Evaluation of Left Ventricular Diastolic Function After Valve Replacement in Aortic Stenosis Using Exercise Doppler Echocardiography

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Background: The aim of the present study was to evaluate the mechanism of diastolic dysfunction (DD) after aortic valve replacement (AVR) in patients with aortic stenosis (AS).

Methods and Results: Supine bicycle exercise Doppler echocardiography (EDE) with measurement of early diastolic peak velocities of transmitial flow (E) and mitral septal annular movement (E') was performed in 38 patients with AS at least 24 months after AVR and in 19 sex- and age-matched normal controls. AS patients had a 27.4±32.7% decrease in the ratio of left ventricular (LV) mass index to LV end-diastolic volume index (LVMI/LVEDVI) after AVR. Pre-AVR E' was significantly lower in AS patients (4.3±1.6 cm/s vs. 7.7±1.6 cm/s, P<0.005), resulting in a higher E/E' (16.7±5.4 vs. 9.3±1.8, P<0.001). E/E' at rest did not change significantly after AVR. Both E and E' increased progressively with exercise, and the increase in E' (P<0.001) but not E (P=0.675) was greater in normal controls than in AS patients (P<0.001). Peak E/E' >13 during EDE was more common in AS patients than in controls (89.5%, 34/39 vs. 0%, 0/19, P<0.001). On multivariate analysis, LVMI/LVEDVI (Y=8.703+4.199X, r=0.433, P=0.001) was the only factor associated with peak E/E' during EDE.

Conclusions: Persistent DD is present after AVR, due primarily to failure in normal physiologic augmentation of LV relaxation during exercise, associated with incomplete or inadequate regression of LV hypertrophy. (Circ J 2012; 76: 2792–2798)

Key Words: Aortic stenosis; Diastolic dysfunction; Doppler echocardiography; Exercise; Left ventricular hypertrophy
prehensively evaluate LV diastolic function and its mechanism, EDE was performed after AVR.

**Methods**

**Subjects**

Patients with AS who underwent uneventful AVR and who had regular follow-up were candidates for this study. Patients with significant coronary artery disease, LV dysfunction, or arrhythmias, and those with a combination of AS and other valvular heart disease were excluded. Patients with dyspnea of New York Heart Association functional class ≥3 or who were admitted to hospital to control heart failure after AVR were also excluded. Patients who underwent both comprehensive echocardiography (before and after AVR) and EDE at least >24 months after AVR were included. The study cohort consisted of 38 patients with AS and 19 sex- and age-matched normal controls. This study was approved by the institutional review board.

**Echocardiography**

Echocardiographic evaluation included LV dimensions and volumes. LV ejection fraction (LVEF) was calculated by modified Simpson’s method from apical views. LV mass was calculated using the ASE formula. The LV mass index (LVMI, LVM/body surface area) and LV end-diastolic volume index (LVEDVI, LVEDV/body surface area) were calculated, and the ratio of LVMI to LVEDVI (LVMI/LVEDVI) was used as an indicator of LV geometry.

Conventional and tissue Doppler techniques were used to evaluate LV diastolic function. Spectral Doppler tracing of diastolic transmitral inflow velocity was obtained using pulsed Doppler imaging, and peak velocities were measured at early (E) and late diastole (A). The tissue Doppler imaging technique was used to record mitral annular velocity at the medial mitral annulus. Early diastolic mitral annular velocity (E’) was measured and the E/E’ ratio was calculated to estimate LV filling pressure.

**EDE**

Multistage supine bicycle exercise testing was performed with a variable load bicycle ergometer (Medical Positioning, Kansas City, MO, USA). The starting workload was 25 W, with increments of 25 W every 3 min to a peak of 50 W. Various hemodynamic variables were measured at each step, including blood pressure, heart rate, LV volumes, and diastolic Doppler indices. From the apical window, a 1–2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from 5 to 10 cardiac cycles were recorded. The mitral inflow velocities were traced and the peak velocities of E and A waves, and the deceleration time of the E wave velocity were determined. The tricuspid regurgitant jet velocity, obtained using continuous wave Doppler, was used to estimate pulmonary artery systolic pressure.

Mitral annulus velocity was measured on tissue Doppler imaging using the pulsed wave Doppler mode. The filter was set to exclude high-frequency signals, and the Nyquist limit was adjusted to a range of 20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. E’ was measured from the apical 4-chamber view with a 2–5-mm sample volume placed at the septal corner of the mitral annulus. These measurements were made at baseline, at each stage of exercise, and during recovery in the same sequence. Measurements were recorded with simultaneous electrocardiography at a sweep speed of 50–100 mm/s. All data were stored digitally and measurements were made at the completion of each study.

Measurement variability was examined in 15 randomly selected subjects, and 3 different stages of EDE were used. Observer variability was examined by comparing the means of Doppler parameters. The intraclass correlation coefficient was used as an index of intra- and inter-observer variability. The coefficients for intra- and inter-observer variability were 0.98 and 0.88, respectively.

**Statistical Analysis**

Results are expressed as mean±SD. Continuous variables in AS patients and normal controls were compared using the Student’s unpaired t-test, and frequency ratios were compared using the chi-square test or Fisher’s exact test, as appropriate. Changes in hemodynamic and echocardiographic variables during exercise or after AVR were compared using the paired t-test. Linear mixed models were used to detect interactions between groups and exercise load for each outcome (E veloc-
ity, E’ velocity and E/E’ ratio). Multiple linear regression models with backward elimination were used to determine independent predictors of peak E/E’ during EDE. Variables with P<0.20 on univariate analysis (age, body surface area, hypertension, LVMI/LVEDVI, and LVEF) were included in multivariate analysis. All statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) and P<0.05 was considered statistically significant.

Results

The study cohort included 38 patients with AS (25 male; mean age, 57.8±12.1 years) and 19 normal controls (11 male; mean age, 55.9±5.2 years). The prevalence of hypertension and diabetes mellitus was 36.8% (n=14) and 5.3% (n=2), respectively. Underlying etiology of AS consisted of degenerative (n=15, 39.5%), bicuspid (n=22, 57.9%) and rheumatic AS (n=1, 2.6%). Among 38 patients with AS, mechanical and tissue valves were used in 30 and in 8 patients, respectively; 6 different types of mechanical valves with 5 different sizes were used, whereas 4 different tissue valves with 4 different sizes were implanted. The most commonly used valve was the St. Jude valve (26 mm), which was implanted in 6 patients, and the other types were implanted in only 1 or 2 patients. The indexed aortic valve area and mean pressure gradient for AS patients before AVR were 0.41±0.08 cm²/m² and 60.8±12.2 mmHg, respectively. EDE was performed 59.2±33.0 months after AVR in AS patients and the indexed valve area and mean pressure gradient were 0.85±0.28 cm²/m² and 20.5±9.8 mmHg, respectively.

LV Geometry and Diastolic Function at Rest

Before AVR, AS patients had significantly higher LVMI and LVMI/LVEDVI than controls, but these parameters decreased dramatically in AS patients after AVR (Table 1), by 25.0±17.7% and 27.4±32.7%, respectively. Follow-up LVMI/
Diastolic Dysfunction After AVR in AS

LVEDVI in AS patients, however, remained significantly higher than in controls (1.9±0.6 g/ml vs. 1.4±0.3 g/ml, P<0.001). Although pre-AVR E velocity was similar in AS patients and controls, pre-AVR E’ velocity was significantly lower (4.3±1.6 cm/s vs. 7.7±1.6 cm/s, P<0.005), resulting in a higher E/E’ in AS patients than in controls (16.7±5.4 vs. 9.3±1.8, P<0.001). Both E and E’ increased after AVR (Figure 1). E/ E’ did not change significantly after AVR in AS patients (from 16.7±5.4 to 15.5±4.7, P=0.573) despite a significant increase in E’ velocity (from 4.3±1.6 cm/s to 6.3±1.8 cm/s, P<0.001). Pre-AVR LVMI/LVEDVI showed a significant negative correlation with E’ (r=−0.499, P<0.001; Figure 2A) and a sig-

![Figure 3](representative_doppler_tracings_during_exercise_doppler_echocardiography_in_a_normal_control_and_patient_who_underwent_aortic_valveReplacement AVR due to aortic stenosis (AS). s/p, status post.)

| Table 2. Changes in Hemodynamic and Echocardiographic Parameters During EDE |
|------------------------|------------------------|------------------------|------------------------|------------------------|
|                        | Baseline | 25 W | 50 W |                        |
| **SBP (mmHg)**         | AS       | Controls | AS       | Controls | AS       | Controls |
| 131.4±12.6*            | 117.4±12.4 | 147.8±18.1† | 143.4±14.9† | 153.7±18.2† | 150.8±19.3† |
| **DBP (mmHg)**         | 79.5±7.4 | 76.4±11.0 | 86.0±10.4† | 90.6±10.1† | 85.9±9.1† | 93.5±14.3† |
| **Heart rate (beats/min)** | 64.7±9.2 | 66.6±10.6 | 84.1±16.3† | 96.8±11.5† | 97.7±15.2† | 105.4±12.0† |
| **E (cm/s)**           | 90.8±22.5* | 69.2±7.6 | 125.2±19.5† | 106.3±16.8† | 137.2±20.8† | 120.7±19.6† |
| **A (cm/s)**           | 81.8±19.2* | 63.4±11.9 | 101.5±26.3† | 95.4±25.8† | 109.3±30.0† | 102.4±28.6† |
| **E/A**                | 1.2±0.4 | 1.1±0.2 | 0.9±0.3† | 1.1±1.2 | 0.9±0.3† | 0.8±0.2† |
| **DT (ms)**            | 237.8±54.4 | 229.0±28.4 | 177.8±30.6† | 175.1±27.4† | 162.7±35.6† | 152.8±31.2† |
| **E’ (cm/s)**          | 6.3±1.8* | 7.7±1.6 | 7.8±2.0† | 11.3±2.2† | 9.2±3.3† | 11.8±1.8† |
| **E/E’**               | 15.5±4.7* | 9.3±1.8 | 16.9±4.8† | 9.7±1.9 | 17.8±5.0† | 10.4±1.7† |
| **TR Vmax (m/s)**      | 2.5±0.2* | 2.3±0.2 | 2.9±0.3† | 2.7±0.3† | 3.2±0.3† | 2.9±0.3† |

Data given as mean±SD. *P<0.005 (AS vs. control) and †P<0.05 (baseline vs. 25 or 50 W).

DBP, diastolic blood pressure; EDE, exercise Doppler echocardiography; SBP, systolic blood pressure. Other abbreviations as in Table 1.
significant positive correlation with E/E' (r=0.376, P=0.011; Figure 2B).

EDE Data
Representative Doppler tracings during EDE are shown in Figure 3. Changes in hemodynamic and echocardiographic variables during exercise testing are summarized in Table 2. Blood pressure and heart rate responses during exercise testing were similar in AS patients and controls. In both groups, E and E' velocities increased progressively with exercise. At baseline and at each exercise stage of EDE, E and E' velocities were higher in AS patients than in normal controls. E/E' increased during exercise in both AS patients (from 15.5±4.7 to 17.8±5.0, P=0.012) and controls (from 9.3±1.8 to 10.4±1.7, P=0.028). Linear mixed model analysis showed that the amount of E velocity increase during exercise did not differ between these 2 groups (P=0.675), whereas E' velocity during exercise was significantly greater in controls than in AS patients (P<0.001; Figure 4) and peak E/E' during exercise was significantly higher in AS patients than in controls (17.8±5.0 vs. 10.4±1.7, P<0.05). Peak E/E' >15 (68.4%, 26/38 vs. 0%, 0/19; P<0.001) and peak E/E' >13 (89.5%, 34/39 vs. 0%, 0/19; P<0.001) during EDE were more common in AS patients than in controls.

Age (r=0.240, P=0.072), body surface area (r=0.205, P=0.125), hypertension (r=0.237, P=0.076), and LVMI/LVEDVI (r=0.409, P=0.002) had a positive association with peak E/E' during EDE, whereas LVEF had a negative association (r= –0.272, P=0.042). On multivariate analysis, LVMI/LVEDVI (Y=8.703 + 4.199X, r=0.433, P=0.001) was the only factor associated with peak E/E' during EDE. In patients with AS, peak E/E' had a positive correlation with post-AVR mean pressure gradient (r=0.386, P=0.017).

Discussion
Doppler Echocardiography of Diastolic Dysfunction in AS
The pattern of recovery of diastolic dysfunction after AVR is unclear. Previous studies using repeated catheterization and cardiac magnetic resonance imaging in small numbers of AS patients reported contradictory results. Other studies have focused on LV geometry, its impact on the outcome of AVR and postoperative regression of LV mass, but few studies have focused on the relationship between LV geometry or the degree of LVH and diastolic dysfunction and its potential impact on the recovery of diastolic dysfunction after AVR.

Modern Doppler echocardiographic techniques have several advantages over previous techniques in evaluating diastolic function. For example, they allow the direct calculation of E/E' as a measure of LV filling pressure, can be combined with exercise during the comprehensive assessment of diastolic function, and can easily be performed repeatedly. The present study found an increase in both E and E' velocity after AVR with persistently elevated E/E' at rest. Increase of E velocity can be explained by increase of stroke volume and persistent diastolic dysfunction. Stroke volume increased significantly after AVR (from 55.4±19.1 ml to 62.2±14.0 ml, P=0.040). It is interesting to note that E and E' velocity increased differently after AVR. Heterogeneous change of E velocity with significant overlap was present after AVR, but E' had a homogeneous increase, probably associated with relief of LV pressure overloading after successful AVR (Figure 1). Recovery of LV relaxation after AVR, however, is suboptimal, and this is represented by lower post-AVR E' velocity compared to that in normal controls (P=0.006), and thus, E velocity is expected to increase to accommodate increased stroke volume after AVR.

We are not the only group primarily interested in using E/E' as a parameter to evaluate diastolic dysfunction in AS patients. Good correlations between pre-AVR E/E' and LV end-diastolic pressure and pre-A pressure have been observed in AS patients; that is, an E/E' ratio ≥13 identified an LV end-diastolic pressure >15 mmHg with a sensitivity of 93% and a specificity of 88%, In addition, E/E', rather than AS severity or systolic function, has been reported to be an independent determinant of pulmonary artery pressure in patients with moderate to severe AS, indicating that superimposed diastolic function likely contributes to clinical symptoms observed in patients with moderate to severe AS. Moreover, E/E' was
found to be the most important preoperative predictor of early and midterm postoperative cardiovascular events after AVR in patients with severe AS.25

Besides having a persistent increase in E/E′ at rest, AS patients had a progressive increase in E/E′ during exercise. During exercise, LV stroke volume is maintained or increased with a marked increase in heart rate, which decreases the duration of diastole, resulting in less time for diastolic filling of the LV. In normal hearts, LV filling can be maintained, despite the shortening of diastole during exercise, by a rapid decrease in LV early diastolic pressure that augments the early diastolic transmitral gradient without increasing left atrial or LV filling pressure.26 In an elegantly designed animal experiment, it was shown that, during normal exercise, mitral valve flow is augmented by a fall of early diastolic LV pressure without a rise in left atrial pressure.27 The failure to enhance LV relaxation was shown to increase early diastolic LV pressure and contribute to exercise intolerance in heart failure. Enhancement of LV relaxation during exercise can be easily estimated during EDE by measuring E′ velocity at each stage of exercise.28

An inadequate increase of E′ velocity in AS patients after AVR would thus represent failure of adequate LV relaxation or a rapid decrease in LV early diastolic pressure, which has been associated with persistent histologic abnormalities or incomplete regression of LVH.

Although the protocols for exercise stress testing to detect coronary artery disease have been established with regard to target heart rate and criteria for positive test results, exercise testing to evaluate diastolic dysfunction has not yet been standardized. We used hemodynamic and Doppler data obtained during a relatively early stage (≤50 W) of supine bicycle exercise to avoid rapid heart rate, which can cause fusion of transmural inflow or annular velocities of longitudinal movement, thus making measurements difficult or impossible. The present findings indicate that analysis of changes in hemodynamic and Doppler variables up to a fixed low level of exercise is a better method of evaluating diastolic dysfunction than symptom-limited maximal exercise. Peak E/E′ during low-level exercise was one of the main parameters in the present study and was <13 in normal controls. Because peak E/E′ >13 has been reported to be an optimal cut-off value for increased LV end-diastolic pressure and is highly specific (90%) for reduced exercise capacity,29 the clinical usefulness of this cut-off value should be re-assessed.

Study Limitations
The present study suffers from selection bias and a small cohort. Regression of LV mass can be affected by many other factors including type and size of the prosthetic valve. Due to the small number of subjects, the impact of different prosthesis valves cannot be fully appreciated. Because we selected patients who had uneventful clinical courses after AVR, these patients do not represent the entire clinical spectrum of AS. Thus, the real clinical impact of persistent diastolic dysfunction on adverse clinical outcomes such as hospital admission or death due to diastolic dysfunction or heart failure has not been adequately investigated. A combination of pre- and post-AVR exercise testing with long-term follow-up of larger groups of AS patients is necessary to determine the clinical significance of diastolic dysfunction.

Conclusions
We found that LV diastolic dysfunction persists for up to 5 years after uneventful AVR and that incomplete or inadequate regression of LVH is an important cause of persistent LV diastolic dysfunction. Incomplete or inadequate regression of LVH may prevent the normal physiologic augmentation of LV relaxation during exercise, demonstrated by inadequate E′ velocity increase during EDE. Along with the better outcomes of early surgical intervention recently reported in asymptomatic patients with very severe AS,29 earlier surgery based on objective evaluation using pre-AVR EDE may be a reasonable option and its efficacy should be assessed in future studies.

References
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