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ORIGINAL RESEARCH

Left Ventricular Contractility and Wall Stress in Patients With Aortic Stenosis With Preserved or Reduced Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to determine the prevalence of reduced contractility and uncompensated wall stress in patients with aortic stenosis (AS) with preserved or reduced left ventricular ejection fraction (LVEF) and their impact on survival.

BACKGROUND LVEF in AS is determined not only by contractility but also by loading conditions.

METHODS Patients with first diagnosis (time 0) of severe AS (aortic valve area [AVA]≤1 cm^2) with prior echo study (−3±1 years) were identified. Contractility was evaluated by plotting midwall fractional shortening (mFS) against circumferential end-systolic wall stress (cESS), stratified by LVEF of 60% at time 0. The temporal changes (from −3 years to time 0) and prognostic value of LVEF, contractility, and wall stress were assessed.

RESULTS Of 445 patients, 290 (65%) had LVEF ≥60% (median: 66% [interquartile range {IQR}: 63% to 69%]) and 155 patients (35%) had LVEF <60% (median: 47% [IQR: 34% to 55%]). Median AVA was 1.27 cm^2 (IQR: 1.13 to 1.43 cm^2) at −3 years and 0.90 cm^2 (IQR: 0.83 to 0.96 cm^2) at time 0. Decreased contractility was already present at −3 years (49 [17%] vs. 59 [38%]; LVEF ≥60% vs. <60%; $p < 0.001$) and became more prevalent at time 0 (69 [24%] vs. 106 [68%]; $p < 0.001$). Overall, wall stress was well controlled in both groups at −3 years (1 [0%] vs. 12 [8%]; $p < 0.001$) but deteriorated over time in patients with LVEF <60% (time 0: 0 [0%] vs. 26 [17%]; $p < 0.001$). During a median follow-up of 3.4 years, LVEF <60%, decreased contractility and high wall stress were associated with worse survival ($p < 0.01$ for all). Decreased contractility remained incremental to LVEF in patients with LVEF ≥60% ($p < 0.01$), but less so when LVEF was <60% ($p = 0.11$).

CONCLUSIONS In patients with severe AS, LVEF <60% is associated with a poor prognosis, being linked with decreased contractility and/or high wall stress. Decreased contractility is also present in a subset of patients with LVEF ≥60% and provides incremental prognostic value. These abnormalities already exist before AVA reaches 1.0 cm^2.
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In patients with aortic stenosis (AS), left ventricular ejection fraction (LVEF) serves as a surrogate for LV systolic function and plays an important role for stratification of prognosis (1-3). Although current American Heart Association/American College of Cardiology valvular heart disease guidelines recommend aortic valve replacement (AVR) in asymptomatic patients with severe AS

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

cESS = end-systolic circumferential wall stress

LV = left ventricle

LVEF = left ventricular ejection fraction

mFS = midwall fractional shortening

RWT = relative wall thickness

SVI = stroke volume index

when LVEF is lower than 50% (4), 3 publications reported that LVEF between 50% and 60% as well as lower than 50% is associated with worse prognosis compared to LVEF ≥60% (3,5,6). Moreover, in patients with severe AS and decreased LVEF, LVEF had declined below 60% several years prior to AS becoming severe (5). In patients with preserved LVEF, their LVEF was maintained >60% for the preceding 10 years until AS became severe (5). Based on these findings, normal LVEF in AS appears to be 60% or higher.

LVEF depends not only on the contractility of LV but also on the loading conditions. In other words, reduced LVEF may be due to excessive afterload (high wall stress), reduced contractility, or a combination of both (7–9). On the other hand, even if LVEF is preserved, LV systolic function is sometimes decreased. Due to LV hypertrophy caused by the addition of sarcomeres in parallel, LVEF may appear to be preserved despite underlying reduced contractility. In such conditions, even subnormal shortening can generate enough thickening to create a normal LVEF, while the reduced midwall shortening better reflects the systolic function. Therefore, endocardial measurements (such as LVEF) can mischaracterize LV systolic function in patients with AS.

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Midwall fractional shortening (mFS), especially adjusted for wall stress, has been proposed as a reliable measure for assessing LV contractile function in AS (10–13).

Thus, we performed a retrospective analysis in patients with severe AS with the following aims: 1) to determine what contributes to decreased LVEF (LV contractile dysfunction, high wall stress, or both) by assessing mFS adjusted for wall stress; 2) to establish their contributions by comparing temporal changes from moderate to severe AS; and 3) to evaluate the impact of LV contractility and wall stress on overall survival, independent of LVEF.

METHODS

The Mayo Clinic Institutional Review Board approved the study. The transthoracic echocardiography database at Mayo Clinic, Rochester, Minnesota, was queried to identify patients who had a first-time diagnosis of severe AS (aortic valve area [AVA] ≤1 cm^2) between January 1, 2009, and December 31, 2012, and who authorized access of their records for research. The day of initial diagnosis of severe AS was defined as time 0. Only patients with a previous echocardiogram at −3 ± 1 years were included. Patients were excluded if they had severe aortic or mitral regurgitation, had undergone previous valve surgery, dilated cardiomyopathy, LV aneurysm, active endocarditis, or prior radiation therapy. Patients were then divided into 2 groups based on their LVEF at time 0 (LVEF <60% vs. ≥60%).

Electronic health records were reviewed, and demographic, clinical, and laboratory data were abstracted. All patients were followed until death or last contact.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive 2-dimensional (2D) and Doppler echocardiographic study. AVA was calculated by using the continuity equation (14). LVEF was calculated by using the modified Simpson or modified Quinones method (15). LV mass index was calculated by using the Devereux formula and indexed for body surface area (15). The relative wall thickness was calculated as: [(2 × posterior wall thickness)/(LV end-diastolic diameter)] (15). LV remodeling pattern was classified based on current guidelines (15). Valvuloarterial impedance (Zva) was calculated as: [Zva (mm Hg/ml per m^2) = (mean systolic aortic valve Doppler gradient + systolic blood pressure) ÷ stroke volume index] (16).

LV end-diastolic (d)/systolic (s) diameters, interventricular septal wall thickness (IVST), and posterior wall thickness (PWT) were measured in all patients from the transthoracic parasternal long axis view at the midlevel on ProSolv cardiovascular analyzer version 3.0 (ProSolv Cardiovascular, Inc., Indianapolis, Indiana).

MIDWALL FRACTIONAL SHORTENING, WALL STRESS, AND CONTRACTILITY. LV contractility was evaluated using the method proposed by De Simone et al. (10), by plotting mFS against the operating wall stress, under the assumption of constant preload as follows:

$$mFS = \frac{(LVIDd + 0.5PWTd + 0.5IVSTs) - (LVIDs + 0.5Hs)}{(LVIDd + 0.5PWT + 0.5IVSTd)} \quad \text{(Equation 1)}$$

$$Hs = 2 \times \left\{ \left[(LVIDd + 0.5SWTd + 0.5PWTd)^3 - LVIDd^3 + LVIDs^3 \right]^{1/3} - LVIDs \right\} \quad \text{(Equation 2)}$$

End-systolic circumferential wall stress (cESS) (10,17,18) was calculated by using the following equation:

$$cESS = LVPes \times (0.5LVIDs)^2 \times \frac{\left\{\left[1+\frac{(0.5LVIDs+PWTs)^2}{(0.5LVIDs+0.5PWTs)^2}\right]\right\}}{\{(0.5LVIDs+PWTs)^2-(0.5LVIDs)^2\}} \quad \text{(Equation 3)}$$

where LVPes is end-systolic LV pressure estimated from the mean arterial pressure (MAP) using blood pressure (BP) measured by brachial cuff as follows (19):

$$MAP = \frac{systolic\ BP + 2(diastolic\ BP)}{3} \quad \text{(Equation 4)}$$

$$LVPes = MAP + 7 \quad \text{(Equation 5)}$$

The mFS-wall stress relationship of a normal population composed of 140 normotensive adults was used as reference (10). The linear regression equation in this population is: mFS = 20.01 − 0.022 × cESS, with the 95% confidence intervals (CI) of ±4.3% (10). These 95% CI were plotted together with the data. Cases that fell below the lowest 95% CI were defined as having decreased contractility (**Central Illustration**, left).

Contractility was quantified by calculating the percentage of predicted mFS relative to that of the normal population (stress-corrected mFS) at the same wall stress level (10,20), as follows:

$$\text{stress-corrected mFS} = (\text{measured mFS})/(\text{mean mFS normal population}) \quad \text{(Equation 6)}$$

A ratio of 1 indicates contractility similar to that of the normal population (14). A smaller ratio indicates decreased contractility.

Aurigemma et al. (21) reported that mean circumferential end-systolic wall stress as 91 ± 27 kdynes/cm² in a normal population (mean age: 74 ± 6 years [43% male]) (21). Based on this report, wall stress values higher than 145 kdynes/cm² were considered abnormal on the basis of mean +2 SD.

STATISTICAL METHODS. Continuous variables were summarized as a mean ± SD or median (interquartile range [IQR]). Categorical variables were expressed as frequency (percentage). For continuous variables, groups were compared using a 2-sample *t*-test or the Wilcoxon rank sum test when data were non-normal. Binary data were compared using a chi-square test or a Fisher exact test where appropriate. A paired *t* test was used for comparing the change of continuous variables. A 2-tailed p value of <0.05 was considered significant.

The relationship between 2 continuous variables was calculated using a linear regression model, and the correlation coefficient (R) was reported. A polynomial term was applied as needed. Survival was estimated using a Kaplan-Meier curve and the curves were compared using a log-rank test. A Cox proportional hazards model was used. The adjusting variables were selected a priori by biological importance in the multivariate model. Hazard ratios (HRs) and 95% CI were reported. Analyses were performed using JMP version 13.0 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

PATIENTS CHARACTERISTICS. LVEF measurements were available in 3,544 patients with severe AS. Of those, 928 patients with first-time diagnosis of severe AS had at least 1 prior echocardiographic examination and met criteria for inclusion in the study. Of 928 patients, 527 patients had an echocardiographic examination at −3 ± 1 years. Of those, 445 patients with echocardiographic images adequate for additional measurements were included in the final analysis (Supplemental Figure 1).

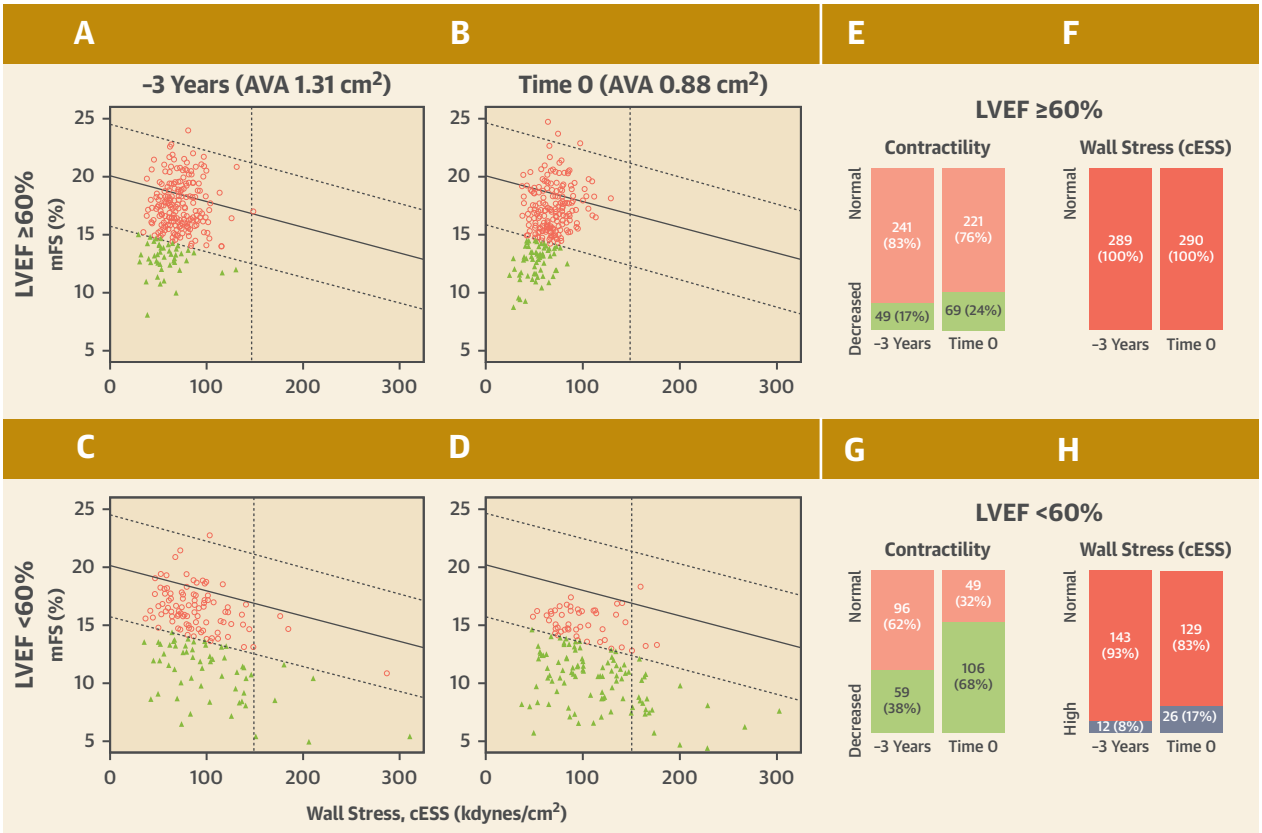
Of those 445 patients, 290 patients (65%) had LVEF ≥60% (LVEF 66% [IQR: 63% to 69%]), and 155 patients (35%) had LVEF <60% (LVEF 47% [IQR: 34% to 55%]) at time 0. AVA was 0.90 cm² (IQR: 0.83 to 0.96 cm²) at time 0 and 1.27 cm² (IQR: 1.13 to 1.43 cm²) at −3 years.

Clinical characteristics at time 0 are summarized in **Table 1**. Patients with LVEF <60% were older, more often male, and frequently had ischemic heart disease ($p < 0.05$). Echocardiographic parameters at time 0 are presented in **Table 2**. Patients with LVEF ≥60% had higher mFS and lower (normal) wall stress than the group with LVEF <60% ($p < 0.001$). Concentric LV remodeling and smaller LV dimension were more common in patients with LVEF ≥60% ($p < 0.001$). Conversely, patients with LVEF <60% more frequently had eccentric LV remodeling and dilated LV ($p < 0.001$).

LV CONTRACTILITY AND WALL STRESS. The mFS was plotted against cESS to identify the patients with abnormal contractility and wall stress (**Central Illustration**, left; summary on the right).

Decreased contractility. Decreased contractility was present, even at 3 years prior to diagnosis of severe AS (−3 years) in both the preserved and reduced LVEF groups, although it was significantly more prevalent in the reduced LVEF group: 49 patients (17%) versus 59 patients (38%), in the LVEF ≥60% versus LVEF <60%, respectively ($p < 0.001$) (**Central Illustration**, panels A, C, E, and G). Decreased contractility was present in a larger number of patients at the time

CENTRAL ILLUSTRATION **LV Contractility and Wall Stress Assessment**



Ito, S. et al. J Am Coll Cardiol Img. 2020;13(2):357-69.

(Left) mFS was plotted against cESS to evaluate LV contractility. The normal range of values for a normal population is shown by **dotted lines** (mean ± 95% confidence intervals). Cases that fell below the lower normal limit were defined as decreased contractility. The upper limit of cESS (145 kdynes/cm^2 **[vertical dotted line]**) also is shown. **(A)** Patients with LVEF ≥60% at −3 years; **(B)** patients with LVEF ≥60% at time 0; **(C)** patients with LVEF <60% at −3 years; and **(D)** patients with LVEF <60% at time 0. **(Right)** Summary of prevalence of decreased LV contractility and cESS are shown at −3 years and at time 0, stratified by LVEF of 60% **(E to H)**. Decreased contractility was already present at −3 years and became more prevalent at time 0 in both groups of patients with LVEF ≥60% and <60% **(A to E and G)**. Overall, wall stress was well controlled in both groups of patients with LVEF of ≥60% and those with <60% at −3 years but deteriorated over time in patients with LVEF <60% **(A to D, F, H)**. AVA = aortic valve area; cESS = circumferential end-systolic wall stress; LVEF = left ventricular ejection fraction; mFS = midwall fractional shortening; LV = left ventricle.

of initial diagnosis of severe AS (time 0), particularly in the reduced LVEF group: 69 patients (24%) vs. 106 patients (68%; p < 0.001) (Central Illustration, panels B, D, E, and G).

LV wall stress. LV wall stress was well controlled in patients with LVEF ≥60%, but high wall stress was present in some patients with LVEF <60% at −3 years: 1 patient (0.3%) vs. 12 patients (8%), LVEF ≥60% vs. LVEF <60%, respectively (p < 0.001) (Central Illustration, panels A, C, F, and H) and at time 0 (n = 0 [0%] vs. n = 26 [17%]; p < 0.001) (Central Illustration, panels B, D, F, and H).

ENDOCARDIAL MEASUREMENTS AND LV CONTRACTILITY. Endocardial measurements (LVEF and endocardial FS) as well as mFS were plotted against wall stress (cESS) at time 0 (Figure 1). These results showed that, even if LVEF or endocardial FS was well preserved, decreased contractility was present in a significant number of cases.

Decreased contractility and/or high wall stress was present in 24% of patients (n = 69) with LVEF ≥60% and 71% of patients (n = 110) with LVEF <60% (p < 0.001). When separate analyses were performed in patients with 50 ≤ LVEF <60% and LVEF <50%,

TABLE 1 Patient Characteristics at Time 0

		LVEF ≥60%			
	Total (N = 445)	Total (n = 290 [65%])	Normal Contractility (n = 221 [76%])	Decreased Contractility (n = 69 [24%])	p Value (Normal vs. Decreased)
Age, yrs	78.6 ± 9.6	77.9 ± 10.1	77.5 ± 9.9	79.1 ± 10.6	0.28
Males	259 (58)	152 (52)	109 (49)	43 (62)	0.06
History					
Hypertension	385 (87)	253 (87)	189 (86)	64 (93)	0.12
Dyslipidemia	380 (85)	246 (85)	189 (86)	57 (83)	0.56
Diabetes mellitus	175 (39)	106 (37)	72 (33)	34 (49)	0.01
Atrial fibrillation/flutter	114 (26)	65 (22)	44 (20)	21 (30)	0.07
Coronary artery disease	204 (46)	138 (48)	105 (48)	33 (48)	0.96
Myocardial infarction	66 (15)	28 (10)	22 (10)	6 (9)	0.76
Coronary artery bypass grafting	77 (17)	33 (11)	24 (11)	9 (13)	0.62
Laboratory					
Hemoglobin, g/dl (n = 435)	12.4 ± 1.9	12.6 ± 1.9	12.7 ± 1.9	12.5 ± 1.8	0.47
Creatinine, mg/dl (n = 433)	1.1 (0.9-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.1 (0.8-1.3)	0.44
NT-proBNP, pg/ml (n = 253)	1,131 (359-3,642)	700 (265-1,966)	534 (244-1,801)	1,115 (643-3,472)	0.01
Heart rate, beats/min	69.5 ± 14.1	67.6 ± 12.9	66.4 ± 11.9	72.2 ± 16.4	<0.01
Systolic blood pressure, mm Hg	127.1 ± 19.3	128.6 ± 18.1	130.9 ± 19.1	126.5 ± 17.2	0.07

TABLE 1 Continued

	LVEF <60%				
	Total (N = 155 [35%])	Normal Contractility (n = 49 [32%])	Decreased Contractility (n = 106 [68%])	p Value (Normal vs. Decreased)	p Value (LVEF ≥60 vs. <60%)
Age, yrs	79.8 ± 8.6	81.2 ± 7.3	79.2 ± 9.1	0.13	0.03
Males	107 (69)	31 (63)	76 (72)	0.29	<0.001
History					
Hypertension	132 (85)	41 (84)	91 (86)	0.72	0.54
Dyslipidemia	134 (86)	42 (86)	92 (87)	0.86	0.64
Diabetes mellitus	69 (45)	19 (39)	50 (47)	0.33	0.10
Atrial fibrillation/flutter	49 (32)	15 (31)	34 (32)	0.86	0.03
Coronary artery disease	103 (66)	31 (63)	72 (68)	0.57	<0.001
Myocardial infarction	38 (25)	10 (20)	28 (26)	0.42	<0.001
Coronary artery bypass grafting	44 (28)	9 (18)	35 (33)	0.06	<0.001
Laboratory					
Hemoglobin, g/dl (n = 435)	12.1 ± 1.9	12.2 ± 1.9	12.0 ± 1.9	0.51	0.01
Creatinine, mg/dl (n = 433)	1.2 (1.0-1.6)	1.1 (1.0-1.4)	1.2 (1.0-1.7)	0.14	<0.001
NT-proBNP, pg/ml (n = 253)	3,509 (823-10,494)	1,519 (285-4,768)	3,871 (1,465-13,760)	<0.01	<0.001
Heart rate, beats/min	73.1 ± 15.3	68.4 ± 12.4	74.5 ± 15.6	0.01	<0.01
Systolic blood pressure, mm Hg	121.1 ± 19.3	128.7 ± 15.7	119.0 ± 20.1	<0.01	<0.01

Values are mean ± SD, n (%), or median (interquartile range, Q1-Q3).
IQR = interquartile range; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

decreased contractility and/or high wall stress was present in 49% of patients (n = 33) with 50 ≤ LVEF <60% and 88% of patients (n = 77) with LVEF <50% (Supplemental Figure 2).

INCREMENTAL PROGNOSTIC VALUE OF CONTRACTILITY AND WALL STRESS TO LVEF. During a median follow-up of 3.4 years (IQR: 1.4 to 4.8 years), there were 216 deaths (49%). LVEF <60%, decreased contractility, and high wall stress were all associated with worse survival ($p < 0.01$ for all) (Figures 2A to 2C). These results were consistent even after adjusting for confounders (Table 3).

The incremental prognostic value of LV contractility and wall stress to LVEF were assessed. Contractility was not associated with survival ($p = 0.11$) (Figure 2D) when LVEF was <60%, whereas decreased contractility was associated with worse survival when LVEF was ≥60% ($p < 0.01$) (Figure 2D).

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TABLE 2 Comparisons of Echocardiographic Parameters at Time 0

		LVEF ≥60%			
	Total (N = 445)	Total (n = 290 [65%])	Normal Contractility (n = 221 [76%])	Decreased Contractility (n = 69 [24%])	p Value (Normal vs. Decreased)
LVEF, %	63 (54-67)	66 (63-69)	66 (63-69)	65 (63-70)	0.78
mFS, %	14.7 ± 3.4	16.1 ± 2.7	17.2 ± 2.0	12.7 ± 1.4	<0.001
Stress-corrected mFS	0.80 ± 0.18	0.87 ± 0.15	0.93 ± 0.11	0.67 ± 0.08	<0.001
End-systolic wall stress (cESS), kdynes/cm^2	79.1 (56.8-88.7)	64.1 (52.8-74.4)	67.2 (57.4-77.5)	52.0 (43.4-60.1)	<0.001
AVA, cm^{2*}	0.90 (0.83-0.96)	0.91 (0.85-0.96)	0.91 (0.85-0.96)	0.90 (0.82-0.96)	0.40
Peak velocity, m/s	4.00 ± 0.62	4.14 ± 0.57	4.12 ± 0.58	4.18 ± 0.53	0.39
Transaortic mean pressure gradient, mm Hg	39.7 ± 12.4	42.3 ± 11.9	41.9 ± 12.1	43.6 ± 11.4	0.28
Cardiac output, l/min	5.69 ± 1.19	5.88 ± 1.17	5.88 ± 1.17	5.91 ± 1.24	0.87
SVI, ml/m^2	44.8 ± 9.5	47.6 ± 8.7	48.5 ± 8.5	44.6 ± 8.9	<0.01
LV mid end-diastolic diameter, mm	47.9 ± 7.5	45.9 ± 6.0	47.7 ± 5.1	40.2 ± 5.1	<0.001
LV mid end-systolic diameter, mm	30.2 ± 8.8	26.0 ± 4.1	26.8 ± 3.7	23.3 ± 4.2	<.001
LV mass index, g/m^2	118.1 ± 31.0	111.3 ± 27.0	110.5 ± 25.9	113.7 ± 30.4	0.45
Relative wall thickness	0.47 ± 0.10	0.48 ± 0.09	0.46 ± 0.08	0.54 ± 0.11	<0.001
E/e′	16.7 (12.9-23.3)	16.0 (12.5-22.0)	16.0 (12.5-20.0)	15.7 (12.5-25.0)	0.52
Right ventricular systolic pressure, mm Hg	39.9 ± 13.8	37.4 ± 12.0	37.1 ± 12.1	38.7 ± 11.4	0.36
Valvuloarterial impedance (Zva), mm Hg/ml/m^2	3.85 ± 0.82	3.72 ± 0.78	3.66 ± 0.74	3.94 ± 0.87	0.02
LV remodeling pattern (n = 423)					<0.001
Normal	56 (13)	37 (13)	33 (15)	4 (6)	0.04
Concentric remodeling	109 (26)	92 (33)	64 (30)	28 (41)	0.09
Concentric hypertrophy	178 (42)	118 (42)	85 (40)	33 (49)	0.21
Eccentric hypertrophy	80 (19)	34 (12)	31 (15)	3 (4)	0.03

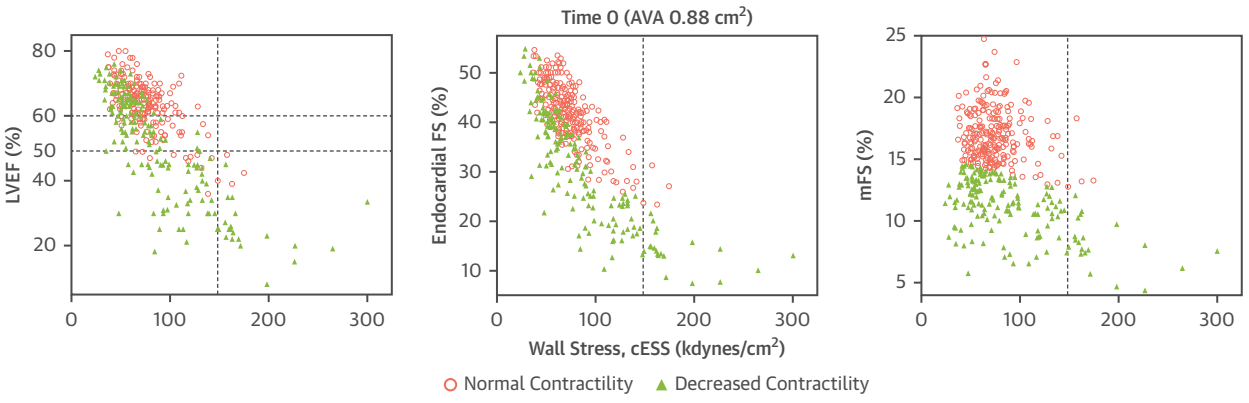
TABLE 2 Continued

	LVEF <60%				
	Total (N = 155 [35%])	Normal Contractility (n = 49 [32%])	Decreased Contractility (n = 106 [68%])	p Value (Normal vs. Decreased)	p Value (LVEF ≥60 vs. <60%)
LVEF, %	47 (34-55)	54 (48-58)	44 (30-52)	<0.001	-
mFS, %	11.9 ± 3.0	15.2 ± 1.3	10.4 ± 2.3	<0.001	<0.001
Stress-corrected mFS	0.67 ± 0.16	0.85 ± 0.07	0.59 ± 0.11	<0.001	<0.001
End-systolic wall stress (cESS), kdynes/cm^2	94.8 (75.0-132.6)	91.5 (72.5-117.6)	98.3 (78.2-137.5)	0.16	<0.001
AVA, cm^{2*}	0.88 (0.80-0.96)	0.92 (0.83-0.98)	0.87 (0.78-0.95)	0.04	0.04
Peak velocity, m/s	3.75 ± 0.63	3.83 ± 0.61	3.71 ± 0.64	0.26	<0.001
Transaortic mean pressure gradient, mm Hg	34.9 ± 11.8	36.9 ± 10.8	34.0 ± 12.2	0.14	<0.001
Cardiac output, l/min	5.32 ± 1.14	5.48 ± 1.10	5.25 ± 1.15	0.25	<0.001
SVI, ml/m^2	39.5 ± 8.7	43.2 ± 7.9	37.8 ± 8.6	<0.001	<0.001
LV mid end-diastolic diameter, mm	51.7 ± 8.5	51.8 ± 5.6	51.7 ± 9.5	0.92	<0.001
LV mid end-systolic diameter, mm	38.2 ± 9.7	34.7 ± 5.4	39.8 ± 10.8	<0.001	<0.001
LV mass index, g/m^2	131.5 ± 33.9	121.2 ± 26.8	136.3 ± 35.8	<0.01	<0.001
Relative wall thickness	0.44 ± 0.10	0.42 ± 0.07	0.45 ± 0.12	0.07	<0.001
E/e′	18.3 (14.0-25.0)	15.0 (11.0-19.4)	16.6 (12.1-22.5)	0.20	<0.01
Right ventricular systolic pressure, mm Hg	44.5 ± 15.6	42.7 ± 15.8	45.4 ± 15.5	0.37	<0.001
Valvuloarterial impedance (Zva), mm Hg/ml/m^2	4.09 ± 0.85	3.90 ± 0.64	4.18 ± 0.92	0.03	<0.001
LV remodeling pattern (n = 423)				0.51	<0.001
Normal	19 (13)	9 (20)	10 (10)	0.11	0.11
Concentric remodeling	17 (12)	5 (11)	12 (12)	0.83	<0.001
Concentric hypertrophy	60 (42)	18 (40)	42 (43)	0.71	0.82
Eccentric hypertrophy	46 (33)	13 (29)	33 (34)	0.54	<0.001

Values are median (interquartile range, Q1-Q3, mean ± SD, or n (%).

AVA = aortic valve area; cESS = end-systolic circumferential wall stress; e′ = mitral annular early diastolic tissue velocity; E/e′ = mitral inflow early diastolic velocity-to-medial mitral annular early diastolic velocity ratio; IQR = interquartile range; LV = left ventricle; mFS = midwall fractional shortening; SVI = stroke volume index.

FIGURE 1 **Endocardial Based Measurements and LV Contractility**



Endocardial measurements (LVEF and endocardial FS) as well as mFS were plotted against cESS. **Pink circles** represent patients with normal contractility. **Green triangles** represent patients with decreased contractility. LVEF of 50% and 60% are represented by the **dotted horizontal lines**. The upper normal limit of wall stress (145 kdynes/cm^2) is shown by the **vertical dotted line**. AVA = aortic valve area; cESS = circumferential end-systolic wall stress; FS = fractional shortening; LV = left ventricle; LVEF = left ventricular ejection fraction; mFS = midwall fractional shortening.

LV wall stress was not associated with survival in either the LVEF ≥60% or the <60% group. No significant interaction has been found between LVEF (LVEF <60%; ≥60%) and LV contractility (normal; decreased) (p = 0.56).

NORMAL VERSUS DECREASED LV CONTRACTILITY. Because LV contractility had incremental prognostic value for LVEF, clinical data were compared amongst groups stratified by LVEF and contractility.

LVEF ≥60% with decreased contractility. Patients with LVEF ≥60% with decreased contractility had a higher prevalence of diabetes mellitus (p = 0.01) and higher N-terminal pro-B-type natriuretic peptide concentrations (NT-proBNP) (p < 0.01) than patients with normal contractility (**Table 1**). Compared to patients with normal contractility, patients with decreased contractility had equivalent LVEF, but they had lower mFS and wall stress (p < 0.001 for all), excessive LV concentric remodeling with larger relative wall thickness (RWT) (p < 0.001), smaller LV dimensions (p < 0.001), and reduced stroke volume index (SVI) (p < 0.01); and higher Zva levels (p = 0.02) were observed (**Table 2**).

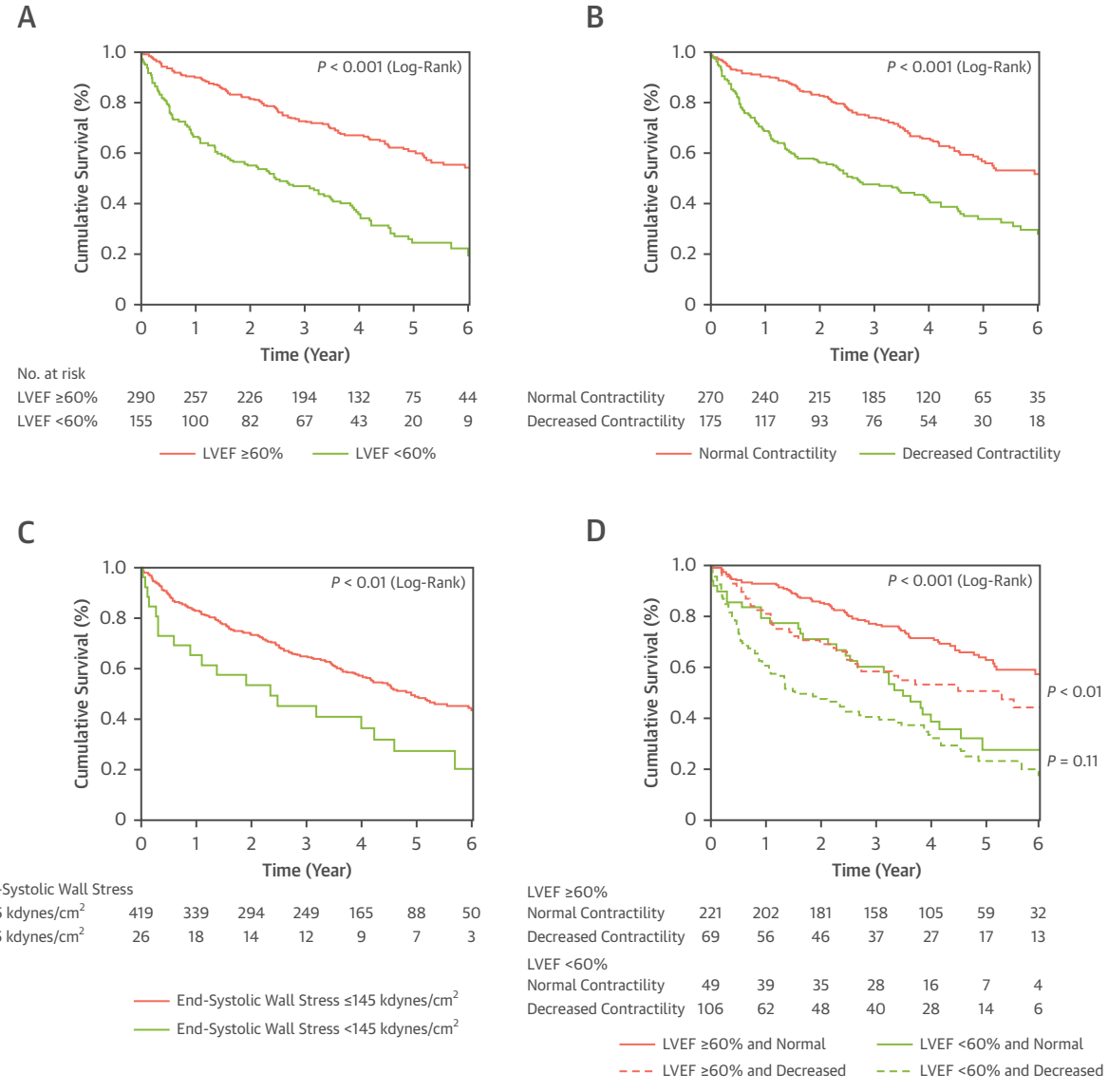
LVEF <60% with decreased contractility. Patients with LVEF <60% with decreased contractility had higher NT-proBNP level (p < 0.01) than patients with normal contractility (**Table 1**). They also had lower levels of LVEF, mFS, and SVI (p < 0.001) and increased wall stress (p = 0.04).

PATIENTS WITH AND WITHOUT LV WALL MOTION ABNORMALITIES AND NORMAL AND DECREASED LV CONTRACTILITY. At time 0, 46% of patients had coronary artery disease. Patients with LV aneurysms were excluded from this study, but 104 patients (24%) had wall motion abnormalities. Thus, separate analyses were performed in patients with and without wall motion abnormalities. In patients with LVEF ≥60%, 14 patients (13%) of 289 had LV asynergy. In patients with LVEF <60%, 90 patients (87%) of 153 had it. Regardless of whether wall motion abnormalities were present or not, reduced LV contractility was well associated with prognosis (p < 0.001 for patients without asynergy; p = 0.03 for patients with asynergy). The results are shown in Supplemental Figure 3, where mFS is plotted against cESS (Supplemental Figure 3, upper panel). Kaplan-Meier survival curves based on contractility are shown in Supplemental Figure 3, lower panel.

LONGITUDINAL CHANGES FROM MODERATE TO SEVERE AS. Longitudinal changes of echocardiographic parameters over 3 years are shown in **Figure 3**.

LVEF ≥60%. In patients with LVEF ≥60%, LVEF did not change over time, and wall stress remained well controlled. In patients with decreased contractility, stress-corrected mFS significantly decreased over time (p < 0.001), whereas LVEF remained preserved; LV end-diastolic diameter and wall stress declined over time (p < 0.001). Conversely, in patients with normal contractility, stress-corrected mFS remained

FIGURE 2 Kaplan-Meier Survival Curves According to Each Variable



(A) All-cause mortality in patients with LVEF ≥60% is compared with that in patients with LVEF <60%. **(B)** Comparison between patients with normal contractility and those with decreased contractility. **(C)** Comparison between patients with normal wall stress and those with increased wall stress. **(D)** Comparison of patients with LVEF ≥60% and normal contractility, patients with LVEF ≥60% and decreased contractility, patients with LVEF <60% and normal contractility and, patients with LVEF <60% and decreased contractility. Abbreviation as in Figure 1.

normal (p = 0.21), whereas wall stress decreased over time (p < 0.001).

LVEF <60%. In patients with LVEF <60% and either normal or decreased contractility, LVEF, stress-corrected mFS, and wall stress had deteriorated over time. In patients with normal contractility, LV end-diastolic diameter increased over time (p < 0.001). For patients with decreased contractility, LV cavity was already dilated at −3 years. Other echocardiographic parameters at −3 years are shown in Supplemental Table 1.

CORRELATIONS BETWEEN LVEF AND CONTRACTILITY, AND WALL STRESS. Overall, there was a quadratic relationship between LVEF and contractility (stress-corrected mFS) (R = 0.68; p < 0.001) (Figure 4A). However, this relationship was different depending

TABLE 3 Multivariate COX Proportional Hazard Model for Predicting Outcomes

	HR (95% CI)	p Value
Model 1 LVEF		
LVEF <60 vs ≥60%	2.30 (1.72-3.07)	<0.001
Age	1.05 (1.03-1.07)	<0.001
Male	0.79 (0.59-1.06)	0.12
Diabetes mellitus	1.46 (1.11-1.93)	<0.01
Myocardial infarction	1.50 (1.04-2.10)	0.02
Creatinine, mg/dl	1.36 (1.21-1.52)	<0.001
AVA, cm^2	0.21 (0.05-0.82)	0.02
Model 2 LV contractility		
Decreased vs. normal contractility	1.87 (1.41-2.48)	<0.001
Age	1.05 (1.04-1.07)	<0.001
Male	0.86 (0.64-1.15)	0.31
Diabetes mellitus	1.41 (1.06-1.86)	0.02
Myocardial infarction	1.73 (1.21-2.42)	<0.01
Creatinine, mg/dl	1.35 (1.21-1.51)	<0.001
AVA, cm^2	0.23 (0.06-0.88)	0.03
Model 3 wall stress (cESS)		
cESS ≥145 vs. <145 kdynes/cm^2	2.10 (1.26-3.29)	<0.01
Age	1.06 (1.04-1.07)	<0.001
Male sex	0.91 (0.69-1.22)	0.55
Diabetes mellitus	1.56 (1.18-2.05)	<0.01
Myocardial infarction	1.75 (1.23-2.45)	<0.01
Creatinine, mg/dl	1.36 (1.21-1.51)	<0.001
AVA, cm^2	0.14 (0.04-0.56)	<0.01

Abbreviations as in Tables 1 and 2.

on the LVEF, that is, for LVEF <60%, there was a direct linear correlation; for LVEF ≥60%, the correlation was lost. LVEF and wall stress were inversely related ($R = 0.75$; $p < 0.001$) (Figure 4).

DISCUSSION

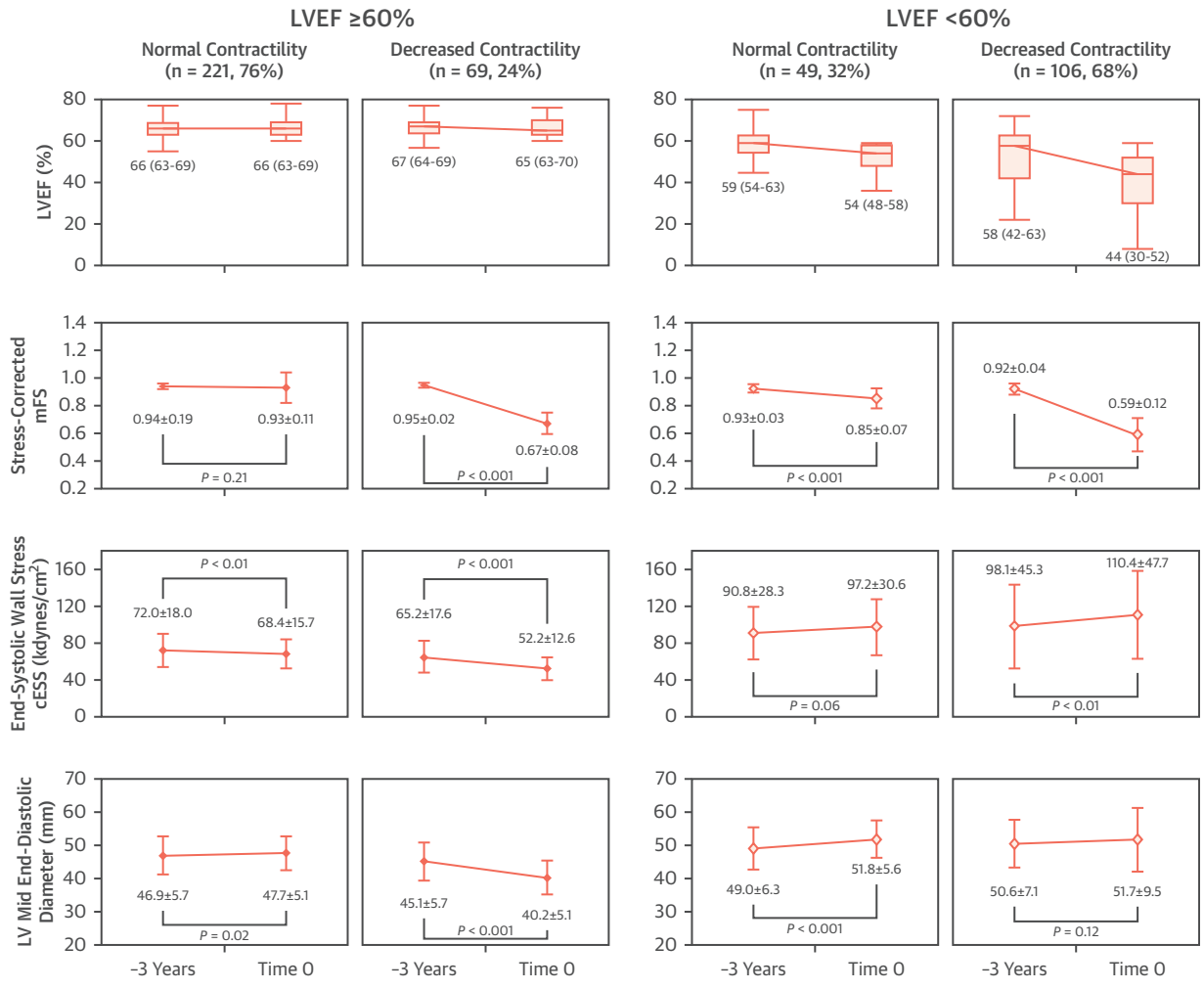
The present study assessed LV contractility and wall stress in patients with AS stratified by LVEF, and their relationship to survival was evaluated. The 2 main findings were as follows. 1) When LVEF was reduced (<60%), decreased LV contractility and/or high wall stress were present in the majority of patients, even before AS became severe; the survival outcome was poor being linked with these abnormalities. 2) When LVEF was preserved (≥60%), wall stress was well preserved. However, LV contractility was decreased in a subset of patients with excessive concentric LV remodeling, and this was associated with poor prognosis.

LVEF, LV CONTRACTILITY AND LV WALL STRESS IN AS. Contractility is the inherent capacity of myocardium to contract independent of changes in heart rate, preload, and afterload (22,23). Because it is difficult to control these factors in the human heart in situ, analyzing mFS while taking into account the level of wall stress has been proposed as a method to evaluate LV contractility (7,10,21). Using this method, Carabello et al. (7) showed, in a small study of 14 patients with severe AS and reduced LVEF (28.0 ± 3.0%), that either excessive wall stress or decreased contractility could explain the decreased LVEF. Ballo et al. (24) investigated LV contractility in patients with AS and preserved LVEF (≥55%) and showed that contractility decreased as the severity of AS progressed (24). Aurigemma et al. (21) showed that sex differences in LV contractility exist in patients with AS, with women having more frequently decreased contractility with higher LVEF, smaller LV cavities, and larger RWT than men. Despite these important findings, the significance of assessing LV contractility or wall stress in our routine clinical practice remained unclear.

Our results showed that 17% of patients with LVEF <60% had high wall stress and that 68% of patients had decreased LV contractility at the time of diagnosis of severe AS (**Central Illustration**). These results confirmed previous reports from smaller studies showing that decreased LVEF in patients with AS is caused by decreased LV contractility or excessive wall stress or a combination of both (7). In the present study, eccentric remodeling and larger LV dimensions were more common in patients with LVEF <60%. Even though most patients had wall stress within normal limits when LVEF was <60%, the wall stress was much higher than in patients with LVEF ≥60%. This finding is consistent with LaPlace's law, which predicts a greater stress for larger chambers. Moreover, the decreased contractility was already present even before AVA became <1.0 cm^2 and deteriorated further as time progressed, with worsening of AS severity. This group may require earlier intervention, even before AVA reaches 1.0 cm^2. However, the survival benefit of an earlier AVR in this group needs to be tested by a randomized clinical trial.

Concentric remodeling and smaller LV sizes were observed in patients with LVEF ≥60%, maintaining wall stress within normal limits (**Central Illustration**). These findings indicate that LV concentric remodeling successfully balances the increased pressure load in these patients. However, in this group, LV contractility was decreased in a minority of patients, at both moderate and severe AS stages (17% and 24%, respectively), despite preserved LVEF. It might seem paradoxical that some patients with LVEF ≥60% would have decreased contractility as this property of decreased contractility lowers, not increases LVEF. However, both LVEF and mFS are also

FIGURE 3 Longitudinal Changes in Echocardiographic Parameters

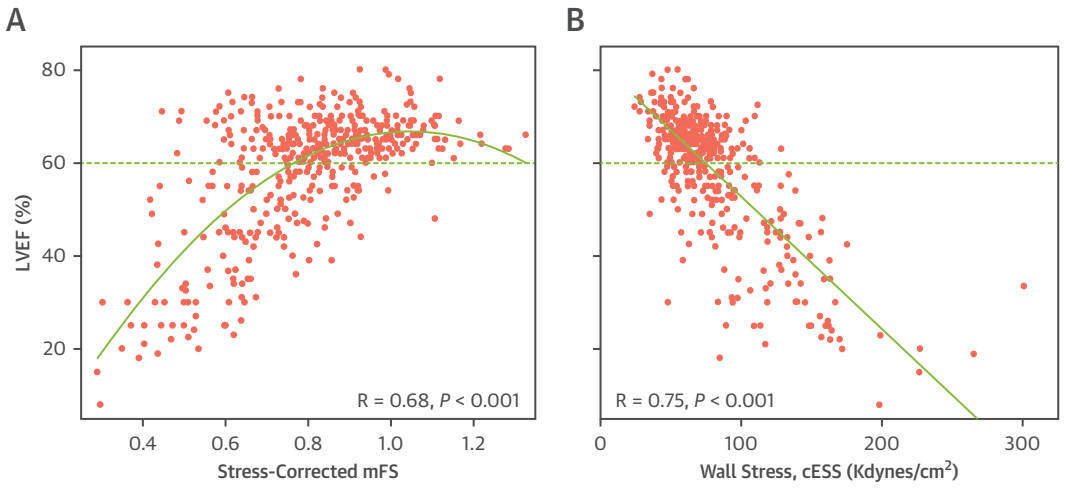


Longitudinal changes in echo parameters are shown over 3 years, stratified by LVEF and contractility groups. A **box plot** was applied for LVEF because of non-normality and mean ± SD was applied in other variables. **(Left)** Patients with LVEF ≥60%. **(Right)** Patients with LVEF <60%. Each **panel** shows the values at −3 years and time at 0. LV = left ventricle; other abbreviations as in Figure 2.

dependent upon preload, and afterload mismatch is compensated by preload reserve (25). The patients with LVEF ≥60% and decreased contractility had NT-proBNP concentrations more than twice those of patients with normal contractility. Although BNP is thought to be an indicator of sarcomere stretch, it is likely that preload excess, together with more ample hypertrophy, maintained high LVEF despite either afterload excess or decreased contractility. This is probably true even though this group had small LV end-diastolic volumes. While acute changes in end-diastolic volume can reflect changes in preload, chronic differences are primarily dependent on sarcomere number, not preload.

Either decreased contractility or high wall stress was present in approximately one-fourth of patients with LVEF ≥60% and in 70% of patients with LVEF <60%. The abnormality was present in one-half of patients with LVEF of 50% to 60% and in almost 90% of patients with LVEF <50%. Presence of LVEF <50% is currently a Class I indication for AVR in asymptomatic patients with severe AS (4). However, even patients with severe AS and LVEF between 50% and 60% were shown to have worse survival than

FIGURE 4 Correlation of LVEF With Contractility (Stress-Corrected mFS) and Wall Stress (cESS)



(A) The correlation between LVEF and stress-corrected mFS is shown. The p value for the polynomial term (quadratic) is reported. **(B)** The correlation between LVEF and cESS is shown. Abbreviations as in Figure 1.

those with LVEF ≥60% (3,5,6). Current findings may provide a pathophysiologic explanation for these previous findings. Although decreased contractility is present in a minority of patients with LVEF ≥60%, the present authors propose that LVEF of 60% may be a more appropriate cutoff value for preventing the development of maladaptive responses in patients with AS, as myocardial characteristics have been shown to be as important as valvular hemodynamics in patients with AS (26).

SURVIVAL OUTCOMES. LVEF, LV contractility, and wall stress were associated with overall survival in patients with AS. The incremental prognostic value of LV contractility in patients with LVEF ≥60% was demonstrated in this study, as these patients with decreased contractility had poorer prognoses (**Figure 2D**). This conclusion is supported by the lack of correlation between LVEF and contractility when LVEF ≥60% (**Figure 4**).

Careful attention should be paid when assessing LV systolic function, especially when LVEF is preserved. Cardiac magnetic resonance imaging or LV strain imaging may be able to detect this group with an increased risk because decreased contractility is most likely related to coronary or microvascular abnormalities or diffuse myocardial fibrosis (27–29). Studies have shown that longitudinal strain is reduced in patients with AS (30,31). However, strain is the result of the complex interactions among intrinsic contractile forces and extrinsic loading conditions. Future studies are warranted for assessing the correlation between strain and mFS, taking into account the level of wall stress. Furthermore, these patients have notable characteristics such as higher Zva and pronounced concentric LV remodeling with large RWT (**Table 2**) that may help identify them. They have smaller LV cavity sizes, lower SVI, and higher NT-proBNP levels. These characteristics are similar to those in patients with paradoxically low-flow, low-gradient AS (32–34), and the present authors believe that these findings may be able to provide additional insights into understanding the possible mechanism of its development.

STUDY LIMITATIONS. This is a large, retrospective, single-center study; however, only 9% of the target sample was included in the analysis. Patients were included in this study if they had at least 1 echocardiogram before time 0, and they probably had some "reasons" for requiring earlier echocardiography before developing severe AS. This can be a selection bias. The authors defined severe AS as AVA ≤1.0 cm^2; therefore, pseudo-severe AS patients were potentially included. Dobutamine stress echocardiography was available only in a limited number of patients. In the present study, mFS and cESS were used for estimation of LV contractility, which is theoretically independent from afterload; however, it depends on preload. Preload was not controlled in this study. Both mFS and cESS were calculated using a

cylindrical model, which may not apply to severely dilated LVs. However, for consistency, the same method was used in all patients to avoid errors introduced by using different formulae; in addition, patients with LV aneurysms were excluded.

CONCLUSIONS

In patients with severe AS, LVEF <60% is associated with a poor prognosis, being linked with decreased contractility and high wall stress. Decreased contractility is also present in a subset of patients with LVEF ≥60% and has an incremental prognostic value. Decreased contractility and high wall stress already existed exist before AVA reaches 1.0 cm^2.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The main pathophysiology characteristics of decreased LVEF (<60%) in AS are decreased LV contractility and/or high wall stress. An LVEF cutoff value of 60% could improve risk stratification in severe AS. Particularly when LVEF is ≥60%, the assessment of LV contractility could improve risk stratification. These abnormalities are present even before AS becomes severe.

TRANSLATIONAL OUTLOOK: The study findings indicate a need for a clinical trial to examine whether aortic valve replacement based on the LVEF <60%, reduced LV contractility, excessive concentric hypertrophy, or high myocardial fibrosis is beneficial in symptomatic or asymptomatic patients with less severity than currently defined severe aortic stenosis.

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KEY WORDS afterload, AS, contractility, LVEF, wall stress

APPENDIX For a supplemental table and figures, please see the online version of this paper.