Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Myocardial Fibrosis in Classical Low-Flow, Low-Gradient Aortic Stenosis

Insights From a Cardiovascular Magnetic Resonance Study

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BACKGROUND: Few data exist on the degree of interstitial myocardial fibrosis in patients with classical low-flow, low-gradient aortic stenosis (LFLG-AS) and its association with left ventricular flow reserve (FR) on dobutamine stress echocardiography. This study sought to evaluate the diffuse interstitial fibrosis measured by T1 mapping cardiac magnetic resonance technique in LFLG-AS patients with and without FR.

METHODS: Prospective study including 65 consecutive patients (41 LFLG-AS [mean age, 67.1±8.4 years; 83% men] and 24 high-gradient aortic stenosis used as controls) undergoing dobutamine stress echocardiography to assess FR and cardiac magnetic resonance to determine the extracellular volume (ECV) fraction of the myocardium, indexed ECV (iECV) to body surface area and late gadolinium enhancement.

RESULTS: Interstitial myocardial fibrosis measured by iECV was higher in patients with LFLG-AS with and without FR as compared with high-gradient aortic stenosis (35.25±9.75 versus 32.93±11.00 versus 21.19±6.47 mL/m^2, respectively; P<0.001). However, both ECV and iECV levels were similar between LFLG-AS patients with and without FR (P=0.950 and P=0.701, respectively). Also, FR did not correlate significantly with ECV (r=–0.16, P=0.31) or iECV (r=0.11, P=0.51). Late gadolinium enhancement mass was also similar in patients with versus without FR but lower in high-gradient aortic stenosis (13.3±10.2 versus 10.5±7.5 versus 4.8±5.9 g, respectively; P=0.018).

CONCLUSIONS: Patients with LFLG-AS have higher ECV, iECV, and late gadolinium enhancement mass compared with high-gradient aortic stenosis. Moreover, among patients with LFLG-AS, the degree of myocardial fibrosis was similar in patients with versus those without FR. These findings suggest that diffuse myocardial fibrosis may not be the main factor responsible for the absence of FR in LFLG-AS patients.

Key Words: aortic valve stenosis ■ fibrosis ■ heart ■ humans ■ magnetic resonance imaging

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CLINICAL PERSPECTIVE

Patients with classical low-flow, low-gradient aortic stenosis have a higher extent of cardiac magnetic resonance extracellular volume fraction of the myocardium, indexed extracellular volume to body surface area, and late gadolinium enhancement as compared with patients with high-gradient aortic stenosis with normal left ventricular ejection fraction, irrespective of the flow reserve status, as determined by dobutamine stress echocardiography. These findings suggest that the absence of flow reserve on dobutamine stress echocardiography is not associated with the amount of interstitial myocardial fibrosis. The results of this study also suggest that flow reserve as measured by dobutamine stress echocardiography should not be used as a prognostic tool in patients with classical low-flow, low-gradient aortic stenosis because it does not associate with parameters of myocardial damage on cardiac magnetic resonance. Dobutamine stress echocardiography is still helpful to confirm stenosis severity and thus to manage such challenging group of patients with classical low-flow, low-gradient aortic stenosis. Further larger studies with longer term follow-up should evaluate the potential prognostic impact of the degree of interstitial myocardial fibrosis in patients with low-flow, low-gradient aortic stenosis and reduced left ventricular ejection fraction.

Low-flow, low-gradient aortic stenosis (LFLG-AS) with low ejection fraction is an advanced stage of aortic stenosis (AS), which not only has a poor prognosis with medical treatment but also carries out high operative mortality with surgical aortic valve replacement (AVR).[1,2] In such patients, dobutamine stress echocardiography (DSE) is essential to assess the presence of left ventricular flow reserve (FR) and thus to confirm the AS severity and the indication of AVR.[1–5] There are conflicting data on FR mortality predictive value. Although FR does not predict mortality or left ventricular ejection fraction (LVEF) improvement after transcatheter AVR, absence of FR is associated with high 30-day mortality after surgical AVR, and previous studies have suggested that this association could be related to extensive interstitial fibrosis.[1,4–8] Nonetheless, there is a lack of data on the mechanisms determining FR in LFLG-AS, and studies to date have focused on focal fibrosis as evaluated by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) or tissue biopsy.[9–11]

The extracellular volume (ECV) fraction of the myocardium determined by CMR is a novel parameter that is well correlated with the extent of diffuse myocardial fibrosis.[12–14] ECV is a valuable tool to distinguish early from late ventricular dysfunction in nonvalvular cardiomyopathy.[15] However, patients with severe AS have higher amount of interstitial fibrosis, even with normal systolic ventricular function, and no study to date has compared the diffuse myocardial fibrosis by ECV between high-gradient AS (HG-AS) and LFLG-AS patients with and without FR on DSE.[16–18] The main objective of the present study was to evaluate the myocardial diffuse interstitial fibrosis as measured by ECV using T1 mapping CMR in patients with LFLG-AS and to compare them with HG-AS patients. This study also attempts to evaluate whether FR status is associated with different degrees of myocardial fibrosis measured by ECV.

METHODS

Study Population

Between March 2013 and March 2016, we prospectively enrolled 41 consecutive patients with symptomatic LFLG-AS (ie, mean gradient <40 mm Hg and indexed aortic valve area (AVA) ≤0.6 cm^2/m^2), with reduced LVEF (<50%; Figure 1). Patients were excluded if they presented the following criteria: (1) severe primary mitral valve disease, (2) severe aortic regurgitation, (3) CMR incompatible devices or contraindications to gadolinium-enhanced CMR, (4) previous valve surgery, (5) nonischemic cardiomyopathies, or (6) diagnosis of pseudosevere AS on DSE (n=4). We have further included 24 additional patients with symptomatic HG-AS (AVA ≤1.0 cm^2 and mean gradient >40 mm Hg) with normal LVEF and isolated surgical AVR indication for comparison and similar demographic characteristics in terms of age and sex. The study protocol was reviewed and approved by the local institutional ethics committee. All patients provided written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Protocol

Clinical data included age, sex, body surface area, New York Heart Association functional class, documented diagnosis of traditional cardiovascular risk factors, and comorbidities such as hypertension, diabetes mellitus, and coronary artery disease. All of the patients with LFLG-AS underwent DSE, transthoracic echocardiography, T1 mapping and LGE CMR, and laboratory tests, including troponin I (ADVIA Centaur TnI-Ultra; Siemens Healthcare Diagnostics, Tarrytown, NY) and B-type natriuretic peptide (ADVIA Centaur; Siemens Medical Solutions Diagnostic, Los Angeles, CA). All patients underwent coronary angiography, and coronary artery disease was defined as the presence of >50% luminal stenosis on major epicardial coronary arteries. Residual SYNTAX score (The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) was used to estimate the severity of coronary artery disease.[19]

Echocardiography

All transthoracic Doppler-echocardiographic exams were analyzed in a central echocardiography laboratory at our institution. All exams were performed at rest and at DSE as

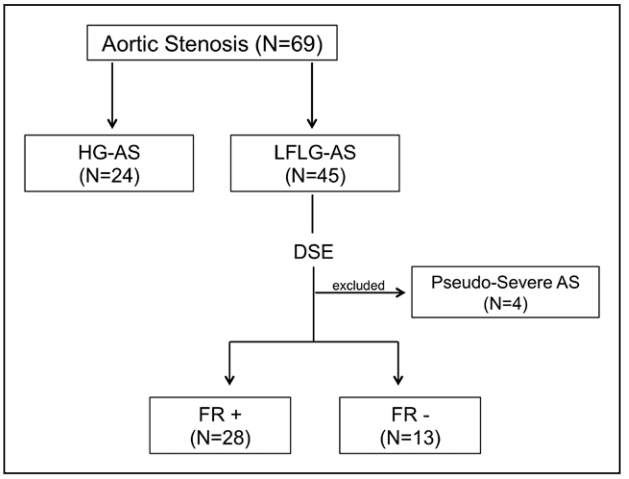

Figure 1. Study flowchart.
Selection of the study population. AS indicates aortic stenosis; DSE, dobutamine stress echocardiography; FR, flow reserve; HG, high gradient; and LFLG, low flow, low gradient.

described previously,[3,20] using a commercially available ultrasound system (Vivid 9; GE Healthcare, Milwaukee, WI). Briefly, the dobutamine infusion protocol consisted of 5-minute increments of 2.5 to 5 μg/kg per minute up to a maximum dosage of 20 μg/kg per minute. A minimum of 3 consecutive cycles were recorded. Continuous-wave Doppler of the aortic valve velocity spectrum, as well as pulsed-wave Doppler of the left ventricular outflow tract velocity spectrum, was recorded at rest and at each step of the dobutamine protocol. Patients in use of β-blockers or digoxin had these medications stopped or reduced to the lower tolerable dose. LVEF was measured by the biplane Simpson method, and AVA was measured by continuity equation. Left ventricular outflow tract diameter was assumed to be constant at different flow states, and the baseline value was used to calculate stroke volume at baseline and during dobutamine infusion according to standard formulae. The presence of FR was defined as the percentage increase in stroke volume ≥20%. The presence of true-severe AS was defined by a mean gradient ≥40 mm Hg with an AVA ≤1.0 cm^2 during DSE, and pseudosevere AS was defined by a mean gradient <40 mm Hg and an AVA >1.0 cm^2. In the absence of FR, AS severity was further confirmed with aortic valve calcium score on computed tomography (≥1200 AU in women and ≥2000 AU in men).[6,21–23] Patients with no FR, low aortic valve calcium score, and no other pathology that could explain the low LVEF were evaluated by an institutional Heart Team for indication of intervention, and AS severity was confirmed during AVR in all of such patients. The stroke volume index, left ventricular end-diastolic volume, left ventricular end-systolic volume, LVEF, and AVA were measured using the methods recommended by the American Society of Echocardiography.[24,25] In patients with atrial fibrillation, all FR echocardiographic parameters were measured in a mean of 10 consecutive heart beats.[24] Left ventricular global longitudinal strain was measured by speckle tracking with dedicated commercial software (EchoPAC V 110.0.x; GE Healthcare, Milwaukee, WI) as previously reported.[26] Global longitudinal strain data were expressed in absolute value (|%|) and were defined as the average of longitudinal strain of the 2-chamber, 3-chamber, and 4-chamber apical views.

CMR Protocol

All patients underwent CMR using a clinical 1.5-T CMR scanner (Achieva; Philips, Best, the Netherlands), and the analyses were performed by 2 investigators in a central CMR core laboratory at our Institution, blinded to clinical and echocardiographic parameters. Images were acquired and coupled to the electrocardiography during breath-hold, and the analyses were performed using CVi42 (Circle CVi; Calgary, Canada) software. Endocardial and epicardial delineations were manually traced in all end-diastolic and end-systolic phase short-axis images. Based on these contours, biventricular end-diastolic volume, end-systolic volume, ejection fraction, and left ventricular mass were automatically calculated. LGE imaging for myocardial fibrosis was performed 10 minutes after a bolus (0.2 mmol/kg body weight) of gadolinium-based contrast. LGE images were acquired using a phase-sensitive inversion recovery sequence and the inversion time was individually determined to null the normal myocardial signal. LGE quantification was obtained with thresholding technique by 3 SDs above remote myocardium.

The Modified Look-Locker inversion-recovery sequence was performed in expiratory apnea, into 3 segments of the left ventricle short axis (base, mid, and apex) before and 15 to 20 minutes after the intravenous injection of 0.2 mmol/kg of gadolinium-based contrast to calculate the native T1 mapping and T1 postcontrast mapping, respectively. Because some of the patients had areas of focal fibrosis by LGE, we performed an analyses including and other excluding all areas of focal fibrosis. Endocardial and epicardial delineations were manually traced in all images of the short-axis 3 segments. In the first analysis, we calculated the T1 value of each segment, which resulted in a global myocardial T1 (pre- and post-gadolinium). In the second analysis, it was used a region of interest in areas without late enhancement, and the myocardial T1 was calculated excluding subendocardial and transmural fibrosis areas (segments with midwall LGE were included). In both analyses, we also placed a region of interest in heart cavity for the T1 calculation of the blood pool (Figure 2). In patients with atrial fibrillation, T1 mapping image acquisition was repeated, and an average of T1 values was calculated in both pregadolinium and postgadolinium sequences.[27] Besides, all these patients had controlled heart rate (60–90 bpm) at the time of CMR. ECV was calculated from pregadolinium and postgadolinium T1 measurements of blood and myocardium, and adjusted to patient's hematocrit (collected on the same day of the CMR exam), as follows: $ECV_{myo}=(1-h\text{ematocrit})\times\Delta R1_{myo}/\Delta R1_{blood}$. Where ΔR1=(1/T1 precontrast−1/T1 postcontrast). We also calculated the indexed ECV (iECV) using the following formula: ECV (excluding areas of focal fibrosis)×indexed left ventricular end-diastolic myocardial volume, as previously described.[18]

Statistical Analysis

Continuous variables were presented as mean±SD or median (interquartile range). Categorical variables were presented as percentages. Kolmogorov-Smirnov test was used to test normality of the variables. *t* test, Kruskall-Wallis, or ANOVA test was applied for continuous variables, and Fisher exact test or χ^2 test was applied for categorical variables, as appropriate. The post hoc analysis was performed with

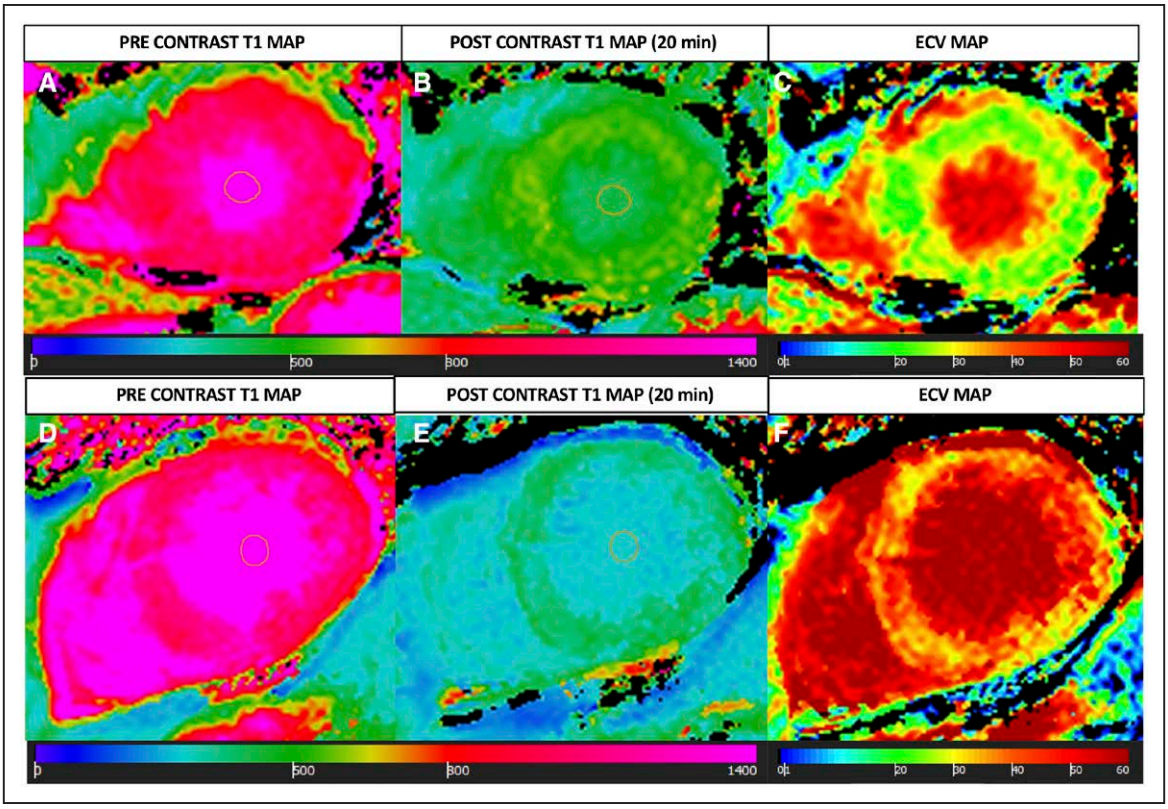

Figure 2. The extracellular volume (ECV) fraction calculation using the T1 mapping cardiovascular magnetic resonance.
Native T1 map (**A**) and postcontrast T1 map (**B**), with normal T1 values, were used to calculate the ECV map (**C**) of a high-gradient aortic stenosis patient (ECV: 26.1% and iECV: 23.2 mL/m^2). Native T1 map (**D**) and postcontrast T1 map (**E**) show few regions with lower T1 values in native T1 map (yellow and green regions) and even lower values in postcontrast T1 map (green regions) that results in increased ECV values in the ECV map (**F**) in a low-flow, low-gradient aortic stenosis with low ejection fraction patient (ECV: 31.0% and iECV: 23.2 mL/m^2).

Tukey test. Log transformation was applied to normalize the distribution of troponin I, B-type natriuretic peptide, LGE mass, ECV including delayed-enhancement images, ECV excluding delayed-enhancement images, iECV, CMR right ventricular end-diastolic volume index, CMR right ventricular end-systolic volume index, CMR left ventricular end-diastolic volume index, and CMR aortic valve area. Residual SYNTAX score and CMR LVEF were analyzed using Kruskal-Wallis test. Pearson or Spearman correlation coefficients were used to evaluate data correlation, as appropriate. A logistic regression analysis was used to evaluate the predictors of FR. ECV measurements were repeated after 2 weeks by the same and by another observer to test the interobserver and intraobserver variability, using the Bland-Altman method. Variables with a P <0.10 in univariable analyses were entered in the multivariable model. All tests were 2 tailed, and a P <0.05 was used to indicate statistical significance. All analyses were conducted using the statistical package SPSS, version 20 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

The main baseline clinical and laboratory data are shown in Table 1. Among the 41 included patients with LFLG-AS (Tables I and II in the Data Supplement), the mean age was 67.1±8.4 years, and 82.9% were men. DSE confirmed the presence of FR in 28 patients (68.2%), and 13 patients (31.7%) had no FR. There were no demographic differences between patients with or without FR. Nonetheless, when comparing both groups with LFLG-AS in relation to those with HG-AS, there was a significantly lower incidence of male sex (75.0% versus 100.0% versus 62.5%, respectively; P=0.010), atrial fibrillation (17.8% versus 38.4% versus 0%, respectively; P=0.002), and coronary artery disease (32.1% versus 53.8% versus 0%, respectively; P<0.001) in the HG-AS group, whereas the estimated glomerular filtration rate was higher (55.4±17.1 versus 58.8±20.1 versus 73.8±18.8 mL/min, respectively; P=0.001). LFLG-AS patients with and without FR had also higher levels of B-natriuretic peptide when compared with HG-AS (378 [142–650] versus 449 [86–449] versus 47 [28–153] pg/mL, respectively; P<0.001) and troponin I (0.04 [0.02–0.10] versus 0.04 [0.01–0.16] versus 0.02 [0.01–0.04] ng/mL, respectively; P=0.001). Among patients with LFLG-AS and no FR, the severity of AS was assessed by computed tomography in all patients, and the median valve calcium score was 2600 (1497–5875) AU. There were 2 male patients in the group with LFLG-AS and

Table 1. Baseline Clinical and Laboratory Data of the Study Population

Variable	LFLG-AS		HG-AS (n=24)	*P* Value*
	FR+ (n=28)	FR– (n=13)		
Clinical data				
Age, y	67.1±9.4	67.1±5.6	64.4±8.0	0.445
Body surface area, m^2	1.79±0.14	1.85±0.13	1.79±0.16	0.195
Male sex	21 (75.0)	13 (100.0)	15 (62.5)	0.010†
Diabetes mellitus	11 (39.2)	5 (38.4)	6 (25.0)	0.505
Hypertension	21 (75.0)	7 (53.8)	12 (50.0)	0.148
Atrial fibrillation	5 (17.8)	5 (38.4)	0 (0)	0.002†‡
Coronary artery disease	9 (32.1)	7 (53.8)	0 (0)	<0.001†‡
Previous myocardial infarction	9 (32.1)	4 (30.8)	0 (0)	0.009†‡
Previous CABG	5 (17.8)	1 (7.6)	0 (0)	0.035‡
Residual SYNTAX score	12.0 (8.0–21.5)	13.0 (9.0–14.5)	0	0.002†‡
Symptoms				
NYHA III/IV	15 (53.5)	7 (53.8)	12 (50.0)	0.960
Angina	10 (35.7)	1 (7.6)	9 (37.5)	0.085
Medications				
ACE inhibitors or ARB	19 (67.8)	11 (84.6)	11 (45.8)	0.046†
β-Blockers	15 (53.5)	7 (53.8)	2 (8.3)	<0.001†‡
Antiplatelets	17 (60.7)	6 (46.1)	5 (20.8)	0.015‡
Diuretics	24 (85.7)	11 (84.6)	17 (70.8)	0.377
Statins	20 (71.4)	9 (69.2)	11 (45.8)	0.136
Digoxin	4 (14.2)	4 (30.7)	2 (8.3)	0.220
Oral anticoagulation	5 (17.8)	6 (46.1)	0 (0)	0.001†
ECG				
Left bundle branch block	8 (28.6)	4 (30.8)	2 (8.3)	0.110
Laboratory data				
Hematocrit, %	41.1±4.9	43.1±3.1	40.9±4.3	0.352
eGFR, mL/min	55.4±17.1	58.8±20.1	73.8±18.8	0.001‡
CKD (eGFR <60 mL/min)	9 (32.14)	4 (30.76)	6 (25.0)	0.238
Troponin I, ng/mL	0.04 (0.02–0.10)	0.04 (0.01–0.16)	0.02 (0.01–0.04)	0.001†‡
B-type natriuretic peptide, pg/mL	378 (142–650)	449 (86–449)	47 (28–153)	<0.001†‡

Values are mean±SD, median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FR, flow reserve; HG-AS, high-gradient aortic stenosis; LFLG-AS, low-flow, low-gradient aortic stenosis with low ejection fraction; NYHA, New York Heart Association; and SYNTAX, The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

*Overall *P* value among groups: LFLG-AS with FR, LFLG-AS without FR and HG-AS groups.

†Significant difference ($P<0.05$) between LFLG-AS without FR vs HG-AS groups.

‡Significant difference ($P<0.05$) between LFLG-AS with FR vs HG-AS groups.

no FR with the aortic valve calcium score <2000 AU (patient 1, 1041 AU; patient 2, 1650 AU). In these cases, AS severity was confirmed during surgical AVR, having both cases predominantly fibrotic AS, with a low opening valve area according to pathological evaluation. An additional analysis excluding patients with atrial fibrillation and coronary artery disease (Tables III and IV in the Data Supplement) and excluding patients without FR and an aortic valve calcium score <2000 AU was also performed (Tables V and VI in the Data Supplement).

Echocardiography Data

The main baseline echocardiographic and DSE parameters are shown in Table 2. As expected, HG-AS patients had several echocardiographic differences compared with LFLG-AS patients with or without FR. LFLG-AS patients presented a mean AVA of 0.81±0.18 cm^2 and LVEF of 35.0±9.6% (Table II in the Data Supplement). There was no significant difference between LFLG-AS patients with FR versus those with no FR, except for a smaller AVA among those with FR (0.77±0.17 ver-

Table 2. Baseline Echocardiographic and DSE Data

Variable	LFLG-AS		HG-AS (n=24)	*P* Value*
	FR+ (n=28)	FR– (n=13)		
Baseline echocardiography				
LVEF, %	34.6±10.0	37.7±6.8	64.0±5.0	<0.001†‡
LVEDV, mL	209.5±52.6	194.4±58.3	110.1±30.1	<0.001†‡
LVESV, mL	137.1±41.2	123.6±51.8	41.5±15.6	<0.001†‡
LV mass, g/m^2	160.0±54.0	143.3±28.5	133.3±42.5	0.121
Mean gradient, mm Hg	28.1±8.3	24.4±9.4	54.7±15.2	<0.001†‡
Peak aortic valve velocity, m/s	3.2±0.3	3.2±0.6	4.6±0.6	<0.001†‡
Aortic valve area, cm^2	0.77±0.17	0.94±0.10	0.72±0.15	<0.001‡§
Aortic valve area index, cm^2/m^2	0.42±0.09	0.50±0.05	0.41±0.09	0.007‡§
Stroke volume index, mL/m^2	36.9±10.3	35.7±7.8	38.0±10.2	0.780
Moderate/severe functional mitral regurgitation	7 (25.0)	6 (46.1)	0 (0)	<0.001†‡
Moderate/severe functional tricuspid regurgitation	4 (14.2)	1 (7.6)	0 (0)	0.073
DSE				
Peak stress aortic valve area, cm^2	0.79±0.16	0.94±0.03	…	0.018
ΔAortic valve area, cm^2	–0.007±0.134	–0.062±0.123	…	0.233
Basal mean gradient, mm Hg	28.1±8.3	24.4±9.4	…	0.226
Peak stress mean gradient, mm Hg	43.5±13.1	25.6±12.3	…	0.008
ΔMean gradient, mm Hg	13.7±10.9	3.3±3.2	…	0.003
ΔStroke volume index, mL/m^2	8.9±6.1	1.1±4.0	…	0.001
Basal heart rate, bpm	70±9	68±14	…	0.750
Peak stress heart rate, bpm	90±16	86±27	…	0.683
ΔHeart rate, bpm	19±12	17±1 6	…	0.725
Basal indexed flow rate, mL/m^2·s	107.6±33.0	108.1±35.2	…	0.972
Peak indexed flow rate, mL/m^2·s	142.2±34.4	109.3±23.2	…	0.020
ΔIndexed flow rate, mL/m^2·s	34.6±17.4	1.1±25.5	…	0.001
Global longitudinal strain ([–]%)	10.01±2.69	10.21±3.72	…	0.845

Values are mean±SD or n (%). Δ indicates difference between peak and baseline dobutamine stress value; DSE, dobutamine stress echocardiography; FR, flow reserve; HG-AS, high-gradient aortic stenosis; LFLG-AS, low-flow, low-gradient aortic stenosis with low ejection fraction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and LVESV, left ventricular end-systolic volume.

*Overall *P* value among groups: LFLG-AS with FR, LFLG-AS without FR and HG-AS groups.

†Significant difference (*P*<0.05) between LFLG-AS with FR vs HG-AS groups.

‡Significant difference (*P*<0.05) between LFLG-AS without FR vs HG-AS groups.

§Significant difference (*P*<0.05) between LFLG-AS with FR vs LFLG-AS without FR groups.

sus 0.94±0.10 cm^2, respectively; *P*=0.001 [post hoc test]; Table VII in the Data Supplement) and indexed AVA (0.42±0.09 versus 0.50±0.05 cm^2/m^2, respectively; *P*=0.004 [post hoc test]).

Baseline CMR Data

CMR parameters are shown in Table 3. LGE mass was similar between LFLG-AS patients with and without FR; however, they had higher rates of LGE mass when compared with HG-AS (13.3±10.2 versus 10.5±7.5 versus 4.8±5.9 g, respectively; *P*=0.018; Figure 3A and 3B). LFLG-AS patients had also a higher prevalence of transmural delayed-enhancement images than HG-AS (28.5% versus 38.4% versus 0%, respectively; *P*=0.001 [*P*=0.720 for post hoc test between LFLG-AS patients with FR versus those without FR]). With respect to interstitial fibrosis, mean ECV excluding delayed-enhancement images was similar among LFLG-AS patients with and without FR, as well as among those with HG-AS (29.35±4.70% versus 29.76±2.84% versus 27.63±3.53%, respectively; *P*=0.196; Figure 4A and 4B). iECV was higher in patients with and without FR when compared with HG-AS (35.25±9.75 versus 32.93±11.00 versus 21.19±6.47 mL/m^2, respectively; *P*<0.001). However, iECV was also similar between LFLG-AS patients, irrespective of the presence of FR (*P*=0.701 for post hoc analysis between FR+ versus FR– groups; Figure 5A and 5B). After excluding the patients with coronary artery disease and atrial fibrillation (41

Table 3. Cardiac Magnetic Resonance Data

Variable	LFLG-AS		HG-AS (n=24)	*P* Value*
	FR+ (n=28)	FR– (n=13)		
RVEDV index, mL/m²	66.5±23.5	81.4±38.3	61.2±16.6	0.089
RVESV index, mL/m²	35.6±22.9	50.8±40.5	22.6±10.7	0.002†
RV ejection fraction, %	49.5±17.3	42.2±16.9	64.7±8.8	0.001†‡
LVEDV index, mL/m²	121.6±33.9	110.5±31.6	75.9±16.7	<0.001†‡
LVESV index, mL/m²	85.0±34.0	70.5±30.3	24.8±12.7	<0.001†‡
LVEF, %	32.4±10.9	39.0±13.3	67.7±9.3	<0.001†‡
Aortic valve area, cm²	0.74±0.23	0.99±0.35	0.71±0.21	0.035§
Positive mesocardial delayed-enhancement images	7 (25.0)	2 (15.4)	5 (20.8)	0.773
Positive subendocardial delayed-enhancement images	7 (25.0)	5 (38.5)	2 (8.3)	0.076
Positive transmural delayed-enhancement images	8 (28.5)	5 (38.4)	0 (0)	0.001†‡
LV mass, g	208.1±49.8	206.9±45.1	164.2±57.8	0.009‡
LGE mass, g	13.3±10.2	10.5±7.5	4.8±5.9	0.018‡
Native myocardial T1, ms	997.9±114.0	936.2±122.5	978.3±117.9	0.305
ECV including delayed-enhancement images, %	29.30±4.49	31.27±5.00	27.39±3.85	0.043†
ECV excluding positive delayed-enhancement images, %	29.35±4.70	29.76±2.84	27.63±3.53	0.196
iECV, mL/m²	35.25±9.75	32.93±11.00	21.19±6.47	<0.001†‡

Values are mean±SD or n (%). ECV indicates extracellular volume; FR, flow reserve; HG-AS, high-gradient aortic stenosis; iECV, indexed extracellular volume; LFLG-AS, low-flow, low-gradient aortic stenosis; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.

*Overall *P* value among groups: LFLG-AS with FR, LFLG-AS without FR and HG-AS groups.

†Significant difference (*P*<0.05) between LFLG-AS without FR vs HG-AS groups.

‡Significant difference (*P*<0.05) between LFLG-AS with FR vs HG-AS groups.

§Significant difference (*P*<0.05) between LFLG-AS with FR vs LFLG-AS without FR groups.

patients remained for analysis: 17 patients in LFLG-AS group versus 24 in HG-AS), there was no difference in the ECV excluding delayed-enhancement images between LFLG-AS and HG-AS patients (27.93±3.82% versus 27.63±3.53%, respectively; *P*=0.799; Table IV in the Data Supplement). The interobserver and intraobserver reproducibility of ECV is shown in Figure I in the Data Supplement.

Correlation Between Echocardiographic and CMR Data in LFLG-AS Patients

Table 4 presents the correlations between ECV, iECV, FR and echocardiographic parameters and blood biomarkers in LFLG-AS patients. The FR did not significantly correlate with the amount of interstitial fibrosis measured by ECV (r=–0.164, *P*=0.306), iECV (r=0.106, *P*=0.508), LGE mass (r=0.140, *P*=0.478), or echocardiographic parameters of left ventricular function or AS severity. The ECV had a weak positive correlation with troponin I (r=0.388, *P*=0.013), and iECV had a weak correlation with mean transaortic gradient (r=–0.345, *P*=0.027), Simpson LVEF (r=–0.423, *P*=0.006), global longitudinal strain (r=–0.484, *P*=0.002), CMR right ventricular ejection fraction (r=–0.500, *P*=0.001), and B-type natriuretic peptide (r=0.463, *P*=0.003).

FR Predictors

The only independent predictor of FR in the multivariate analysis was the AVA (Odds Ratio: 0.625; 95% CI, 0.393–0.850 for each increase of 0.05 cm² in aortic valve area; *P*=0.014). The presence of atrial fibrillation, coronary artery disease, positive transmural delayed-enhancement images, positive mesocardial delayed-enhancement images, positive subendocardial delayed-enhancement images, ECV of the myocardium excluding positive delayed-enhancement images, iECV, and β-blocker use were not associated with FR in the univariate analysis (Table VIII in the Data Supplement).

DISCUSSION

The main findings of the present study were that (1) iECV and LGE mass measured by CMR were higher in pooled LFLG-AS patients when compared with HG-AS; (2) both ECV and iECV were similar between those with and without FR on DSE; (3) no significant correlation was found between FR, iECV, and ECV with respect to other echocardiographic parameters of left ventricular function.

LFLG-AS represents only 5% to 10% of the AS population; nonetheless, this is one of the most challenging subsets of patients with AS.[2,4,5] This is related to higher

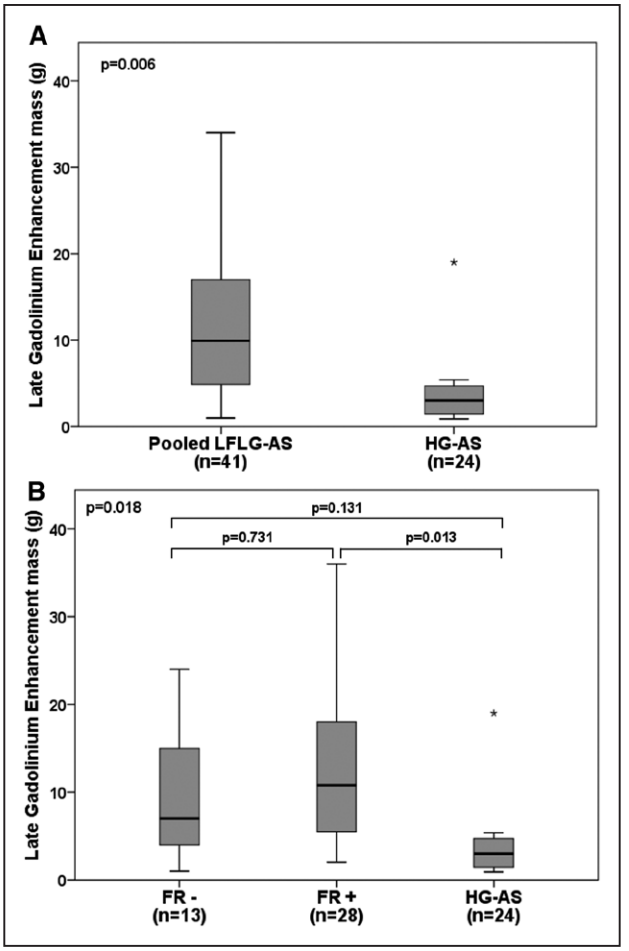

Figure 3. LGE mass between patients with low-flow low-gradient aortic stenosis (LFLG-AS) and high-gradient aortic stenosis (HG-AS). Comparison of late gadolinium enhancement mass (LGE) between the pooled patients with LFLG-AS vs HG-AS (**A**) and comparison between LFLG-AS with flow reserve (FR), without FR, and HG-AS (**B**). Solid horizontal line indicates mean value; gray box, 1 SD; and vertical line, high and the lowest mean values.

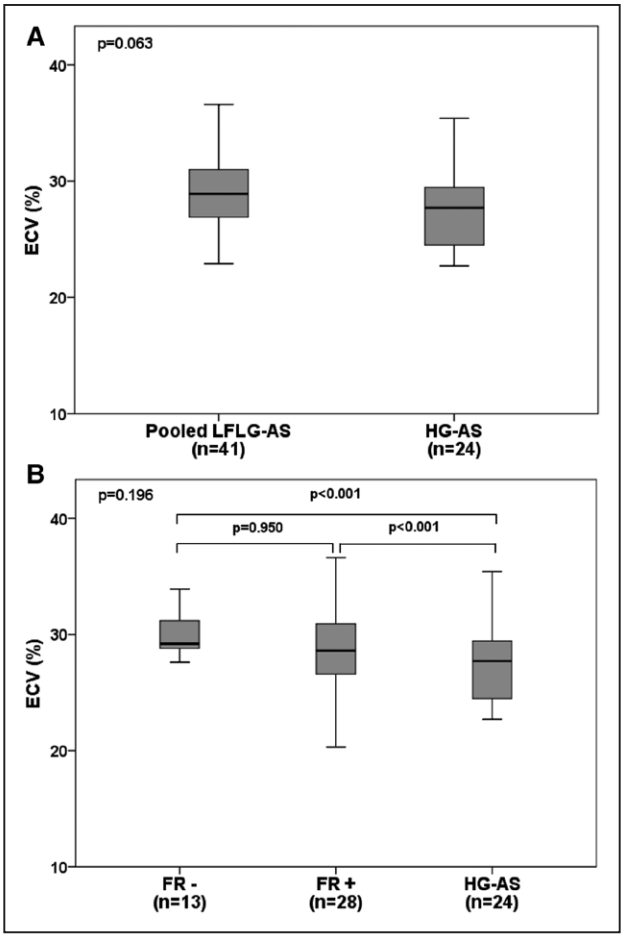

Figure 4. Extracellular volume (ECV) in patients with low-flow, low-gradient aortic stenosis (LFLG-AS) vs high-gradient aortic stenosis (HG-AS). Comparison of ECV fraction between the pooled patients with LFLG-AS vs HG-AS patients (**A**) and comparison between LFLG-AS with flow reserve (FR), without FR, and HG-AS (**B**). Solid horizontal line indicates mean value; gray box, 1 SD; and vertical line, high and the lowest mean values.

mortality rates when compared with HG-AS, with an increased surgical risk in those without FR on DSE.[1–5] Despite the high operative mortality, patients with LFLG-AS and no FR have better survival with surgical AVR than with medical therapy alone. Furthermore, the postoperative recovery of left ventricular function and patient's functional status were similar among these patients irrespective of the FR status.[1,2,8,10] To date, there are few data on the mechanisms underlying the lack of FR, and prior studies have suggested that this could be related to a more extensive interstitial fibrosis.[1,4–7] Initial studies evaluating myocardial fibrosis in patients with AS used the LGE technique by CMR, as well as myocardial biopsy in patients eventually undergoing surgical AVR.[11,28] LGE demonstrated good correlation with histopathologic fibrosis, both associating with impaired postoperative survival and less postoperative improvement in LVEF and functional class.[11,28] A prior study comparing LGE and myocardium biopsy evaluated 86 patients according to the flow state.[10] A total of 9 patients with LFLG-AS (mean LVEF of 36%) presented significantly more focal fibrosis than those with HG-AS, and this is consistent with our study. Of note, the larger LGE mass observed among LFLG-AS versus HG-AS patients, in this previous study, as well as in our study, is likely related to the higher prevalence of coronary artery disease in LFLG-AS group. However, the LGE technique only detects focal fibrosis and is unable to properly identify extracellular expansion. Hence, LGE represents focal irreversible fibrosis and may not be a good marker of diffuse interstitial myocardial fibrosis.[29,30] Importantly, in our study, the LGE mass did not correlate with FR on DSE.

Myocardial T1 mapping is a novel technique that allows measurements of interstitial fibrosis estimated by ECV, and this method has been validated histologically presenting a good correlation with diffuse tissue collagen matrix.[12,13] In patients with HG-AS with normal LVEF, ECV is a predictor of heart failure after transcatheter AVR and has also shown a significant correlation with valve disease severity and left ventricular

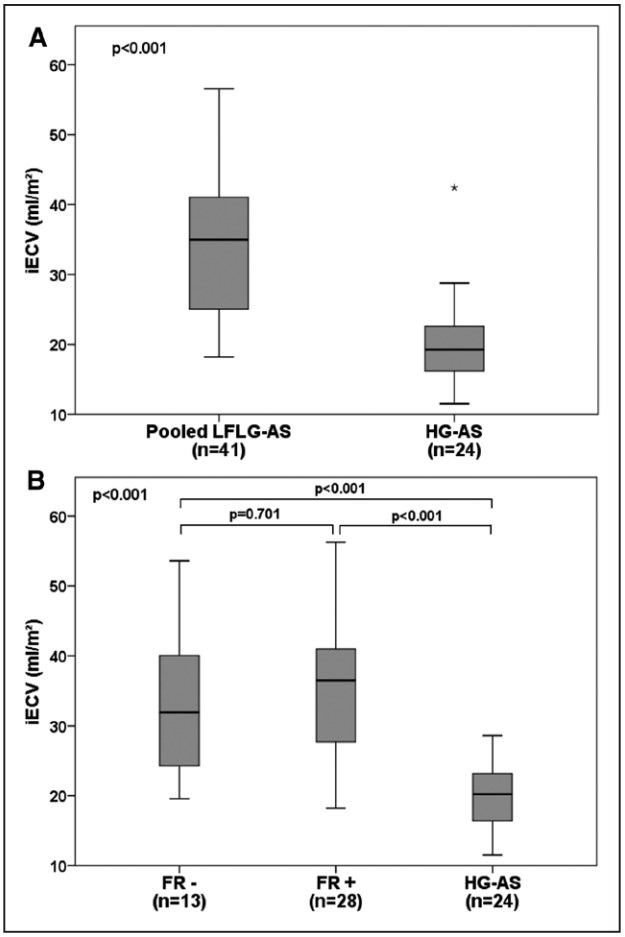

Figure 5. Indexed extracellular volume (iECV) in patients with low-flow low-gradient aortic stenosis (LFLG-AS) vs high-gradient aortic stenosis (HG-AS).
Comparison of iECV fraction between the pooled patients with LFLG-AS vs HG-AS patients (**A**) and comparison between LFLG-AS with flow reserve (FR), without FR, and HG-AS (**B**). Solid horizontal line indicates mean value; gray box, 1 SD; and vertical line, high and the lowest mean values.

decompensation.[18,31] Besides, ECV evaluation in HG-AS patients undergoing surgical AVR suggests that diffuse fibrosis is a reversible process while focal fibrosis measured by LGE do not regress.[29,30] However, there is evidence that ECV values may overlap between controls and early stages of AS, and iECV—a novel parameter that combines ECV and left ventricular end-diastolic myocardial volume—could better discriminate the stages of AS progression.[18]

Our study is the first to prospectively evaluate ECV and iECV in LFLG-AS patients and to compare them with HG-AS. It has been hypothesized that patients with LFLG-AS without FR could have larger amounts of intertitial fibrosis, in addition to focal fibrosis, when compared with those with FR, possibly explaining the increased operative risk.[1,4–6] Our findings diverge from this hypothesis and reveal similar amounts of interstitial fibrosis as measured by ECV and iECV between LFLG-AS with and without FR. The amount of interstitial fibrosis as determined by the iECV was, however, ≈2-fold higher in the LFLG-AS versus the HG-AS patients, irrespective of the FR state. These findings suggest the superiority of the iECV compared with ECV in discriminating HG-AS with preserved LVEF from more advanced stages of AS such as LFLG-AS.[18] However, there was no difference in both ECV and iECV between LFLG-AS patients with versus without FR. Thus, our study does not support the concept that diffuse interstitial fibrosis contributes to the lack of FR in LFLG-AS.[5,7] These findings also subsidize the reason why patients with LFLG-AS without FR display similar improvement in LVEF compared with those with FR after surgical AVR, transcatheter AVR, or resynchronization therapy.[1,8] Other possible reasons that could explain the absence of FR,[1,4–6] such as coronary artery disease, use of β-blockers, and positive transmural delayed-enhancement images, were also similar between LFLG-AS patients with and without FR, and the only independent predictor of FR on DSE found was the AVA. In the present study, the AVA and indexed AVA were in fact smaller in patients with FR, refuting the hypothesis that more severe AS ensuing afterload mismatch could also contribute to the lack of FR. The patients included in this study had also no evidence of cardiac amyloidosis, that could justify LFLG-AS phenotype. Our mean ECV value of ≈30% is much lower than the 46.9% cutoff suggested for the diagnosis of cardiac amyloidosis.[32] These results do not support the presence of cardiac amyloidosis diagnosis in our cohort.[32]

Although ECV had only a weak correlation with troponin I and iECV had weak correlation with mean transaortic gradient, LVEF, global longituidinal strain, CMR right ventricular ejection fraction, and B-type natriuretic peptide, there was no correlation between FR and myocardial fibrosis as measured by either ECV or iECV. These findings provide further support to the concept that the lack of FR per se should not preclude aortic valve intervention, if the procedure is otherwise clinically indicated. Prior study has shown good short- and mid-term outcomes in such patients with LFLG-AS and no FR with transcatheter AVR.[8] In this previous study, the survival rate at 2 years was similar in patients with versus without FR (71.3% versus 64.7%; *P*=0.704), and the postprocedure LVEF improvement was not associated with the absence of FR, suggesting that DSE must be used only for AS severity confirmation and not for prognostic information. Besides, ECV and iECV are surrogate of a rapid progressive but reversible interstitial myocardial fibrosis, and its nature may not be sufficient to explain left ventricular response during DSE.[30] Probably, cellular and metabolic mechanisms may have a central role in the FR pathophysiology, and future studies with a larger number of patients should further determine whether ECV and iECV may have a prognostic role in such patients with LFLG-AS.

Table 4. Correlation Between ECV, iECV, FR, and Echocardiographic Parameters, CMR Parameters, and Blood Biomarkers in LFLG-AS Patients

	FR		ECV		iECV	
	r	*P* Value	r	*P* Value	r	*P* Value
Echocardiographic parameters						
Mean transaortic gradient, mm Hg	0.169	0.292	−0.223	0.161	−0.345	0.027*
Simpson LVEF, %	−0.223	0.173	−0.037	0.825	−0.423	0.006*
Stroke volume index, mL/m^2	0.031	0.853	−0.233	0.158	−0.082	0.614
FR	…	…	−0.164	0.306	0.106	0.508
ΔIndexed flow rate, mL/m^2·s	−0.645	0.001	0.215	0.324	−0.204	0.349
Moderate/severe functional mitral regurgitation	−0.202	0.184	0.013	0.934	0.146	0.362
Moderate/severe functional tricuspid regurgitation	0.094	0.560	0.138	0.390	0.113	0.480
Global longitudinal strain	−0.017	0.918	−0.199	0.225	−0.484	0.002*
CMR parameters						
LGE mass, g	0.140	0.478	0.250	0.199	0.139	0.481
RVEF, %	0.195	0.221	−0.252	0.111	−0.500	0.001*
Positive mesocardial delayed-enhancement images	0.108	0.501	0.224	0.159	0.134	0.402
Positive subendocardial delayed-enhancement images	−0.138	0.391	0.172	0.282	−0.077	0.632
Positive transmural delayed-enhancement images	−0.099	0.538	0.280	0.076	0.213	0.182
Blood biomarkers						
B-type natriuretic peptide, pg/mL	−0.009	0.954	0.177	0.274	0.463	0.003*
Troponin I, ng/mL	0.047	0.772	0.388	0.013*	0.132	0.050
ECG						
Left bundle branch block	−0.022	0.889	−0.118	0.463	−0.109	0.499

CMR indicates cardiac magnetic resonance; ECV, extracellular volume; FR, flow reserve; iECV, indexed extracellular volume; LFLG-AS, low-flow, low-gradient aortic stenosis; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and RVEF, right ventricular ejection fraction.

*Indicates statistical significance.

Limitations

This is a single-center study with a relatively small number of patients, albeit large for this clinical entity. Despite the small sample size, our study had an alpha level of 0.05 and a statistical power of 80% to determine differences in ECV ≥4.6%. Of note, prior study has shown that an ≈5% increase in ECV is associated with >2-fold risk of major adverse cardiovascular events, and it is considered a clinically relevant effect size.[33] As expected, the HG-AS cohort presents significant baseline differences as compared with LFLG-AS patients, especially related to the absence of atrial fibrillation and coronary artery disease. Thus, the differences in the fibrosis rates, and particularly those of LGE, may be related, at least in part, to such differences in the baseline characteristics. Global longitudinal strain was measured only before DSE, so these data are lacking in the control group (HG-AS). Although this was a prospective cohort and the HG-AS patients were concomitantly selected, future studies with a larger number of patients are still warranted to further evaluate the ECV and iECV by CMR in LFLG-AS patients.

Conclusions

Interstitial fibrosis measured by ECV and iECV was similar between LFLG-AS with and without FR on DSE, and no significant correlation was found between ECV, iECV, and FR. These findings indicate that the absence of FR is not related to the amount of diffuse interstitial fibrosis on CMR. Hence, the independent prognostic value of FR may be lower than initially anticipated by earlier series. The main objective of DSE remains to differentiate true versus pseudosevere AS, which is key to determine the need for AVR.

ARTICLE INFORMATION

Received August 23, 2018; accepted March 27, 2019.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.118.008353.

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Sources of Funding

This study was supported by a PhD grant (2013/06149-6) from Fundação de Amparo à Pesquisa do Estado de São Paulo. Dr Pibarot, PhD, holds the Canada

Research Chair in Valvular Heart Diseases. Dr Rodés-Cabau holds the Canadian Research Chair Fondation Famille Jacques Larivière for the Development of Structural Heart Interventions.

Disclosures

Dr B. Ribeiro is consultant for Edwards Lifesciences, Medtronic, and Scitech Medical. Dr Pibarot has Core Lab contracts with Edwards Lifesciences for which he receives no direct compensation. Dr Rodés-Cabau received research grants from Edwards Lifesciences and Medtronic. The other authors report no conflicts.

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