNP was the result of complex interactions between multiple determinants, including AS severity and symptomatic status but also age ($p = 0.0008$), history of coronary artery disease ($p = 0.03$), rhythm ($p = 0.007$) and diastolic function ($p < 0.0001$). Consequently, in asymptomatic patients with moderate/severe AS, normal ejection fraction and in sinus rhythm, Nt-proBNP was associated with AS-related events in univariate analysis ($p = 0.009$) but not after adjustment for AS severity ($p = 0.12$). Repeated Nt-proBNP measurements at one year did not improve their predictive value ($p = 0.43$).
Conclusion: This study highlights the limitations of Nt-proBNP in AS and raises caution regarding its use, at least as a single factor, in the decision-making process regarding asymptomatic patients with AS.

1. Introduction

Aortic valve stenosis (AS) is the most common valvular heart disease in Western countries. AS affects 2%–7% of the population above 70 years and its prevalence is due to increase dramatically with population aging [1,2]. Symptoms are the main trigger for aortic valve replacement but treatment of asymptomatic patients remains controversial due, on the one side, to the risk of sudden death without preceding symptoms and irreversible myocardial dysfunction and, on the other side, to the risk of surgery and prosthetic valve complications. Identifying subsets of asymptomatic AS patients with preserved left ventricular ejection fraction (LVEF) who may benefit from early or prophylactic surgery is therefore a critical clinical challenge.

B-type natriuretic peptide (BNP) is a peptide secreted by cardiomyocytes in response to pressure overload. Previous studies have shown that plasma levels of BNP/Nt-proBNP (N-terminal fragment of proBNP) are elevated in AS, increase with AS severity and symptomatic status, and may provide independent prognostic information [3–8]. The European Society of Cardiology (ESC) guidelines introduced the use of natriuretic peptides in the management of patients with AS in 2012

Abbreviations: ACE, Angiotensin-converting enzyme; AF, Atrial fibrillation; ARB, Angiotensin II receptor blocker; AS, Aortic valve stenosis; AUC, Area under the curve; AVA, Aortic valve area; BNP, Brain natriuretic peptide; BMI, Body mass index; CAD, Coronary artery disease; LV, Left ventricle; LVEF, Left ventricular ejection fraction; MPG, Mean pressure gradient; NYHA, New York Heart Association; Nt-proBNP, N-terminal fragment of pro B-type natriuretic peptide; PV, Peak velocity; R, Correlation coefficient; ROC, Receiver operator characteristic; SD, Standard deviation; TTE, Transthoracic echocardiography.

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[9] (class IIb recommendation, level of evidence C) but these do not feature in the newly updated American Heart Association/American College of Cardiology (ACC/AHA) guidelines [10]. In a previous study we found that Nt-proBNP had a poor diagnostic value for severe symptomatic AS and that Nt-proBNP was not an independent predictor of outcome in asymptomatic patients [11]. However, sample size was limited, we only focused on elderly patients and the prognostic value of repeated measurements could not be evaluated. Thus, in a large ongoing prospective cohort of AS patients with a wide range of AS severity, symptomatic status and age, we sought to confirm and broaden our previous findings firstly by assessing the determinants of Nt-proBNP and, more specifically, the impact of age and gender; secondly by evaluating the independent prognostic value of Nt-proBNP in asymptomatic patients and thirdly by evaluating the prognostic value of serial Nt-proBNP measurements.

2. Methods

2.1. Study design

Our study population comprised symptomatic and asymptomatic patients with pure isolated at least mild degenerative AS enrolled between November 2006 and July 2013 in our ongoing prospective cohort, COFRASA (clinicaltrial.gov number NCT 00338676) and GENERAC (clinicaltrial.gov number NCT00647088) seeking to evaluate the determinants of AS occurrence and progression. Exclusion criteria were: AS due to rheumatic valve disease or radiotherapy; previous infective endocarditis; more than mild associated valvular disease; and severe respiratory or renal insufficiency (creatinine clearance ≤30 ml/min). Clinical and biological measurements, including Nt-proBNP and echocardiographic evaluation, were performed at study entry for all patients. Asymptomatic patients were contacted every six months and seen at our research center every year. In asymptomatic patients at enrolment, Nt-proBNP was also measured again at one year. Our regional ethics committees approved the study and all patients gave written informed consent.

2.2. Clinical assessment

Medical history, cardiovascular risk factors and medications were recorded prospectively. A physical examination including blood pressure measurement and ECG was performed at study entry. Body mass index (BMI) was calculated for each patient and obesity was defined as a BMI > 30 kg/m^2. Assessment of symptoms was performed by experienced cardiologists blinded to Nt-proBNP values. The extent of dyspnea was assessed based on the NYHA classification. Asymptomatic patients had to be free of dyspnea, angina and syncope. Coronary artery disease (CAD) was defined as a history of angina, coronary angioplasty, coronary artery bypass or myocardial infarction. In the subset of asymptomatic patients, the occurrence of AS-related events—sudden death, congestive heart failure or new onset of symptoms (dyspnea, angina or syncope)—was recorded prospectively.

2.3. Echocardiography

A comprehensive Doppler echocardiography was performed for all patients at baseline. Assessment of AS severity was based on peak velocity (PV), mean gradient (MG) and aortic valve area (AVA) calculated using the continuity eq. [12] Mild AS was defined by an AVA between 1.5 and 2 cm^2, moderate AS by an AVA between 1 and 1.5 cm^2, and severe AS by an AVA < 1 cm^2. Apical 4-, 3- and 2-chamber cine loops, parasternal long-axis and short-axis views were obtained, while the LVEF was determined visually or using the Simpson method. LVEF ≥50% was considered normal. Mitral inflow velocities (E- and A-waves) using pulsed-wave Doppler and mitral annular velocities (E′-wave) using pulsed-wave tissue Doppler imaging at the septal level were recorded in the apical four-chamber view. Diastolic function grade was established based on E/A and E/E′ ratios, as recommended [13]. Left atrial volume was measured using the biplane area-length method. Left ventricular mass was calculated using the Devereux formula [14].

2.4. Laboratory analysis

All blood samples were taken at inclusion in identical conditions—at 08:00 AM, after 12 h of fasting, within 24 to 48 h of the scan—and were processed immediately. Nt-proBNP was measured by chemiluminescent immunoassay (Dimension Vista, Siemens). Nt-proBNP was considered normal when <300 pg/ml, intermediate between 300 and 700 pg/ml and high at >700 pg/ml. Creatinine clearance was calculated using the modified diet in renal disease (MDRD) formula.

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD, median [interquartile range] or patient numbers (percentages). Comparisons between symptomatic/asymptomatic patients and comparisons of Nt-proBNP values between grades of AS severity or NYHA classes were performed using *t*-test, one-way analysis of variance, χ^2 or Wilcoxon–Kruskall–Wallis tests, as appropriate. Association between Nt-proBNP values and hemodynamic parameters of AS severity was evaluated using linear regression. As Nt-proBNP was not normally distributed, a log transformation was used. Univariate and stepwise multiple linear regression analyses were used to identify determinants of Nt-proBNP. Event-free survival—composite endpoint of AS-related events defined by sudden death, congestive heart failure or new onset of symptoms (dyspnea, angina or syncope)—was assessed using the Kaplan–Meier analysis in asymptomatic patients. Comparison of event-free survival by Nt-proBNP level was performed with a log-rank test. Cox proportional-hazard analyses evaluated the predictive value of Nt-proBNP for event-free survival in univariate and multivariate analysis. Event-free survival by absolute (Nt-proBNP at one year—baseline Nt-proBNP) or relative ((Nt-proBNP at one year—baseline Nt-proBNP)/baseline Nt-proBNP) Nt-proBNP progression was also assessed using the Kaplan–Meier analysis. All tests were two-sided and performed using JMP7® software. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Eight hundred and nine patients were enrolled prospectively. Baseline characteristics of the population are presented fully in Table 1; 506 (63%) were male; mean age was 75 ± 10 years (median 77, range [70–83]). Most of the patients were in sinus rhythm (725 patients, 90%). One hundred and fifty-four patients (19%) had a bicuspid aortic valve. Eighty patients (10%) had mild AS, 180 patients (22%) moderate AS and 549 patients (68%) severe AS. Among the 549 patients with severe AS, 107 (19%) were asymptomatic and 442 patients (81%) were symptomatic: 417 (94%) presented with dyspnea, 125 (28%) with angina and 50 (11%) with syncope. All symptomatic patients had severe AS, and all patients with mild/moderate AS were asymptomatic by design. Comparison between symptomatic and asymptomatic patients is presented in the third and fourth columns of Table 1. Mean Nt-proBNP serum level was 1381 ± 3515 pg/ml but values were widely scattered (median 376 [141–1124]).

3.2. Determinants of Nt-proBNP

3.2.1. Impact of AS severity

Nt-proBNP increased with the grade of AS severity defined using AVA ($p < 0.0001$), mean gradient ($p = 0.0006$) or peak velocity ($p = 0.0002$), but correlations between Nt-proBNP and hemodynamic parameters were modest ($R = -0.24$, $R = 0.12$ and $R = 0.13$, respectively) (Fig. 1A–C). Furthermore, Nt-proBNP values were widely scattered with a large overlap between patients with mild, moderate and severe AS (Fig. 1D–F).

3.2.2. Impact of symptomatic status

Nt-proBNP was higher in symptomatic patients than in asymptomatic patients, overall (2141 ± 4561 vs. 464 ± 813 pg/ml, $p < 0.0001$) (Fig. 2A) and in the subgroup of 549 patients with severe AS (AVA < 1 cm^2) (2141 ± 4561 vs. 491 ± 839 pg/ml, $p = 0.0001$) (Fig. 2B) but Nt-proBNP values were widely scattered with a large overlap between asymptomatic and symptomatic patients. Furthermore, among the 442 symptomatic patients, 130 patients (29%) had normal Nt-proBNP values (<300 pg/ml), while 96 (22%) had intermediate values and 216 (49%) high Nt-proBNP values (>700 pg/ml). The percentage of patients with severe symptomatic AS referred for surgery with normal Nt-proBNP values was also similarly high, excluding obese patients, patients with LVEF < 50%, those in AF or all three (29%, 34%, 33% and 37%, respectively).

3.2.3. Impact of age

Age was modestly but significantly correlated with Nt-proBNP ($R = 0.42$, $p < 0.0001$) (Fig. 3B). Nt-proBNP values were higher in patients ≥70 years ($N = 620$) than in patients <70 years ($N = 189$) in all subsets—overall (1669 ± 3946 pg/ml vs. 426 ± 798 pg/ml; $p < 0.0001$) (Fig. 3A), in each grade of AS severity (all $p < 0.05$), in symptomatic patients ($p < 0.0001$) and in asymptomatic patients ($p < 0.0001$)—but

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