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Original article

Prognostic implications in patients with symptomatic aortic stenosis and preserved ejection fraction: Japanese multicenter aortic stenosis, retrospective (JUST-R) registry

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ABSTRACT

Background: Current prognostic implication of symptomatic patients with aortic stenosis (AS) remains undetermined. This study investigated the current prognostic implications of AS-related symptoms and the effect of aortic valve replacement (AVR) on outcome.
Methods: We enrolled 586 consecutive patients with severe AS (aortic valve area $<1.0\ cm^2$) with preserved left ventricular ejection fraction ($\geq$50%). All patients were stratified into the following four groups based on the predominant symptoms: Group 1, asymptomatic ($n = 316$); Group 2, chest pain ($n = 41$); Group 3, heart failure ($n = 192$); or Group 4, syncope ($n = 37$).
Results: AS-related symptoms were diagnosed in 270 patients (46.1%), among whom 182 patients (32.2%) received AVR. Thirty-nine patients (6.7%) had cardiac death during the mean follow-up of 16 ± 14 months. AVR was associated with significant reduction in cardiac death in Groups 3 ($p < 0.001$) and 4 ($p = 0.004$) whereas no significant prognostic advantage of AVR was observed in Groups 1 or 2. Cox proportional-hazard multivariate analysis revealed that age, heart failure, and mean pressure gradient (PG) were associated with increased risk of cardiac death in all patients regardless of AVR [hazard ratio (HR): 1.079, 2.090, and 1.008 respectively, all $p < 0.05$]. In the patients without AVR, age, heart failure, syncope, and mean PG were independently associated with cardiac death (HR: 1.130, 3.639, 4.638, and 1.008, all $p < 0.05$).
Conclusion: This retrospective study demonstrated the current associations between the types of AS symptoms and prognosis in Japanese patients with severe AS.

Introduction

Senile degenerative aortic stenosis (AS) is the most common form of valvular heart disease in developed countries, and its prevalence is rapidly increasing along with the aging population [1]. There is general agreement among physicians and surgeons that aortic valve replacement (AVR) should be performed in patients with symptomatic severe AS because of the well-established unfavorable outcomes in unoperated cases and overall excellent surgical outcomes with relatively low perioperative mortality and morbidity [2–8]. Despite the lack of data from randomized clinical trials, various professional organizations consider symptomatic severe AS as a class I indication for aortic valve surgery [9,10]. Nowadays, the predominant cause of AS has changed from rheumatic valve disease to degenerative disease [11]; the number of aging patients has been increasing over the past few decades in developed countries [12]. The current associations between the types of symptoms and prognosis in

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severe degenerative AS patients treated with and without AVR are not readily available in Japan. Therefore, this multicenter study investigated the impact of symptomatic status on future prognosis in severe AS patients with preserved left ventricular ejection fraction (LVEF) treated with AVR and those treated with conservative medical therapy.

Methods

Study population

This retrospective study included 663 patients with aortic valve area (AVA) $<1.0\ cm^2$ treated at one of the four Japanese tertiary cardiovascular centers between 2008 and 2012, St Marianna University ($n = 100$), University of Occupational and Environmental Health ($n = 254$), University of Tsukuba ($n = 122$), and Gunma Prefectural Cardiovascular Center ($n = 187$). Patients with additional hemodynamically significant (moderate and severe) valve lesions were excluded from the study. The study protocol was approved by the ethics committee in each hospital.

Demographic data collection

Clinical data, including age, sex, body surface area, brachial blood pressure, heart rate, documented diagnoses of hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, previous history of myocardial infarction, coronary artery bypass grafting, and hemodialysis due to chronic renal failure, were collected at the time of echocardiographic examination. Echocardiographic measurements and prognoses were compared across the groups. The medical records of all patients reported by the primary physicians in each hospital were carefully reviewed by cardiologists. All study patients were stratified into the following four groups based on predominant symptoms at baseline: Group 1, asymptomatic; Group 2, chest pain (Canadian Cardiovascular Society class $\geq$I); Group 3, heart failure (New York Heart Association functional classification $\geq$II); and Group 4, syncope. Patients with presyncope were also included in Group 4, and patients with chest heaviness and chest discomfort were included in Group 2. When the patients had multiple symptoms, primary physicians or experienced cardiologists who reviewed the medical records diagnosed their predominant symptoms. Follow-up information was obtained regularly at the outpatient clinics. Patients, physicians, and next of kin were contacted by telephone when patients had been treated in the other hospitals.

Echocardiographic study

Comprehensive transthoracic echocardiography, including M-mode, two-dimensional, and Doppler echocardiography, was performed using commercially available ultrasound equipment in each hospital according to the guidelines described by the American Society of Echocardiography [13]. An aortic valve jet velocity was recorded from multiple acoustic windows, such as apical, right parasternal, and suprasternal windows, to yield the highest-velocity signal [9]. The LV end-diastolic and end-systolic volumes, stroke volume (SV), and LVEF were measured according to the biplane Simpson's method in the apical 4- and 2-chamber views. Relative wall thickness was estimated as 2 $\times$ (diastolic LV posterior wall thickness)/LV end-diastolic diameter [13]. LV mass was calculated using Devereux's formula [14]. The maximum left atrial volume was measured using the biplane Simpson's method and indexed to body surface area [13]. Peak early and late diastolic velocities of the left ventricular inflow (E and A velocities), deceleration time of E velocity, and peak early diastolic velocity at the septal corner of the mitral annulus (ε') were measured in the apical 4-chamber view. As a measure of global LV afterload, the valvulo-arterial impedance was determined using the following formula: valvulo-arterial impedance = (systolic arterial pressure + mean pressure gradient)/SV index. Systemic arterial compliance was calculated using the following formula: systemic arterial compliance = stroke volume index/brachial pulse pressure [15]. Using the aortic cross-sectional area at the sinotubular junction, energy loss coefficient was determined as AVA $\times$ aortic cross-sectional area at the sinotubular junction/(aortic cross-sectional area at the sinotubular junction $-$ AVA) [15]. AVA was calculated using the continuity equation [9,10]. SV was determined by two-dimensional echocardiography, and AVA was calculated as AVA = SV (two-dimensional biplane Simpson's method)/velocity time integral of peak aortic valve velocities [9,10]. AVA was indexed to body surface (indexed AVA).

Study endpoint

The primary study endpoint was cardiac death regardless of aortic valve surgery. The secondary endpoint was major cardiocerebrovascular events defined as AVR plus cardio-cerebrovascular events, including cardiac death, nonfatal myocardial infarction, hospitalization for heart failure, stroke and ventricular tachyarrhythmia.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation or percentage unless otherwise specified. Data were compared among the four subgroups using one-way analysis of variance with post hoc Turkey's test. Probabilities of event-free survival among the four subgroups were obtained using Kaplan–Meier analysis and compared using the two-sided log-rank test. The impact of group classification on event-free survival was assessed using the Cox proportional-hazard model in univariate and multivariate analyses. Variables with a univariate value of $p < 0.05$ were incorporated into the multivariate models. Because of collinearity, the variables included in the multivariate models were selected with special care. The group classification was entered into the model; Group 1 was considered as a reference. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS 18.0 (SPSS, Inc, Chicago, IL, USA).

Results

Patients' characteristics

Among the 663 study patients, 77 patients were excluded from the analysis due to LVEF $< 50\%$ ($n = 55$), unknown symptoms ($n = 6$), and follow-up data unavailable ($n = 16$). Thus, the final group consisted of 586 patients (mean age, 76 $\pm$ 9 years, 211 men) with severe AS and LVEF $\geq 50\%$ were included. According to their predominant symptoms at baseline, all patients were stratified into asymptomatic (Group 1, $n = 316$); chest pain (Group 2, $n = 41$); heart failure (New York Heart Association functional class $\geq$II, Group 3, $n = 192$), and syncope (Group 4, $n = 37$; Fig. 1). Clinical characteristics of the total population are shown in Table 1. Most of the patients were female, with a higher prevalence of hypertension. No differences in the demographic findings except systolic and diastolic blood pressure or the use of β-blockers and diuretics were observed across the four subgroups (Table 1). The baseline echocardiographic findings of the four groups are shown in Table 2. Asymptomatic group (Group 1) demonstrated greater AVA, indexed AVA, and energy loss coefficient and lower peak velocity and mean pressure gradient (PG) compared to the other three symptomatic groups. No significant differences in the LV end-diastolic volume, end-diastolic volume index, SV, or SV index were observed among the four groups, whereas the group of

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