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Original article

Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis

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ABSTRACT

Background: Once aortic stenosis (AS) is severe, patients develop symptoms at different stages. Indeed, symptom status may correlate poorly with the grade of valve narrowing. Multiple pathophysiological mechanisms, other than valvular load, may explain the link between AS and symptom severity. We aimed to describe the relationship between the severity of symptoms and the characteristics of a cohort of patients with severe AS already referred for aortic valve replacement (AVR).

Methods: We analyzed 118 consecutive patients (70 ± 9 years, 55% men) with severe AS referred for AVR. We identified 84 patients with New York Heart Association (NYHA) I–II, and 34 with NYHA III–IV symptoms. Clinical and echocardiographic parameters were compared between these two groups. Left ventricular ejection fraction (LVEF), global longitudinal peak systolic strain (GLPS), NT-pro-B-type natriuretic peptide (BNP), and high-sensitive troponin T (hs-TNT) were determined at the time of admission.

Results: AS severity was similar between groups. Compared with the NYHA I–II group, patients in NYHA III–IV group were older and more likely to have comorbidities, worse intracardiac hemodynamics and more LV damage. Variables independently associated with NYHA III–IV symptomatology were the absence of sinus rhythm, higher E/e′ ratio, and increased hs-TNT. GLPS showed a good correlation not only with hs-TNT as a marker of myocardial damage, but also with markers of increased afterload imposed on LV, being not directly related with advanced symptoms.

Conclusions: Advanced symptoms in patients with severe AS referred for AVR are associated with worse intracardiac hemodynamics, absence of sinus rhythm, and more myocardial damage. It supports the concept of transition from adaptive LV remodeling to myocyte death as an important determinant of symptoms of heart failure.

Introduction

Aortic stenosis (AS) is a progressive disease characterized by a long asymptomatic period. Once symptoms occur, patient survival is markedly limited. Progressive pressure overload imposed on the left ventricle (LV) in the presence of longstanding AS often leads to LV remodeling and hypertrophy, even in the absence of symptoms [1]. These structural changes may gradually cause diastolic and, at a later stage, systolic dysfunctions [2]. Furthermore, it has been demonstrated that the cardiac structural and functional alterations are associated not only with the development of symptoms [3,4], but also with the type of symptom (i.e. angina, dyspnea, or syncope) [5,6]. However, it has been never investigated which clinical and echocardiographic characteristics are associated with the presence of advanced symptoms in patients with severe AS referred for aortic valve replacement (AVR). Whether the severity of valve narrowing itself or the cardiac structural changes secondary to valvular afterload determines the severity of symptoms is still not well understood. Hence, we aimed to describe the relationship between the presence of advanced symptoms and the clinical and echocardiographic characteristics of a cohort of patients with severe AS referred for AVR.

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Methods

Population

Between August 2012 and February 2013, 118 patients (70 ± 9 years, 55% men) referred to our center with severe AS for AVR were evaluated by our echocardiographic laboratory and prospectively enrolled in this study. Severe AS was the principal indication for surgery, and patients having an associated cardiac valve lesion more than moderate were excluded. Symptoms related to AS were recorded by a cardiologist at admission and before echocardiographic evaluation. According to a combination of the Canadian Cardiovascular Society score (CCS) and the New York Heart Association (NYHA) functional class, the symptoms were represented as follows: NYHA-I, no symptoms; NYHA-II, symptoms with moderate exertion (including CCS II and I); NYHA-III, symptoms with mild exertion (CCS III); and NYHA-IV, symptoms at rest (CCS IV). Patients presenting an isolated episode of syncope with moderate exertion without other symptoms in daily activity were considered to be at NYHA class II. Afterwards, the whole population was divided into two groups: 84 with NYHA I–II and 34 with NYHA III–IV (advanced) symptoms. Within patients in NYHA-I class, the indication for surgery was assessed by the referring cardiologist, usually by an abnormal exercise test or the rate of peak transvalvular velocity progression. Other data collected at the time of admission included the cardiovascular risk factors, previous history of renal injury (diagnosed chronic renal failure, history of even mild acute renal injury in the last 6 months, or rise in the preoperative serum creatinine), stroke or transient ischemic attack, presence of coronary artery disease (CAD: stenosis >50% on angiography), N-terminal-pro-B-type natriuretic peptide (BNP), C-reactive protein (CRP), and high-sensitive troponin T (hs-TNT). The BNP ratio (the ratio of BNP to the reference BNP value for age and sex) was also measured. BNP ratio >1 was interpreted as clinical BNP activation as already suggested [7]. Finally, absence of sinus rhythm was defined as history of permanent or persistent atrial fibrillation (AF), or presence of AF at the time of submission.

Echocardiographic study

Commercially available ultrasound machines (Vivid-7 and E9, General Electric Healthcare, Wauwatosa, WI, USA) equipped with an M4S or M5S probe were used for all echocardiographic examinations. For LV and left atrial (LA) chamber quantification, we followed the recommendations [8]. LA volume (LAV) was obtained with the biplane area-length technique, and LA area (LAA) was measured in an apical four-chamber view. LV volumes and ejection fraction (EF) were calculated using the biplane Simpson disk method. LV mass was estimated using the linear method with the formula recommended by the American Society of Echocardiography [9]. Continuous wave Doppler was used to measure the aortic transvalvular peak velocities; peak and mean gradients were calculated using the simplified Bernoulli equation, and aortic valve area (AVA) using the continuity equation. AS severity was graded according to recommended guidelines [10]. Peak velocities during early diastole (e′) were obtained at the level of septal mitral annulus using pulsed wave tissue Doppler. The E/e′ ratio was then calculated. Mitral annular plane systolic excursion (MAPSE) was measured in an apical four-chamber view with M-mode beam positioned on the lateral mitral annulus. In patients with AF, measurements were averaged from five heart cycles.

Left ventricular strain

Using the two-dimensional speckle-tracking approach, the global longitudinal myocardial deformation was evaluated as the average of the segment strains from the apical four-chamber, two-chamber, and long-axis views. Endocardial borders were traced with a software tool (AFI: Automated Function Imaging, GE Healthcare) that automates 2D speckle tracking to measure real-time deformation of the myocardial wall. After the tracking quality was verified for each segment, myocardial motion was analyzed by speckle tracking within the region of interest [11]. In patients with AF, we recorded apical loops with similar R–R intervals. When not possible, global longitudinal peak systolic strain (GLPS) was recorded as missed.

GLPS could be successfully measured in 114 of 118 patients (97%). Additionally, intraobserver and interobserver variability was assessed in 20 patients. The intraobserver analysis showed a mean absolute difference of 0.1% (95% confidence interval, −0.18 to 0.39%) for GLPS. The interobserver analysis showed a mean absolute difference of −0.55% (95% CI, −0.98 to −0.12%) for GLPS, with good intraclass correlation (0.99, 95% CI 0.96–0.99; $p < 0.001$).

Statistical analysis

Continuous variables are expressed as mean ± SD. Dichotomous data are presented as percentages. Statistical differences between groups were assessed using Student's *t*-test for continuous variables or Fisher's exact test for categorical variables. Multigroup comparisons of continuous variables were performed using an analysis of variance. Continuous data that were not normally distributed (i.e. BNP, hs-TNT, CRP, and EuroSCORE) are presented as median values and corresponding interquartile ranges (IQR: 25th and 75th percentiles), and were analyzed using non-parametric statistical tests, as the Mann–Whitney test, and their natural logarithms were used for logistic regression and correlation. Variables associated with more advanced symptoms were determined with binary logistic regression analyses. Those with a good correlation and assumed to have a clinical implication (i.e. age, diabetes, hypertension, and CAD) were incorporated into the model and selected by a backward procedure. Two-tailed *p*-values <0.05 were considered statistically significant. Analyses were performed using SPSS software (IBM-SPSS Statistics, Version 20, IBM Corp., New York, NY, USA).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.

Results

Characteristics of the patients

Tables 1 and 2 list the demographic and echocardiographic characteristics of the study population. In the whole cohort, 16% ($n = 19$) of patients were characterized as being in NYHA class I, and all other patients were symptomatic as follows: 55% ($n = 65$) in NYHA class II, 26% ($n = 31$) in NYHA class III, and 2.5% ($n = 3$) in NYHA class IV. A bicuspid aortic valve was observed in 20 patients (17%). From the total population, 87 patients (74%) had no or mild mitral valve regurgitation (MR), and 31 (26%) had mild to moderate MR. The median overall logistic EuroSCORE was 3.7 (IQR: 1.95–6.5). The indexed AVA was 0.37 ± 0.09 cm^2/m^2 and LVEF 58 ± 10%.

Surgical characteristics

A total of 68 (57.6%) patients underwent isolated AVR. A biological prosthesis was inserted in 93% of patients. A coronary artery bypass graft (CABG) was performed in 21 patients (17.8%) with no differences between groups. Interestingly, of the 54 patients presenting with chest pain (angina), only 13 (24%) had a CAD on angiography, and 12 (22%) received a revascularization (one patient underwent a surgical AVR with one vessel CAD considered to be non-revascularizable). A higher rate of concomitant pulmonary vein

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