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Impact of aortic plaque on progression rate and prognosis of aortic stenosis☆

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ABSTRACT

Backgrounds: Patients with aortic stenosis (AS) have a high prevalence of aortic plaque. However, no data exist regarding the clinical significance and prognostic value of aortic plaque in AS patients. This study examines the impact of aortic plaque on the rate of progression and clinical outcomes of AS.

Methods: We retrospectively investigated 1812 transesophageal echocardiographic examinations between 2008 and 2015. We selected 100 consecutive patients (mean age; 75.1 ± 7.4 years) who showed maximal aortic jet velocity (AV-Vel) ≥2.0 m/s by transthoracic echocardiography (TTE) and received follow-up TTE (mean follow-up duration 25 ± 17 months), and the mean progression rate of AV-Vel was calculated. Clinical and echocardiographic characteristics, including severity of aortic plaque, and cardiac events were examined.

Results: At initial TTE, mean AV-Vel was 3.68 ± 0.94 m/s and mean aortic valve area 0.98 ± 0.32 cm^2. Mean progression rate of AV-Vel was 0.41 m/s/year in 38 patients with severe aortic plaque, and −0.03 m/s/year in the remaining 62 patients without severe aortic plaque. Severe aortic plaque (odds ratio[*OR*], 8.32) and hemodialysis (OR, 6.03) were independent predictors of rapid progression. The event-free survival rate at 3 years was significantly lower in patients with severe aortic plaque than in those without (52% vs 82%, $p = 0.002$). Severe aortic plaque (hazard ratio[*HR*], 2.89) and AV-Vel at initial TTE (HR, 3.28) were identified as independent predictors of cardiac events.

Conclusion: Severe aortic plaque was a predictor of rapid progression and poor prognosis in AS patients. Evaluation of aortic plaque provides additional information regarding surgical scheduling and follow-up.

1. Introduction

Aortic stenosis (AS) is a chronic and progressive disease and its prevalence increases with age [1,2]. The population affected by AS has been growing in parallel with prolonged life expectancy. AS is considered to be the result of a degenerative process of the aortic valve with some similarities to other atherosclerotic diseases [3].

Previous studies showed that severe aortic plaque detected by transesophageal echocardiography (TEE) was related to the incidence of significant coronary artery disease [4–6]. This finding suggests that aortic plaque may be a manifestation of a systemic atherosclerotic process. Furthermore, recent studies have reported that patients with severe AS have a high prevalence of severe aortic plaque [7–9]. There is a possibility that the presence of aortic plaque may be related to rapid progression and/or poor prognosis of AS. The purpose of this study is to examine the impact of aortic plaque on the progression rate and clinical outcomes of AS.

2. Methods

2.1. Study population

We retrospectively investigated 1812 consecutive TEE examinations conducted in Tenri Hospital between January 2008 and July 2015, among which 251 showed maximal aortic jet velocity (AV-Vel) of ≥2.0 m/s on transthoracic echocardiography (TTE). Of these 251 AS patients, 120 were symptomatic and received aortic valve surgery soon after TEE, 27 did not undergo follow-up TTE, and in 4 patients aortic plaque could not be evaluated because of poor image quality.

After excluding these 151 patients, the study population consisted of 100 asymptomatic AS patients (mean age 75.1 ± 7.4 years) with AV-Vel ≥2.0 m/s who received follow-up TTE. The progression rate of AS and clinical outcomes were evaluated and its predictors were investigated. Furthermore, we also evaluated the progression rate and clinical outcomes of AS dividing into the subgroup of patients with severe AS (AV-Vel ≥4.0 m/s) and mild to moderate AS (AV-Vel <4.0 m/s). The study protocol was approved by the institutional ethics committee at Tenri Hospital.

☆ All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2.2. TTE evaluation and progression rate of AS

Comprehensive echocardiographic assessments were conducted by experienced sonographers using commercially available ultrasound systems. Quantification of left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension, and thickness of interventricular septum (IVST) and left ventricular posterior wall (LVPWT) were measured according to established guidelines [10]. Left ventricular mass was also calculated according to the guidelines as follows; left ventricular mass = $0.8(1.04[LVDd + LVPWT + IVST]^3\text{-}[LVDd]^3) + 0.6$ [10]. Left ventricular ejection fraction was measured using the modified Simpson method. AV-Vel was measured, and the aortic valve area (AVA) was obtained using the standard continuity equation. The transmitral flow signal was traced manually, and the peak early filling velocity was obtained. The mean progression rate of AV-Vel (m/s/year) was calculated as follows:

Mean progression rate of AV-Vel = (AV-Vel at follow-up measurement − AV-Vel at initial diagnosis)/time interval between the two measurements.

Rapid progression was defined as a mean progression rate of AV-Vel ≥0.3 m/s/year and slow progression as a mean progression rate of AV-Vel <0.3 m/s/year. This cut-off value was determined based on previous reports [11,12].

2.3. TEE evaluation of aortic plaque in the thoracic aorta

TEE was conducted by experienced cardiologists using commercially available ultrasound systems to observe the horizontal and longitudinal views of the aortic arch and descending thoracic aorta. At our institution, all of the original TEE data were recorded in video tape. Experienced cardiologists who were unaware of patient's background examined aortic plaque at the aortic arch and descending thoracic aorta from original TEE images. Aortic plaque was defined as severe if there was protruding plaque of ≥4 mm thickness and/or complex plaque according to previous studies [13,14]. Complex plaque included mobile plaque or ulceration. The thickness of plaque was defined as the distance between the media-adventitial border and the lumen of the aorta, measured at its maximal site. Ulceration was defined as plaque which appeared crater-like and >2 mm in depth and width. Mobile plaque was defined as plaque protruding into the aortic lumen and presenting any degree of mobility. Intra- and inter-observer reproducibility in evaluating severe aortic plaque was assessed using κ coefficient. The median time interval between TEE and TTE at diagnosis was 8 days (interquartile range, 2–25 days).

2.4. Predictors of rapid progression and clinical outcomes of AS

The clinical follow-up data were obtained from medical records. To evaluate predictors of rapid progression and clinical outcomes of AS, we examined clinical factors, medications, laboratory data and echocardiographic parameters at diagnosis. Clinical factors comprised age, gender, smoking habit, and underlying disease including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and hemodialysis. Hypertension was defined by a systolic blood pressure of ≥140 mm Hg and/or a diastolic pressure of ≥90 mm Hg, or use of anti-hypertensive medications. Dyslipidemia was defined by a serum cholesterol level of ≥220 mg/dL or the use of cholesterol-lowering medications. Diabetes mellitus was defined as hyperglycemia requiring medications. Coronary artery disease was defined by previous histories of angina, myocardial infarction or percutaneous coronary intervention, or a significant coronary artery stenosis revealed by coronary angiography. Medications included statins and aspirin. Laboratory data included C-reactive protein and estimated glomerular filtration rate. Echocardiographic parameters, including the severity of aortic plaque, were as stated above.

Cardiac events were defined as cardiac death or adverse valve-related events. Cardiac death was defined as sudden death or death from congestive heart failure related to AS. Adverse valve-related events were defined as eventual aortic valve replacement (AVR). In addition, our study population included several patients who became symptomatic but did not undergo intervention due to patient refusal or advanced frailty. Therefore, we also defined the emergence of AS-related symptoms (congestive heart failure, syncope, chest pain) as adverse valve-related events for these patients.

2.5. Statistical analysis

Statistical analysis was performed using JMP version 8 (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as mean ± SD or median and interquartile range. The difference in a parameter between two groups was determined using an unpaired *t*-test for continuous variables and Fisher's exact test for non-continuous variables. A logistic regression model was used to assess the contribution of clinical and echocardiographic parameters to the rapid progression of AS. Event-free survival rates are presented as Kaplan–Meier curves, and the comparison between two groups was performed using a log-rank test. The relative risks and 95% confidence interval were calculated using Cox proportional hazards analysis. We selected variables with $p < 0.05$ in the univariate model and included them in the multivariate model. When two variables correlated closely, for example AV-Vel and AVA, we included one of them in the multivariate model. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline patient characteristics and echocardiographic data

The study population comprised 42 men and 58 women with a mean age of 75 ± 7.4 years. The mean follow-up period was 25 ± 17 months (median, 22 months; interquartile range, 12–34 months). At initial TTE, the mean AV-Vel was 3.68 ± 0.94 m/s and mean AVA 0.98 ± 0.32 cm^2. There were 38 patients (38%) with severe aortic plaque and 62 (62%) without severe aortic plaque. The intra- and inter-observer reproducibility in evaluation of severe aortic plaque were 0.92 (κ coefficient: 95% confidence interval, 0.83–1.00) and 0.83 (κ coefficient: 95% confidence interval, 0.72–0.94), respectively. The indication for TEE were as follows; assessment for the severity of AS in 78 patients, evaluation for thrombus or aortic plaque in 12 patients, exclusion for infective endocarditis or shunt disease in 10 patients. The baseline characteristics and echocardiographic data of these 100 patients are shown in Table 1. Patients with severe aortic plaque were older, and had a higher prevalence of smoking habit and coronary artery disease than those without severe aortic plaque. AVA at diagnosis was significantly smaller in patients with severe aortic plaque ($p < 0.001$). AV-Vel at diagnosis was also higher, but was not statistically significant ($p = 0.074$). LVPWT and IVST were thicker, and LVM was higher in patients with severe aortic plaque. The mean progression rate of AV-Vel was significantly higher in patients with severe aortic plaque than in those without ($p < 0.001$). After adjusting AV-Vel at diagnosis by analysis of covariance, mean progression rate of AV-Vel remained significantly higher in patients with severe aortic plaque than in those without ($p < 0.001$).

Among the subgroup of severe AS ($n = 41$), there were 19 patients (46%) with severe aortic plaque and 22 patients (54%) without severe aortic plaque. There was no significant difference in AV-Vel at diagnosis (with severe aortic plaque, 4.66 ± 0.12 m/s; without, 4.58 ± 0.11 m/s; $p = 0.69$), but the mean progression rate of AV-Vel was significantly higher in patients with severe aortic plaque than those without (0.49 ± 0.11 m/s/year vs −0.12 ± 0.11 m/s/year; $p < 0.001$). (Fig. 1A) Among the other subgroup of mild to moderate AS ($n = 59$), there were 19 patients (32%) with severe aortic plaque and 40 patients (68%) without severe aortic plaque. There was no significant difference in AV-Vel at diagnosis (with severe aortic plaque, 3.13 ± 0.46 m/s; without, 2.98 ± 0.55 m/s; $p = 0.32$), but the mean progression rate of AV-Vel was also significantly higher in patients with severe aortic plaque than those without (0.32 ± 0.27 m/s/year vs 0.02 ± 0.26 m/s/year; $p < 0.001$). (Fig. 1B).

3.2. Predictors of rapid progression

Clinical and echocardiographic characteristics were compared between patients with rapid progression (mean progression rate of AV-Vel ≥0.3 m/s/year, $n = 29$) and those with slow progression (AV-Vel <0.3 m/s/year, $n = 79$). In univariate analysis, severe aortic plaque, hemodialysis, AVA at initial TTE, and IVST were related to rapid progression, but there were no significant differences among other clinical characteristics and echocardiographic parameters. In the multivariate logistic regression model, severe aortic plaque (odds ratio, 8.32; 95% confidence interval, 2.86–27.4; $p < 0.001$) and hemodialysis (odds ratio, 6.03; 95% confidence interval, 1.29–31.7; $p = 0.022$) were independent predictors of rapid progression (Table 2).

3.3. Cardiac events and its predictors

There were no cardiac deaths and 32 adverse valve-related events during follow-up. Of 38 patients with severe aortic plaque, 20 became symptomatic (congestive heart failure, 12; syncope, 3; chest pain, 5) at a mean of 20 months after diagnosis. Among these 20 patients, 15 (39%) underwent AVR (surgical, 10; transcatheter, 5) and 1 (2.6%) underwent balloon aortic valvoplasty, but 4 (11%) did not undergo intervention because of the patient's refusal or advanced frailty. No