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CLINICAL RESEARCH

# Diffuse Myocardial Fibrosis and Diastolic Function in Aortic Stenosis

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## ABSTRACT

**OBJECTIVES** The aim of this study was to investigate the relationship between extracellular volume fraction (ECV), a noninvasive parameter that quantifies the degree of diffuse myocardial fibrosis on cardiac magnetic resonance (CMR), and left ventricular diastolic dysfunction (LVDD) in patients with aortic stenosis (AS).

**BACKGROUND** Myocardial fibrosis on invasive myocardial biopsy is associated with LVDD. However, there is a paucity of data on the association between noninvasively quantified diffuse myocardial fibrosis and the degree of LVDD and how these are related to symptoms and long-term prognosis in patients with AS.

**METHODS** Patients with moderate or severe AS (n = 191; mean age 68.4 years) and 30 control subjects without cardiovascular risk factors underwent CMR. LVDD grade was evaluated using echocardiography according to the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines. Clinical outcomes were defined as a composite of all-cause mortality or hospitalization for heart failure aggravation.

**RESULTS** Patients in higher ECV quintiles had a significantly higher prevalence of LVDD. Higher ECV was particularly associated with decreased myocardial relaxation (septal e′ <7 cm/s) and increased LV filling pressure (E/e′ ratio ≥15). Although both impaired diastolic function and higher ECV were significantly associated with a worse degree of dyspnea, patients with higher ECV showed greater dyspnea within the same grade of LVDD. During a median follow-up period of 5.6 years, 37 clinical events occurred. Increased ECV, as well as lower septal e′ and higher E/septal e′ ratio, were independent predictors of clinical events, irrespective of age, AS severity, aortic valve replacement, and left ventricular (LV) ejection fraction. ECV provided incremental prognostic value on top of clinical factors and LV systolic and diastolic function.

**CONCLUSIONS** Diffuse myocardial fibrosis, assessed using ECV on CMR, was associated with LVDD in patients with AS, but both ECV and LV diastolic function parameters provided a complementary explanation for dyspnea and clinical outcomes. Concomitant assessment of both LVDD and diffuse myocardial fibrosis may further identify patients with AS with greater symptoms and worse prognosis. (J Am Coll Cardiol Img 2020;■:■–■) © 2020 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**AS** = aortic stenosis

**AV** = aortic valve

**CMR** = cardiac magnetic resonance

**ECV** = extracellular volume fraction

**LA** = left atrial

**LGE** = late gadolinium enhancement

**LV** = left ventricular

**LVDD** = left ventricular diastolic dysfunction

**NYHA** = New York Heart Association

**TR Vmax** = maximal tricuspid regurgitation velocity

Aortic stenosis (AS) is not just a valvular disease; it is also a myocardial disease caused by chronic pressure overload on the left ventricle. This results in left ventricular (LV) hypertrophy and myocardial fibrosis, both of which are related to LV diastolic dysfunction (LVDD) (1,2). Even after reversal of the valvular portion of the disease by aortic valve (AV) replacement, the myocardial portion remains and reverses incompletely (3). Traditionally, the degree of diffuse myocardial fibrosis could be determined only by histological examination of invasively acquired myocardial samples. The recent development of cardiac magnetic resonance (CMR) and the T1 mapping sequence has enabled the noninvasive quantification of myocardial fibrosis. Replacement fibrosis and diffuse interstitial fibrosis are 2 main patterns of myocardial fibrosis. Replacement fibrosis, detected by late gadolinium enhancement (LGE), is irreversible and occurs in the later stages of AS. Diffuse fibrosis begins earlier and may regress after AV replacement (4,5). The extracellular volume fraction (ECV) on CMR reflects diffuse myocardial fibrosis (6–8) and is a robust predictor of outcomes in patients with AS (9,10).

Although the degree of myocardial fibrosis is associated with LVDD (11), our understanding of the association between the 2 is based largely on studies that involved small numbers of human myocardial samples (12–14). Also, there is lack of data on the association between diffuse myocardial fibrosis on noninvasive imaging and the degree of LVDD comprehensively. We hypothesized that it would be possible to understand the association between diffuse myocardial fibrosis and LVDD in patients with AS using a combination of CMR and echocardiography. The aims of this study were to investigate the relation between ECV and LVDD with the updated contemporary guidelines and to analyze how these are related to symptom severity and long-term prognosis in patients with AS.

## METHODS

**STUDY POPULATION.** Consecutive patients with moderate or severe AS (n = 198) were enrolled prospectively from 2011 to 2015 at 2 tertiary medical centers. Control subjects of similar age and sex distributions without cardiovascular risk factors were also enrolled (n = 30). The study protocol was approved by the Institutional Review Boards of both institutions. All patients provided written informed consent and underwent both conventional echocardiography and CMR. Enrollment criteria for each hospital (8,15) are described in the Supplemental Methods. Among the patients enrolled, those without measurements of ECV (n = 7) were excluded from the final analysis.

**ECHOCARDIOGRAPHY AND DIASTOLIC FUNCTION CLASSIFICATION.** Echocardiographic images were acquired using adequate equipment (Vivid 7 or 9, GE Healthcare, Little Chalfont, United Kingdom; i33, Philips Medical Systems, Andover, Massachusetts; Sequoia, Siemens Medical Solutions, Mountain View, California) and measured according to current guidelines (16) (Supplemental Methods). LV diastolic function was evaluated using 2-dimensional and Doppler echocardiography and categorized using the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines on diastolic function (17): normal, indeterminate, or diastolic dysfunction and, in the case of diastolic dysfunction, grade I, II, or III. Those meeting one-half of the LVDD criteria were considered as an intermediate group, between normal diastolic function and LVDD. We performed further exploratory analysis, classifying those with "normal" diastolic function according to septal e′ (i.e., normal diastolic function defined as septal e′ ≥7 cm/s and reduced myocardial relaxation [septal e′ <7 cm/s] with normal filling pressure) (18).

**CMR IMAGING.** CMR images were obtained using either a 1.5-T or a 3-T scanner (8,15,19), within 1 month of echocardiography. Briefly, CMR scans consisted of balanced steady-state free precession cine images, pre- and post-T1 mapping, and LGE images. The degree of diffuse myocardial fibrosis was assessed by calculating ECV from the pre- and post-contrast T1 mapping images at the septal compact myocardium using $[\Delta(1/T1_{myo})/\Delta(1/T1_{blood})] \times (1 - \text{hematocrit})$, as in the guidelines (20), where $\Delta(1/T1)$ is the difference in myocardial or blood T1 values pre- and post-contrast (Supplemental Methods).

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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**CLINICAL ENDPOINTS.** The degree of dyspnea was assessed at the time of echocardiography according to the New York Heart Association (NYHA) functional classification. Clinical outcomes were defined as a composite of all-cause mortality or first hospitalization for heart failure aggravation. The index date was the date of the CMR, and patients were followed until the occurrence of a clinical outcome or the last follow-up visit. Outcomes were assessed by review of medical records, and mortality was confirmed from official nationwide data on death certificates provided by the National Statistical Office. We double-checked the occurrence of clinical events in patients who did not return to the clinic using systematic telephone interviews.

**STATISTICAL ANALYSIS.** Details of the statistical analysis are available in the Supplemental Methods. Associations between ECV and imaging parameters were analyzed using multiple linear regression analysis. Logistic regression was used to evaluate whether ECV was a determinant of LVDD as well as its individual criteria with multivariate adjustment for age, sex, and (in patients with AS) AV area. Patients with AS were divided into ECV quintiles, and the associations among ECV quintile, LVDD, and dyspnea severity were analyzed using the chi-square test and p value for trend shown by linear-by-linear association. Kaplan-Meier survival curves for clinical outcomes according to ECV threshold and LVDD grade were compared using the log-rank test. Univariate and multivariate Cox regression analyses were used to assess whether ECV and LV diastolic function parameters were predictors of clinical outcomes. The incremental value of LV diastolic function and ECV over common AS prognosticators for predicting clinical events was assessed by exploring changes in the global chi-square values in sequentially constructed multivariate Cox models. All analyses were performed using R version 3.6.1 (R Development Core Team, Vienna, Austria) or SPSS version 25 (SPSS, Chicago, Illinois). A 2-sided p value $< 0.05$ was considered to indicate statistical significance.

## RESULTS

**BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS.** A total of 191 patients (mean age 68.4 ± 8.8 years, 50% men) with significant AS and 30 control subjects underwent comprehensive evaluation with echocardiography and CMR, including ECV measurements. Clinical and imaging characteristics are presented in Supplemental Table 1 and **Table 1**, respectively. There were no significant differences between patients with AS and control subjects in terms of age, sex, and body surface area. Most were low risk (median European System for Cardiac Operative Risk Evaluation II score 1.2; interquartile range: 0.9 to 1.7), and the majority (n = 158 [83%]) had severe AS (AV area <1 $cm^2$). During follow-up, 88% of patients underwent AV replacement, and the median time between CMR and AV replacement was 3 days (interquartile range: 1 to 26 days). The proportions of patients with decreased myocardial relaxation (septal e′ <7 cm/s), dilated left atria (left atrial [LA] volume index >34 $ml/m^2$), elevated LV filling pressure (E/septal e′ ratio >15), and elevated pulmonary artery pressure (estimated by maximal tricuspid regurgitation velocity [TR Vmax] >2.8 m/s) were 92%, 88%, 55%, and 17%, respectively (Supplemental Figure 1). The mean ECV was 27.3 ± 3.1%. Although LGE was

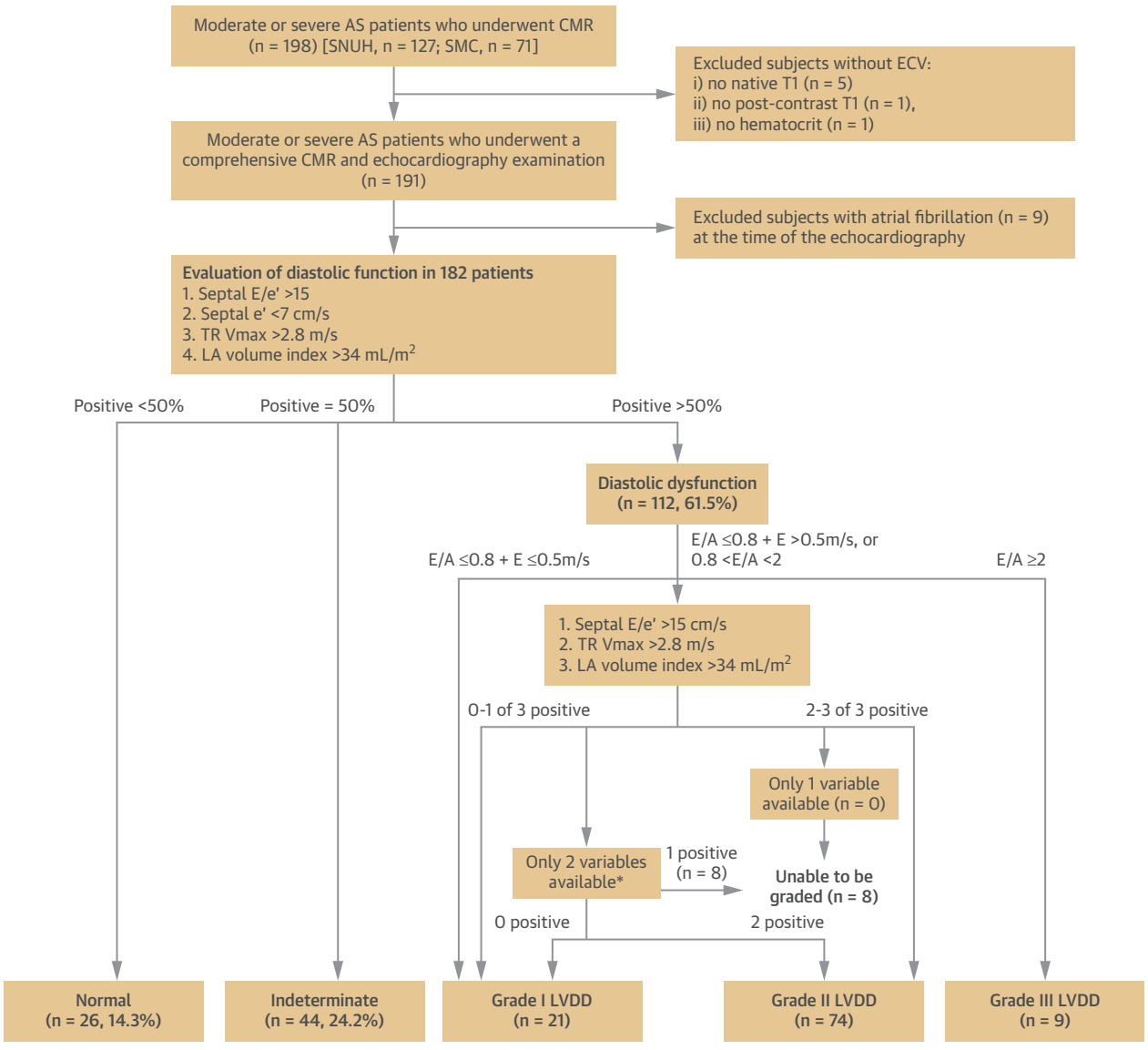
**TABLE 1 Baseline Imaging Parameters of the Study Participants**

| | Significant AS (n = 191) | Controls (n = 30) | p Value |
|---|---|---|---|
| Echocardiography | | | |
| LV end-diastolic dimension, mm | 50.3 ± 6.6 | 46.5 ± 3.2 | <0.001 |
| LV end-systolic dimension, mm | 31.7 ± 7.1 | 28.3 ± 3.1 | <0.001 |
| LV mass index, $g/m^2$ | 131.8 ± 40.2 | 82.9 ± 13.2 | <0.001 |
| LV ejection fraction, % | 60.2 ± 8.8 | 62.7 ± 5.0 | 0.031 |
| LV ejection fraction ≥50% | 179 (93.7) | | |
| Septal s′, cm/s | 5.2 ± 1.4 | 6.8 ± 1.4 | <0.001 |
| LV ejection time, ms | 325 ± 35 | 298 ± 31 | <0.001 |
| E velocity, m/s | 0.73 ± 0.29 | 0.58 ± 0.14 | <0.001 |
| A velocity, m/s | 0.87 ± 0.29 | 0.67 ± 0.12 | <0.001 |
| Deceleration time, ms | 253 ± 82 | 207 ± 28 | <0.001 |
| E/A ratio | 0.94 ± 0.57 | 0.90 ± 0.27 | 0.532 |
| Septal e′, cm/s | 4.6 ± 1.5 | 6.3 ± 1.8 | <0.001 |
| Septal a′, cm/s | 7.3 ± 1.8 | 8.8 ± 1.0 | <0.001 |
| E/septal e′ ratio | 17.4 ± 8.5 | 9.7 ± 2.8 | <0.001 |
| TR Vmax, m/s | 2.4 ± 0.4 | 2.2 ± 0.2 | <0.001 |
| LAVI, $ml/m^2$ | 53.4 ± 18.8 | 36.6 ± 9.4 | <0.001 |
| PASP, mm Hg | 34.7 ± 8.2 | 30.6 ± 3.3 | <0.001 |
| AV Vmax, m/s | 4.7 ± 0.8 | | |
| AV mean pressure gradient, mm Hg | 54.0 ± 21.5 | | |
| AV area, $cm^2$ | 0.78 ± 0.23 | | |
| Cardiac magnetic resonance | | | |
| LV end-diastolic volume index, $ml/m^2$ | 115 ± 51 | 77 ± 11 | <0.001 |
| LV end-systolic volume index, $ml/m^2$ | 48 ± 36 | 28 ± 7 | <0.001 |
| LV stroke volume index, $ml/m^2$ | 59 ± 19 | 49 ± 9 | <0.001 |
| LV cardiac index, $l/min/m^2$ | 4.7 ± 1.8 | 3.3 ± 0.6 | <0.001 |
| LV mass index, $g/m^2$ | 98.1 ± 36.0 | 55.6 ± 8.7 | <0.001 |
| LV ejection fraction, % | 62.6 ± 13.0 | 63.3 ± 7.4 | 0.687 |
| Presence of LGE | 91 (47.6) | 0 (0.0) | <0.001 |
| LGE (% LV mass) | 0.0 (0.0-2.0) | | |
| ECV (%) | 27.3 ± 3.1 | 26.0 ± 2.3 | 0.007 |

Values are mean ± SD, n (%), or median (interquartile range).

A = peak late diastolic mitral inflow velocity; a′ = septal late diastolic mitral annular velocity; AS = aortic stenosis; AV = aortic valve; E = peak early diastolic mitral inflow velocity; e′ = septal early diastolic mitral annular velocity; ECV = extracellular volume fraction; LAVI = left atrial volume index; LGE = late gadolinium enhancement; LV = left ventricular; PASP = pulmonary artery systolic pressure; s′ = septal systolic mitral annular velocity; TR = tricuspid regurgitation; Vmax = maximal velocity.

**FIGURE 1** **Classification of Patients With AS by LV Diastolic Function Grading According to the Most Updated Current Guidelines**




*All lacked maximal tricuspid regurgitation velocity (TR Vmax). AS = aortic stenosis; CMR = cardiac magnetic resonance; ECV = extracellular volume fraction; LA = left atrial; LVDD = left ventricular diastolic dysfunction; SMC = Samsung Medical Center; SNUH = Seoul National University Hospital.

present in 48% of the patients, the absolute amount (percentage of LV mass) was small (mean 1.8 ± 3.2% in patients with LGE).

After excluding patients with atrial fibrillation at the time of echocardiography (n = 9), LV diastolic function was analyzed in 182 patients with AS. One hundred twelve patients (62%) had LVDD (Figure 1). Excluding 8 patients whose degrees of LVDD could not be determined because of the lack of TR Vmax, the majority with LVDD had grade II diastolic dysfunction: 21 (20%), 74 (71%), and 9 (9%) were classified with grade I, II, and III LVDD, respectively. There were 26 (14%) and 44 (24%) patients with normal and indeterminate diastolic function, respectively. In the control group, 20 (66.7%), 8 (26.7%), and 2 (6.7%) patients had normal, indeterminate, and

**TABLE 2** Association Between ECV and Diastolic Function Parameters in the Entire Study Population of Patients With Aortic Stenosis and Control Subjects

| | ECV (per 1% Increase) | | | |
|---|---|---|---|---|
| | Unadjusted | | Adjusted* | |
| | OR (95% CI) | p Value | OR (95% CI) | p Value |
| Diastolic dysfunction† | 1.15 (1.04–1.27) | 0.005 | 1.15 (1.04–1.26) | 0.006 |
| Septal e′ <7 cm/s | 1.19 (1.02–1.39) | 0.030 | 1.19 (1.01–1.39) | 0.038 |
| E/septal e′ ratio >15 | 1.16 (1.05–1.27) | 0.003 | 1.15 (1.05–1.27) | 0.003 |
| TR Vmax >2.8 m/s | 1.12 (0.99–1.27) | 0.064 | 1.12 (0.99–1.27) | 0.075 |
| LAVI >34 ml/m$^2$ | 1.11 (0.98–1.27) | 0.113 | 1.10 (0.97–1.26) | 0.145 |

*Adjusted for age and sex. †Normal + indeterminate as reference.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

LVDD, respectively; of the 2 patients with LVDD, 1 had grade I LVDD, whereas LVDD in another could not be determined, because of the lack of TR Vmax (Supplemental Figure 2).

**RELATIONSHIP BETWEEN ECV AND LV GEOMETRY AND FUNCTION.** On multiple linear regression analysis adjusting for age and sex in the entire population (n = 221) (i.e., control subjects and patients with AS altogether), ECV was significantly associated with LV dimensions and systolic and diastolic function parameters (Supplemental Table 2). ECV showed negative correlations with LV systolic function, specifically LV ejection fraction on echocardiography and CMR, and with septal s′ velocity. Regarding diastolic function parameters, ECV showed negative correlations with septal e′ velocity and the deceleration time of mitral inflow E velocity and positive correlations with E/e′ ratio and TR Vmax. ECV was positively correlated with the amount of LGE. These associations were consistent in the analysis limited to patients with AS, with multivariate adjustment for age, sex, and AV area.

**ECV AND DIASTOLIC FUNCTION CRITERIA.** ECV was significantly associated with higher odds for LVDD in the entire study population and in patients with AS (**Table 2** and Supplemental Table 3). Among the individual LVDD criteria, ECV was significantly associated with decreased myocardial relaxation (septal e′ <7 cm/s) and high LV filling pressure (E/e′ ratio >15). Although the overall odds were higher than 1, ECV was not significantly associated with a dilated left atrium (LA volume index >34 ml/m$^2$) or pulmonary hypertension (TR Vmax >2.8 m/s). In the analysis of patients with AS only, ECV was significantly associated with increased LV filling pressure (E/e′ ratio >15). These tendencies were not different by each site (Supplemental Table 4).

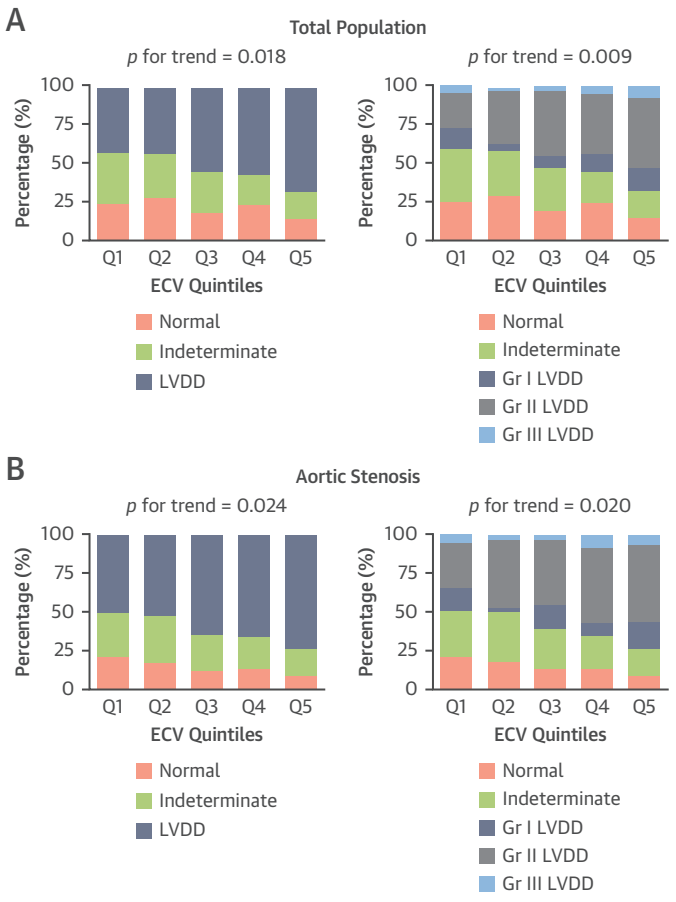
Those in higher ECV quintiles in the entire study population had a significantly higher prevalence of LVDD (p for trend = 0.018), as well as higher grades of LVDD (p for trend = 0.009) (**Figure 2A**). This trend was consistent in the analysis of patients with AS only (**Figure 2B**). Further analysis classifying patients with "normal" diastolic function by septal e′ into "normal diastolic function (e′ ≥7 cm/s)" and "reduced myocardial relaxation (e′ <7 cm/s) with normal filling pressure" also showed that higher ECV quintiles were associated with greater LVDD in both entire population and patients with AS only (Supplemental Figure 3).

**ECV, DIASTOLIC FUNCTION, AND SEVERITY OF DYSPNEA IN PATIENTS WITH AS.** Impaired diastolic function was significantly associated with worse degree of dyspnea (p for trend = 0.041) (**Figure 3A**). Although only 3.8% of the patients (n = 1) with normal diastolic function had NYHA functional class III dyspnea, 22% (n = 24) of patients with LVDD had NYHA functional class III or IV dyspnea. Higher ECV quintiles were also associated with a greater degree of dyspnea (p for trend = 0.004) (**Figure 3B**).

Further classification of diastolic function by low and high ECV according to the median ECV value (27.0%) refined the association between LVDD and the degree of dyspnea; patients with higher ECV had greater dyspnea even within the same degree of diastolic dysfunction (**Figure 3C**). In patients with LVDD, only 14% of those with low ECV had NYHA functional class III dyspnea, and none had NYHA functional class IV dyspnea, while 23% of those with high ECV had NYHA functional class III dyspnea and 5% had NYHA functional class IV dyspnea. All patients with NYHA functional class IV dyspnea had LVDD and high ECV.

**ECV, DIASTOLIC FUNCTION, AND CLINICAL OUTCOMES IN PATIENTS WITH AS.** Patients with AS were followed for a median of 5.6 years (interquartile range: 3.9 to 6.6 years). There were 37 clinical events (19.4%): 11 deaths and 27 admissions for heart failure, including 1 patient with both events. The optimal ECV

**FIGURE 2 Association Between ECV and Degree of LVDD**




**(A)** Entire study population and **(B)** patients with aortic stenosis only. Gr = grade; Q = quintile; other abbreviations as in Figure 1.

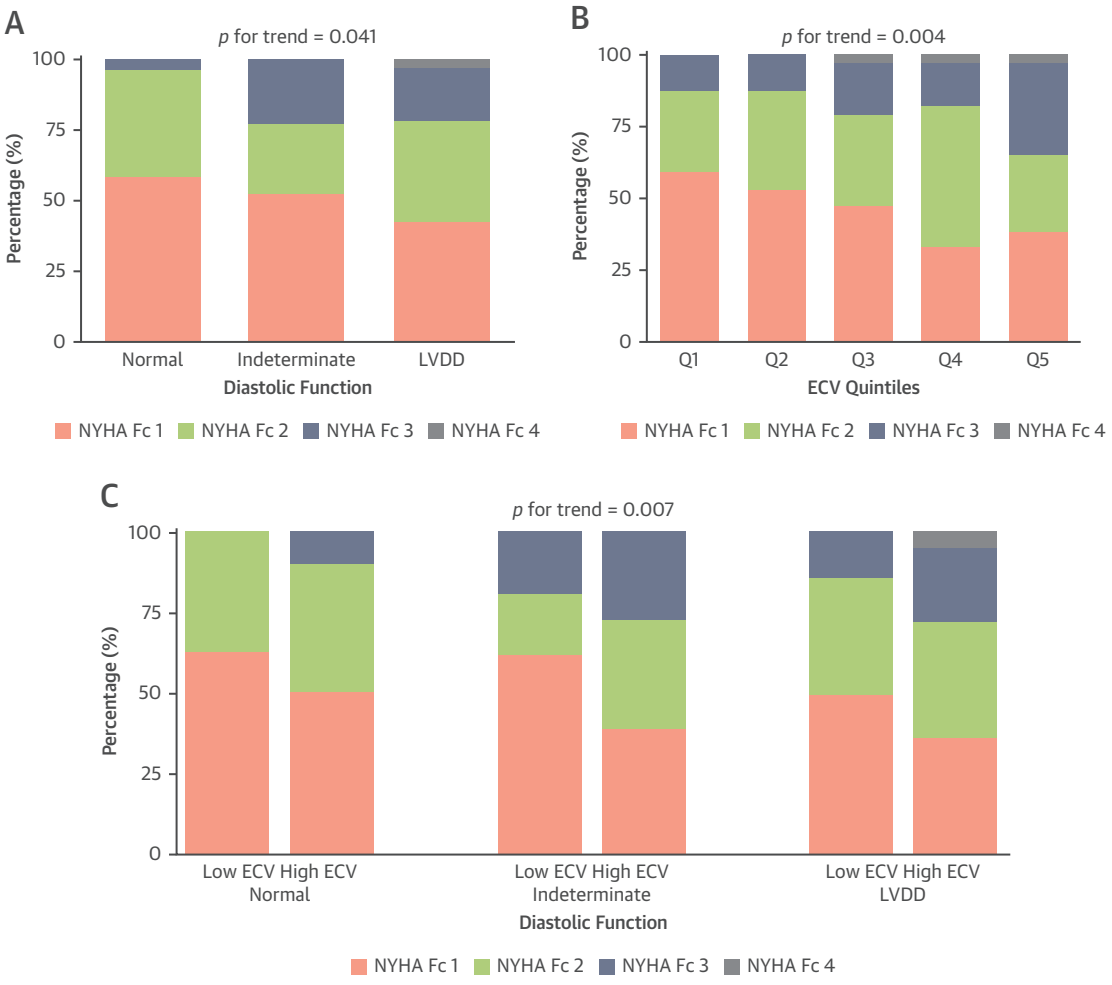
threshold for predicting clinical outcomes was 28% by receiver-operating characteristic curve analysis and spline regression curves (Supplemental Figure 4). Kaplan-Meier curves showed a significantly higher incidence of death or heart failure admission in patients with increased ECV (>28%) compared with those with preserved ECV (≤28%) (log-rank p = 0.005) (Figure 4A). On multivariate Cox regression analysis adjusting for age, sex, AV area, AV replacement, and LV ejection fraction, increased ECV was an independent predictor of clinical outcomes (Table 3). Although the presence of baseline LVDD according to the guidelines was not significantly associated with clinical outcomes (Figure 4B), lower septal e′ and higher E/e′ ratio were independent predictors of outcomes (Table 3). Increased ECV was a significant predictor of clinical outcome even after further adjustment for LVDD, despite the statistically significant associations between LV diastolic function and ECV. Conversely, E/e′ ratio was also predictive of outcome after adjusting for ECV (Supplemental Table 5). Compared with the clinical model including age, sex, AV area, AV replacement, and LV ejection fraction, the sequential addition of significant LV diastolic function parameters and high ECV all had incremental prognostic value for predicting outcomes (Supplemental Figure 5).

## DISCUSSION

In the present study of patients with moderate or severe AS who underwent combined evaluation using echocardiography and CMR, we comprehensively analyzed the relationship between diffuse myocardial fibrosis and LVDD in patients with AS, together with its clinical relevance. We demonstrated that diffuse myocardial fibrosis quantified noninvasively with ECV on CMR was significantly associated with LVDD according to the latest guidelines, especially decreased myocardial relaxation (septal e′ <7 cm/s) and increased LV filling pressure (E/e′ ratio ≥15). Furthermore, ECV had incremental value in addition to LV diastolic function for identifying patients with greater severity of dyspnea and higher risk for future clinical events (Central Illustration). Hence, the combination of ECV and LV diastolic function provided a more precise explanation of exertional dyspnea and clinical outcomes in patients with AS. To the best of our knowledge, this is the first study to investigate the association of a noninvasive measure of diffuse myocardial fibrosis with LVDD comprehensively in a sizable population according to the most updated guidelines and their association with clinical symptoms and prognosis.

**MECHANISTIC LINK BETWEEN MYOCARDIAL FIBROSIS AND DIASTOLIC FUNCTION.** The collagen network in the extracellular space of the myocardium is composed primarily of type I and III collagens (21), which serve to store the potential energy during systole and to release this energy like a coiled spring at diastole. However, there is inevitable loss of energy through the internal friction during this process, which is called viscoelasticity (11,22). The tensile strength of the collagen is related to tissue stiffness. An increased amount of collagen in the myocardium is related to greater viscous loss of energy during relaxation and also greater tissue stiffness that hinders LV filling throughout the diastole. As pressure overload of the heart is associated with myocardial hypertrophy with diffuse fibrosis (23), these concepts led us to analyze the relation between diffuse fibrosis on noninvasive imaging and degree of LVDD.

**FIGURE 3** **Degree of Dyspnea According to ECV and Left Ventricular Diastolic Function**

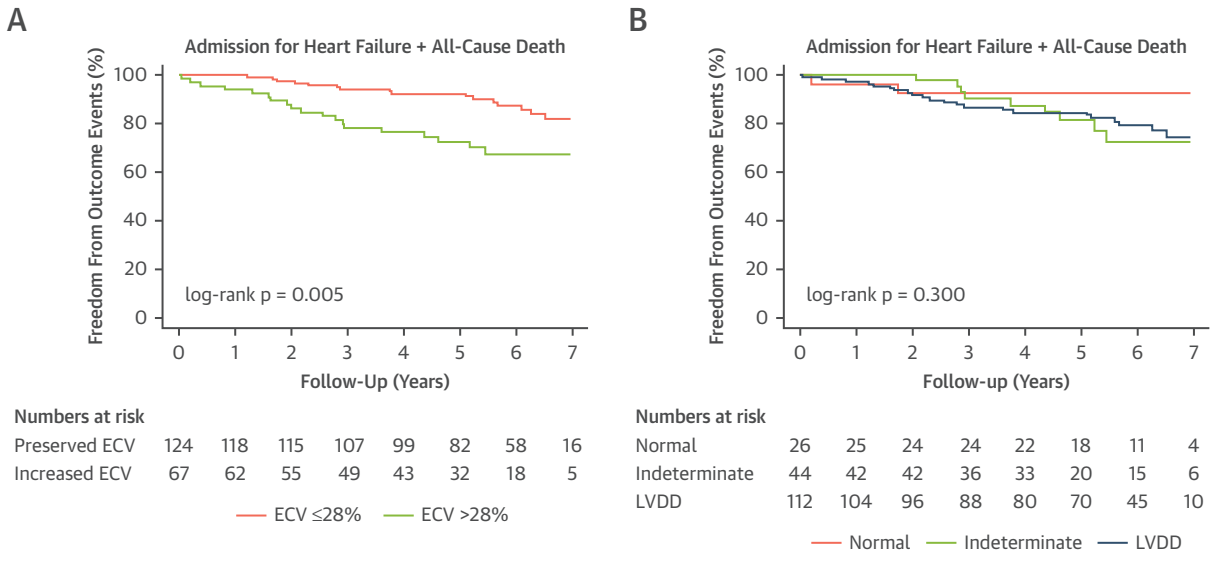



Relationship between dyspnea degree and **(A)** diastolic function or **(B)** ECV. **(C)** Association between ECV with dyspnea within the same degree of diastolic dysfunction. NYHA Fc = New York Heart Association functional class; other abbreviations as in Figures 1 and 2.

**MYOCARDIAL FIBROSIS AND DIASTOLIC FUNCTION IN AS.** Focal replacement fibrosis has been associated with diastolic dysfunction (24). However, there is a lack of data on the association between diffuse interstitial fibrosis and diastolic dysfunction, especially using noninvasive imaging. Using ECV, a CMR parameter that estimates the degree of diffuse myocardial fibrosis on histological analysis (6–8), we found that a higher degree of myocardial fibrosis by ECV was associated with a deterioration of LV relaxation and compliance. Previously, ECV was associated with increased E/e′ ratio, LA volume (25,26), and invasively measured passive LV stiffness (27), but no studies have looked into diastolic function in detail according to the latest guidelines on diastolic function (17).

Diastole consists of an early rapid filling phase related to myocardial relaxation, a midphase of diastasis, and a late phase of filling by active atrial systole. Myocardial relaxation is an active, energy-dependent sucking process that causes pressure to decrease rapidly in the left ventricle during early diastole. Mitral annular velocity e′ reflects LV longitudinal myocardial relaxation at early diastole and is relatively load independent. Deterioration of e′ is an early marker of LVDD (17,28), and in our study, the majority of patients with AS showed impaired myocardial relaxation. ECV was significantly

**FIGURE 4 Clinical Outcomes According To ECV And Left Ventricular Diastolic Function**




Event-free survival from a composite of all-cause death and admission for heart failure aggravation according to **(A)** the ECV threshold of 28% and **(B)** degree of left ventricular diastolic function. Abbreviations as in Figure 1.

associated with lower septal e′ velocity in our patients with AS. In studies with invasive endomyocardial biopsies, the percentage of fibrosis was also significantly correlated with increased isovolumic relaxation time, that is, decreased LV filling during the early diastolic period (13).

In the early diastolic dysfunction phase, myocardial relaxation is impaired but mean LV filling pressure is normal. With more advanced diastolic dysfunction, there is an increase in LV filling pressure. About one-half of the patients with AS in the present study had increased E/e′ ratios, an index of LV filling pressure, implying a progressed state of LVDD. Deceleration time, a parameter that tends to shorten with the progress of myocardial stiffness, was significantly correlated with ECV. This is also supported by studies demonstrating the association between the degree of interstitial fibrosis on endomyocardial biopsies and the degree of LV chamber stiffness and end-diastolic LV distensibility in patients with AS (3,14,29).

With the progression of LVDD, increased LV filling pressure can lead to LA dilatation and post-capillary pulmonary hypertension. Most of our study patients had dilated left atria, while fewer than one-fifth had increased pulmonary pressures. Pulmonary hypertension in AS implies advanced cardiac damage and has been associated with poor prognosis (30). ECV was associated with TR Vmax on linear regression, whereas the association between ECV and LA volume was not significant in the present study. This may be because LA dilatation was prevalent in most patients, is less specific for diastolic dysfunction, and can be easily influenced by other factors such as age, sex, body size, and atrial arrhythmias (31,32).

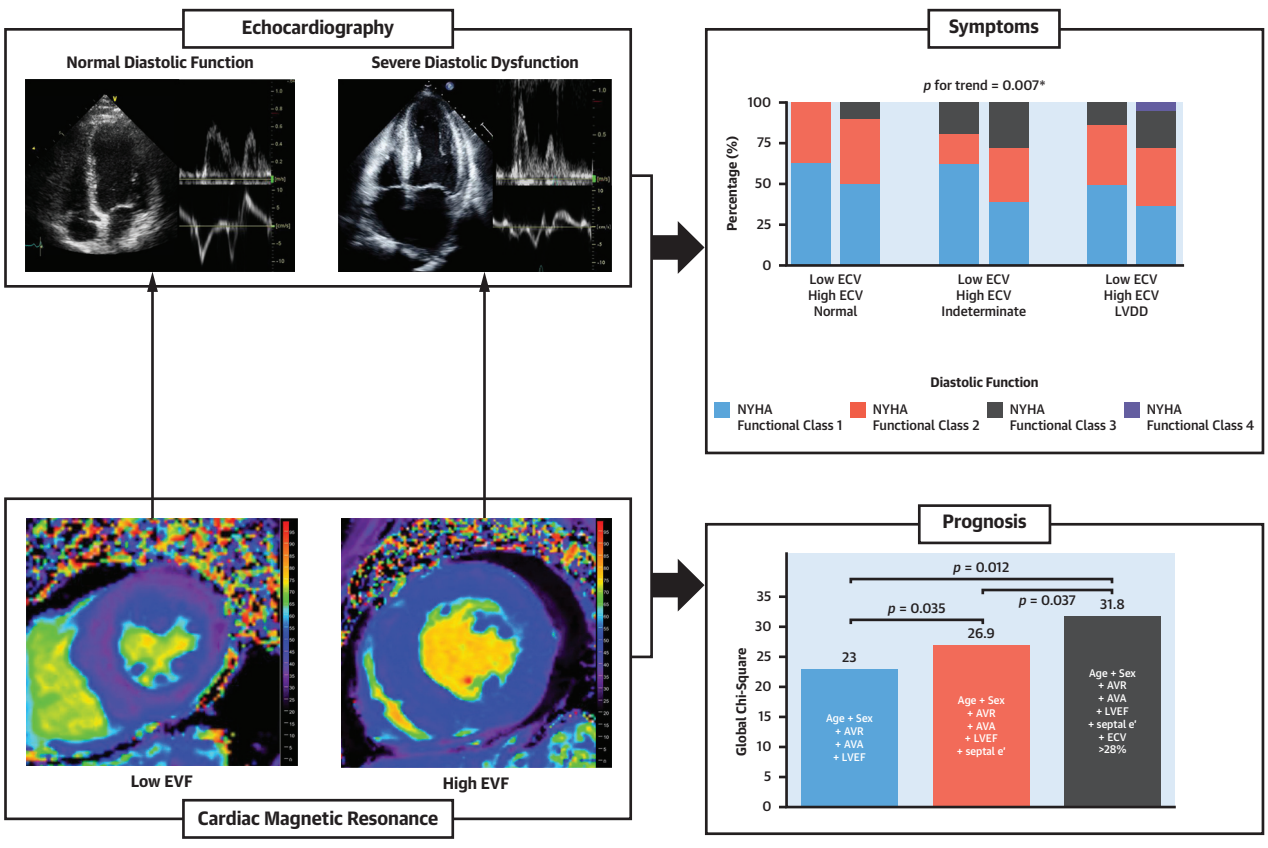
**CLINICAL IMPLICATIONS OF LVDD AND MYOCARDIAL FIBROSIS.** LVDD is associated with symptoms in severe AS independent of LV systolic function (33), and previous studies have demonstrated that patients with dyspnea have the worst diastolic function (34). In the present study, patients with greater degrees of LVDD or diffuse myocardial fibrosis showed greater severity of dyspnea. Interestingly, by amalgamating ECV and LVDD, we demonstrated that even patients with the same grade of LVDD have worse dyspnea if they have a higher degree of diffuse fibrosis. In the present study, diffuse myocardial fibrosis was a significant predictor of long-term clinical outcomes, whereas the presence of baseline LVDD according to the guidelines was not. This may be because LV diastolic function is more volume dependent and variable (35), compared with ECV. Although previous studies have shown that baseline LVDD is associated with poor outcomes after

**TABLE 3** Cox Regression For The Risk For Heart Failure Admission Or All-Cause Death In Patients With Aortic Stenosis

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | HR (95% CI) | p Value | HR (95% CI) | p Value |
| ECV | 1.11 (1.02-1.22) | 0.023 | 1.09 (0.99-1.19) | 0.074 |
| ECV >28% | 2.48 (1.30-4.75) | 0.006 | 2.25 (1.15-4.43) | 0.018 |
| Diastolic dysfunction† | 1.20 (0.59-2.42) | 0.615 | 1.26 (0.58-2.74) | 0.553 |
| Septal e′ | 0.66 (0.50-0.87) | 0.003 | 0.74 (0.55-0.99) | 0.045 |
| E/septal e′ ratio | 1.05 (1.02-1.08) | 0.002 | 1.05 (1.02-1.08) | 0.003 |
| TR Vmax | 1.48 (0.61-3.58) | 0.390 | | |
| LAVI | 1.01 (1.00-1.03) | 0.160 | | |
| LV ejection fraction | 0.97 (0.95-1.00) | 0.061 | 0.97 (0.94-0.99) | 0.030 |
| Presence of LGE | 0.72 (0.38-1.40) | 0.337 | | |
| LGE (% mass) | 0.97 (0.87-1.09) | 0.629 | | |

*Adjusted for age, sex, AV area, AV replacement, and LV ejection fraction. †Normal + indeterminate as reference.
HR = hazard ratio; other abbreviations as in Tables 1 and 2.

**CENTRAL ILLUSTRATION** Complementary Role of Diastolic Function and Diffuse Myocardial Fibrosis for Identifying Patients With Aortic Stenosis With Greater Symptoms and Worse Prognosis




Lee, H.-J. et al. J Am Coll Cardiol Img. 2020;■(■):■-■.

Diffuse myocardial fibrosis, quantified by extracellular volume fraction on cardiac magnetic resonance, was associated with left ventricular diastolic function grading by echocardiography in patients with aortic stenosis and had additive value for explaining symptoms and predicting clinical outcomes. AVA = aortic valve area; AVR = aortic valve replacement; ECV = extracellular volume fraction; LVDD = left ventricular diastolic dysfunction; LVEF = left ventricular ejection fraction; NYHA = new york heart association.

AV replacement (36,37), some patients with AS show immediate improvement in LV diastolic function after appropriate diuretic therapy, even before AV replacement. However, it should be noted that the septal e′ and E/e′ ratio were also independent predictors of clinical outcomes in our patients. This may be because the majority of our patients were at low risk, and both septal e′ and E/e′ ratio are early markers of LVDD and cardiac damage in patients with AS (30). Furthermore, ECV had incremental prognostic value over LV systolic and diastolic function.

Our findings imply that the degree of LVDD and that of myocardial fibrosis are complementary in identifying patients with AS at a more advanced stage. Previous studies have shown conflicting findings on whether patients with heart failure with preserved ejection fraction have increased collagen fraction on endomyocardial biopsies (38–40). Echocardiographic parameters acquired at rest do not necessarily predict the degree of dyspnea at stress (41,42), suggesting that the 2 are closely related but, at the same time, provide information on different aspects of myocardial function and structure following AS. Therefore, the combination of echocardiography and CMR may provide a more accurate and comprehensive evaluation of patients with AS, which is essential when predicting clinical outcomes.

**STUDY LIMITATIONS.** First, we categorized LV diastolic function according to the 2016 guidelines on LVDD, which advocate that the aging-related diastolic pattern with reduced LV relaxation should be graded as normal. As such, patients with only 1 criterion positive for LVDD, such as septal e′ <7 cm/s, were considered to have normal diastolic function. On this basis, we found a 60% prevalence of LVDD in our patients, which is in line with previous studies with similar patient populations (36,37). However, some may consider this to be mild LVDD, and there is ongoing debate on this issue (18).

Second, we used echocardiography-based estimates of hemodynamic measurements, such as the E/e′ ratio to estimate LV filling pressures, and TR Vmax to calculate pulmonary artery pressures, which are indirect measures at best. However, these correlate well with invasive measurements (1), and in clinical practice, diastolic function is evaluated mainly using echocardiography.

Third, the inclusion criteria of the 2 centers were not the same; however, this allowed better generalizability of the results.

Fourth, the severity of dyspnea for each patient was graded using the NYHA functional classification by an experienced physician at the initial evaluation, which may be subjective.

Last, the study population was mostly low risk, which may limit the generalization of the present results to a higher risk population.

## CONCLUSIONS

Using ECV on CMR to noninvasively evaluate the degree of diffuse myocardial fibrosis, this study demonstrated that there is a significant relationship between diffuse myocardial fibrosis and LVDD in patients with AS. However, both ECV and the LV diastolic function parameters provide complementary information on symptoms and clinical outcomes, emphasizing the concomitant assessment of both for further identification of patients with severe AS at a more advanced stage and ultimately at higher risk for clinical events.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Diffuse myocardial fibrosis, noninvasively quantified by ECV, is associated with LVDD in patients with AS.

**COMPETENCY IN PATIENT CARE:** The degree of diffuse myocardial fibrosis by CMR provides additive information to LV diastolic function grading for explaining symptoms and predicting clinical outcomes.

**TRANSLATIONAL OUTLOOK:** Further studies are warranted to evaluate whether incorporating ECV into current LV diastolic function grading better predicts outcomes in patients with severe AS.

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**KEY WORDS** aortic stenosis, diastole, fibrosis, cardiac magnetic resonance

**APPENDIX** For supplemental methods, figures and their legends, tables, and references, please see the online version of this paper.