Association of Thoracic Aorta Calcium Score With Left Ventricular Hypertrophy and Clinical Outcomes in Patients With Severe Aortic Stenosis After Aortic Valve Replacement

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Background. **Substantial aortic calcification is known to be associated with aortic stiffening and subsequent left ventricular (LV) hypertrophy. This study examined whether the thoracic aorta calcium score (TACS) is related to LV hypertrophy and whether it leads to an adverse prognosis in patients with severe aortic stenosis (AS) after aortic valve replacement (AVR).**

Methods. **We retrospectively reviewed 47 patients (mean age, 64 ± 11 years) with isolated severe AS who underwent noncontrast computed tomography of the entire thoracic aorta and who received AVR. TACS was quantified using the volume method with values becoming log transformed ($_{log}$[TACS+1]). Transthoracic echocardiography was performed before and 1 year after the operation.**

Results. **Preoperative LV mass index (LVMI) displayed significant positive correlations with male gender (r = 0.430, p = 0.010) and $_{log}$(TACS+1) (r = 0.556, p = 0.003). In multivariate linear regression analysis, only $_{log}$(TACS+1) was independently associated with LVMI, even after adjusting for age, gender, transaortic mean pressure gradient, and coronary or valve calcium score. Independent determinants for postoperative LVMI included $_{log}$(TACS+1) and preoperative LVMI after 1 year of follow-up echocardiography, adjusting for age, gender, indexed effective orifice area, and coronary or valve calcium score. During a median follow-up period of 54 months after AVR, there were 10 events (21%), which included 4 deaths from all-causes, 3 strokes, 2 inpatient admissions for heart failure, and 1 myocardial infarction. The event-free survival rate was significantly lower for patients with TACS of 2,257 mm^3 or higher compared with those whose TACS was lower than 2,257 mm^3 (log-rank p < 0.001).**

Conclusions. **High TACS was associated with increased LVMI among patients with severe AS. Further, high TACS usefully predicted less regression of LVMI and poor clinical outcomes after AVR. TACS may serve as a useful proxy for predicting LV remodeling and adverse prognosis in patients with severe AS undergoing AVR.**

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Calcific aortic stenosis (AS) is the most commonly acquired valvular disorder found in developed countries [1]. Aortic valve stenosis induces left ventricular (LV) hypertrophy (LVH) as an adaptive response to the chronic overload of the LV and is considered to be the causal link between AS and myocardial ischemia as well as diastolic dysfunction and ventricular arrhythmia associated with sudden death [2]. LVH is linked with an increased risk of postoperative death after aortic valve replacement (AVR) in AS patients [3]. AVR is typically followed by a decline in LVH. Prior studies have further documented gender, preoperative LV mass, and prosthesis-patients mismatch are among the factors that act as independent predictors of postoperative LV mass regression [4, 5].

To date, AS is considered a complex disease associated with the ability of the LV to adapt to increased afterload, the severity of valvular obstruction, and reduced arterial compliance, rather than isolated aortic valve disease [6]. Measurements that integrate the ventricular, vascular, and valvular components of the disease have been reported to advance risk stratification in patients with AS [6], and a close association between arterial stiffness and LV filling pressure or clinical symptoms has further been reported in AS patients [7].

Numerous cohort studies have acknowledged an overlap in several clinical factors (ie, dyslipidemia or hypertension) that are associated with atherosclerosis

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and AS [1]. To this end, atherosclerosis is one of the central factors that leads to the development of vascular calcification. We have previously reported that heavy aortic calcification and resultant arterial stiffening might underlie LVH and diastolic dysfunction in elderly male patients with hypertension [8]. AS is relatively frequent among older patients (predominantly in men) [9] and shares common risk factors with atherosclerosis.

Notably, patients with severe AS reflect a population that is most at risk for heavy aortic calcification and resultant LVH, with the exception of the severity of valvular disease. Despite this, the effect of aortic calcification on LVH and its regression after AVR remains to be investigated in an AS setting. This study sought to test the hypothesis that heavy aortic calcification may result in a more profound LVH and in a worse prognosis after AVR in patients presenting with severe AS.

Patients and Methods

The Institutional Review Board of Yonsei University, Severance Hospital, Seoul, Korea, approved this study.

Study Population

We retrospectively reviewed data of 119 patients who underwent noncontrast computed tomography (CT) of the entire aorta and who received isolated AVR as a consequence of degenerative calcific AS at Severance Cardiovascular Hospital between January 2009 and May 2014. All patients underwent preoperative and postoperative echocardiography. After excluding 10 patients with significant mitral valve dysfunction or aortic regurgitation on preoperative or postoperative echocardiography, 47 patients who underwent concurrent aortic arch replacement along with 15 patients who required concurrent bypass operations, the remaining 47 patients constituted the analytic sample.

Kidney function was ascertained by estimating the glomerular filtration rate (GFR) using the formula according to the Modification of Diet in Renal Disease (MDRD) study as follows [10]: GFR (mL/min/1.73m^2) = 186.3 $\times$ (serum creatinine [mg/dL]$^{-1.154}$ $\times$ age$^{-0.203}$ ($\times$ 0.742, if female). Hypertension was defined as systolic blood pressure of 140 mm Hg higher, diastolic blood pressure of 90 mm Hg or higher, or treatment with antihypertensive agents. Diabetes was defined as treatment with hypoglycemic agents or insulin, or fasting glucose of 126 mg/dL or higher.

The primary end point was defined as the composite of all-cause death, stroke, myocardial infarction, and urgent admission due to heart failure during follow-up. The occurrence of a clinical event was ascertained by review of hospital records and by telephone interview if necessary.

Echocardiographic Measurement

Echocardiography was performed in all 47 patients within 15 $\pm$ 15 days before AVR (range, 1 to 48 days) and within 14 $\pm$ 2 months after AVR (range, 11 to 19 months). The LV dimensions and the ejection fraction were measured as recommended [11]. Septal and LV posterior wall thickness were measured at end diastole. The LV mass was calculated using the formula as recommended [11], and the LV mass index (LVMI) was defined as LV mass indexed for the body surface area. The left atrial (LA) volume was calculated using standard criteria based on the American Society of Echocardiography recommendations, and the LA volume index was defined as the LA volume indexed for the body surface area. Mitral inflow velocities were obtained by pulse-wave Doppler in the apical 4-chamber view. The mitral early diastolic velocity (E) was also measured, whereby peak early diastolic mitral annular (E′) velocity was recorded from the septal mitral annulus. We then calculated the E/E′ ratio, which is a measure of the LV filling pressure.

CT Imaging Protocol and Analysis

CT was performed in all 47 patients within 36 months from the AVR (within –8 $\pm$ 13 months; range, –36 to 12 months). Patients were scanned using a 64-section Sensation 64 CT scanner (Siemens Healthcare, Forchheim, Germany). For calcium scanning, unenhanced CT was performed with prospective electrocardiography-triggered acquisitions in middiastole using 120 to 140 kV with 150 to 220 mAs, depending on the patient's size; 240 ms exposure time per rotation; 330 ms gantry rotation time; and 64-mm $\times$ 0.6-mm slice collimation. Calcium scans were reconstructed at 70% of the R-R interval using a slice thickness of 3 mm with an increment of 3 mm.

Coronary artery, aortic valve, and thoracic aorta calcium scoring were performed on reconstructed images. Foci of coronary artery, aortic valve, and thoracic aorta were identified using semiautomatic Vitrea 2.0 software (Vital Images, Minnetonka, MN) and scored by an experienced technician who was masked to the patient's medical records, as well as being verified by imaging cardiologists (H.J.C. and R.H.) with level 3 clinical competence in cardiovascular CT imaging, in a masked fashion [12].

An objective volume-scoring method included in the system software was determined, which provided a score in cubic millimeters [8]. Lesion-specific calcium scores were summed across all lesions identified within the left main, left anterior descending, left circumflex, and right coronary arteries for estimating the coronary artery calcium score (CACS). Calcification corresponding to the aortic valve leaflets was identified to calculate the aortic valve calcium score (AVCS). The thoracic aorta calcium score (TACS) included calcium scored in the ascending aorta, aortic arch, and descending aorta to the diaphragm level.

Statistical Methods

Variables are reported as percentages or as means $\pm$ standard deviation for normally distributed variables and as the median (interquartile [25% to 75%] range) for nonnormally distributed variables. The nonnormally distributed variables of TACS, CACS, and AVCS were transformed before analysis by adding 1 and obtaining the natural logarithm of the value (eg, $_{\log}$[TACS+1],