ORIGINAL ARTICLE

CME

Left Ventricular Systolic Longitudinal Function, Afterload and Contractility in Severe Aortic Stenosis

La función sistólica longitudinal del ventrículo izquierdo, la poscarga y la contractilidad en la estenosis aórtica grave

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ABSTRACT

Background: In patients with severe aortic stenosis (AS), left ventricular systolic longitudinal function (SLF) is impaired despite preserved ejection fraction (EF). However, similarly to other shortening indexes, SLF depends on afterload and its relationship with contractility has not been thoroughly studied.
Objective: The aim of this study was to evaluate SLF alterations and their relationship with afterload and myocardial contractility in patients with severe AS.
Methods: One hundred and one patients with severe AS (AVA <1 cm2) and 63 normal control subjects were studied with Doppler echocardiography. Left ventricular systolic longitudinal function was evaluated by lateral mitral annulus systolic displacement (MASD) and peak S wave velocity (tissue Doppler imaging). Contractility was assessed by the midwall fractional shortening (mFS)–end-systolic stress (ESS) relationship in control subjects. Contractility level (CL) was defined as measured mFS minus predicted mFS for a defined ESS value.
Results: Lateral mitral annulus systolic displacement and S wave correlated directly with shortening indexes as EF and mFS and inversely with afterload indexes as ESS. There was no correlation between SLF and CL. In the multivariate analysis ESS and EF were predictors of SLF.
Conclusions: In patients with severe AS, SLF correlated inversely with afterload. The presence of decreased MASD or S wave was not associated with abnormal left ventricular contractility.

Key words: Aortic Valve Stenosis - Ventricular Function, Left - Echocardiography, Doppler

RESUMEN

Introducción: En pacientes con estenosis aórtica (EAo) grave, la función sistólica longitudinal (FSL) del ventrículo izquierdo puede estar disminuida a pesar de presentar fracción de eyección (FEy) preservada. Sin embargo, la FSL, como todo índice de acortamiento, es dependiente de la poscarga y su relación con la contractilidad no se ha estudiado suficientemente.
Objetivo: Evaluar en pacientes con EAo grave las alteraciones de la FSL y su relación con la poscarga y la contractilidad miocárdica.
Material y métodos: Se estudiaron 101 pacientes con EAo grave (AVA < 1 cm2) y 63 individuos normales con Doppler cardíaco. La FSL se evaluó por medio de la excursión sistólica del anillo mitral lateral (ESAM) y la velocidad pico de la onda S (Doppler tisular). La contractilidad se evaluó mediante la relación entre la fracción de acortamiento mesoparietal (FAm) – estrés de fin de sístole (EFS) en los individuos normales. El nivel de contractilidad (NC) se definió como la FAm medida menos la FAm predicha para un valor determinado de EFS.
Resultados: La ESAM y la onda S se correlacionaron directamente con índices de acortamiento como la FEy y la FAm e inversamente con índices de poscarga como el EFS. No hubo correlación entre la FSL y el NC. En el análisis multivariado, el EFS y la FEy fueron predictores de la FSL.
Conclusiones: En pacientes con EAo grave, la FSL se relacionó inversamente con la poscarga. La presencia de disminución de la ESAM o de la onda S no se asoció con anormalidades de la contractilidad del ventrículo izquierdo.

Palabras clave: Estenosis de la válvula aórtica - Función ventricular izquierda -Ecocardiografía Doppler

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Abbreviations

AS	Aortic stenosis	**LV**	Left ventricular
AVA	Aortic valve area	**MASD**	Mitral annulus systolic displacement
C	Control	**mFS**	Midwall fractional shortening
CL	Contractility level	**MG**	Mean gradient
EDV	End-diastolic volume	**MI**	Mass index
EF	Ejection fraction	**PG**	Peak gradient
eFS	Endocardial fractional shortening	**RWT**	Relative wall thickness
ESP	End-systolic pressure	**SE**	Standard error
ESS	End-systolic stress	**SLF**	Systolic longitudinal function
ESV	End-systolic volume	**SV**	Stroke volume

INTRODUCTION

In severe asymptomatic aortic stenosis (AS), the presence of decreased ejection fraction (EF) (<50%) is an indication for surgical treatment due to increased morbidity and mortality in these patients. (1-3) Decreased EF may be due to increased afterload with preserved myocardial contractility (afterload mismatch) (4) or to depressed contractility secondary to fibrosis for hypertrophy or associated coronary artery disease. (5, 6) It has been reported that left ventricular (LV) systolic longitudinal function (SLF) may be decreased in patients with severe AS and preserved EF, suggesting that SLF deterioration precedes the decrease in EF. (7, 8) Using various techniques such as mitral annulus systolic displacement (MASD), S wave tissue Doppler and myocardial strain, this finding has been interpreted as incipient contractility impairment in the presence of preserved EF. (9-12) However, all these parameters are related to shortening of longitudinal fibers, which depend on contractile level (CL), but also on geometry, (13) preload and specially afterload. (14-16) The influence that increased afterload or decreased contractility might have on SLF in patients with severe AS is not fully studied. The aim of this study was to analyze LV SLF and its relationship with afterload and contractility in severe AS.

METHODS

A total of 101 patients with mean age of 70±11 years, 61 men and 40 women, with severe AS by Doppler echocardiography were prospectively included in the study. Severe AS was defined as aortic valve area (AVA) <1 cm^2. Patients who had mitral annulus calcification with moderate or severe aortic or mitral regurgitation were excluded. History of ischemic heart disease was based on whether the patient had one or more of the following criteria: 1) history of acute myocardial infarction, percutaneous coronary intervention or bypass surgery, 2) coronary artery obstruction >50% determined by angiography and 3) akinesia on echocardiography. Coronary angiography data were obtained in 39 patients and 14 patients presented coronary artery disease.

The control (C) group included 63 patients with mean age 69±13 years with no history of heart disease, cardiovascular risk factors and systemic diseases. All patients underwent a complete Doppler echocardiography, preceded by a questionnaire to detect the presence of coronary risk factors and symptoms, cardiovascular physical examination, blood pressure measurement and carotid pulse recording.

Echocardiography and cardiac Doppler

The study was performed using a Toshiba SSH140A echocardiograph with 2.5 MHz transducer, with the patient in left lateral decubitus position, using as reference the electrocardiographic DII lead. Two-dimensional M-mode echocardiographic measurements, LV endocardial fractional shortening (eFS) estimation, relative wall thickening (RWT), end-diastolic volume (EDV) (area-length method), end-systolic volume (ESV), EF and stroke volume index (SV) were performed according to the criteria of the ASE (American Society of Echocardiography). (17) Left ventricular midwall fractional shortening (mFS) was calculated with the Koide formula. (18) Left ventricular mass was estimated according to the Devereux formula (19) and mass index (MI) as the normalized mass to body surface area. According to MI and RWT, ventricular geometry was classified as normal, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. (20) Four-chamber view of M-mode mitral annulus motion was used to measure MASD (21). Peak aortic transvalvular gradient (PG), mean gradient (MG) and the integral of the flow curve were recorded with continuous-wave Doppler in apical, right parasternal, subxiphoid and suprasternal views. Using the 5 MHz transducer, mitral annulus pulsed tissue Doppler was recorded, measuring peak wave velocity. The average of three consecutive measurements was considered for each parameter.

Calibrated carotidogram

The carotidogram was recorded after echocardiography using a TPW-01A pulse transducer, and blood pressure was measured in the right arm with a sphygmomanometer with the patient in left lateral decubitus position. The carotidogram was calibrated according to the method used in our laboratory (22) to obtain end-systolic pressure (ESP). End systolic stress (ESS) was estimated as afterload meridional index using Grossman's formula. (23)

Assessment of left ventricular systolic longitudinal function

Left ventricular systolic longitudinal function was evaluated by MASD and peak S wave velocity (tissue Doppler imaging).

Assessment of left ventricular contractility

Contractility was assessed by the mFS–ESS relationship in the control group with the following regression equation: mFS = 28.15 - 0.12 × ESS, with a standard error of the estimate (SEE) of 3.75% (r=0.41; p <0.001). For a given level of ESS (afterload), a value below the mFS predicted by the regression equation minus 2 times the SEE was considered reduced contractility in patients with AS. The CL is defined as measured minus predicted mFS for a given ESS

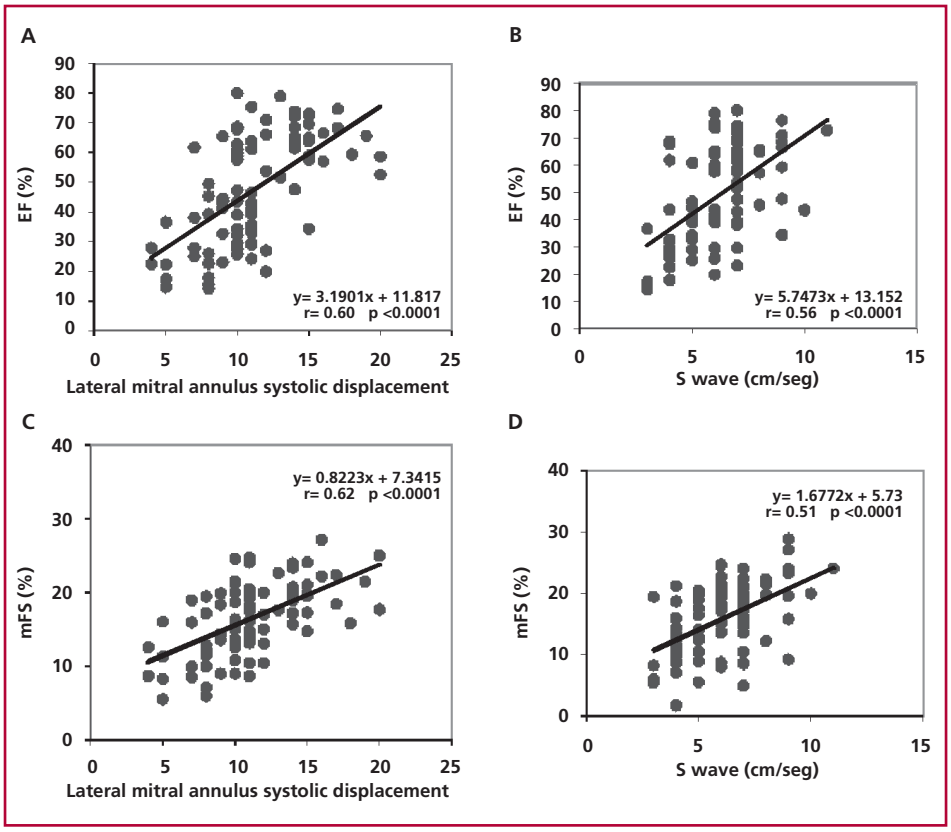

Fig. 1. Correlation between ejection fraction (EF) and lateral mitral annulus systolic displacement (A), EF and S wave (B), midwall fractional shortening (mFS) and lateral mitral annulus systolic displacement (mm) (C), and mFS and S wave (D).

value, so that a positive value indicates normal contractility and a negative value, decreased contractility. Subsequently, to evaluate the relationship between CL and the EF cutoff point to indicate intervention (<50%), patients were divided into two groups: EF ≥50% (n=54) and EF <50% (n=47).

Aortic stenosis evaluation

The effective AVA was calculated using the continuity equation. (24)

Statistical analysis

Continuous variables were expressed as mean±standard deviation, upon proof of normality with a goodness of fit test. Groups were compared using the analysis of variance and Pearson´s coefficient r to analyze correlation. A p value <0.05 was considered statistically significant. A stepwise approach was used for the multivariate analysis. Non-metric variables were expressed as percentages and compared with the chi square test.

Ethical considerations

The protocol was evaluated and approbed by the Institutional Review Board.

RESULTS

In patients with severe AS, effective AVA was 0.66 cm2±0.12 cm^2, PG 71±31 mmHg and MG 42±19 mmHg. Patients with AS showed a decrease in EF, eFS and mFS (Table 1) compared with the C group. Average ESP and ESS were similar in both groups, although in the latter the coefficient of variation (standard deviation/average × 100) was higher in patients with AS than in the C group (57% vs. 10%; p <0.01), indicating greater dispersion of values in the group. In patients with AS, there was reduced MASD as in the S wave tissue Doppler (see Table 1), and MASD and the S wave correlated directly with shortening indexes as EF (see Figure 1) and inversely with afterload indexes as ESS (Figure 2). As expected, mFS also correlated inversely with the ESS (r= -0.65 p <0.00001). In the multivariate analysis, ESS and EF were predictors of SLF, but not CL.

The analysis of CL by means of the shortening - afterload relationship (mFS - ESS) showed that only a third of patients with AS (32/101) had decreased contractility compared to the C group (Figure 3). Although mFS was lower in patients with decreased CL (32/101) compared to patients with normal CL (69/101) (12%±4% vs. 18%±5%; p <0.01), a cut-off value between the two groups was not possible without being accompanied by the corresponding ESS due to the overlap of values obtained with the mean±2 standard deviations. There was no correlation between CL and SLF indexes, suggesting that the main determinant of SLF decrease is increased afterload.

Comparison between patients with ejection fraction <50% and ≥50% (Table 2)

Patients with EF <50% had a higher incidence of coronary artery disease, dyspnea III-IV and, less frequently, syncope and absence of symptoms. In this

group, EF and SV index were significantly lower and EDV and ESV were higher compared with patients with EF ≥50%. Regarding ventricular geometry, patients with reduced EF had a higher frequency of eccentric hypertrophy and MI and lower RWT than patients with preserved EF. Afterload (ESS) was significantly increased in patients with EF <50% in agreement with decreased mFS, keeping an inverse mFS - ESS relationship (mFS=19 - 0.09 × ESS, r=-0.51; p <0.001). Patients with EF ≥50% had lower ESS and higher mFS, also with an inverse correlation between the two parameters (mFS=23 - 0.23 × ESS, r=-0.41 p <0.001), similarly to the overall AS group (see Figure 2C). In patients with EF <50%, CL was lower and the percentage of patients with decreased contractility higher, indicating the presence of mismatch in 53.2% of patients in this group. Mitral annulus systolic displacement and S wave tissue Doppler were significantly decreased in patients with EF <50%, similarly to other indexes depending on fiber shortening (EF and mFS), evidencing inverse correlation with ESS. However, patients with EF ≥50% had decreased MASD, S wave and mFS with respect to the C group despite having lower ESS.

Table 1. Systolic and afterload echocardiographic parameters

	Control (n=63)	AS (n=101)	p
EF, %	65 ± 5	48 ± 18	<0.01
eFS, %	38 ± 9	31 ± 11	<0.01
mFS, %	22 ± 4	16 ± 6	<0.01
ESS, g/cm^2	52 ± 12	53 ± 29	ns
ESP, mm Hg	95 ± 10	93 ± 20	ns
MASD, mm	18 ± 2	11 ± 3	<0.01
S wave, cm/sec.	12 ± 1.6	6 ± 1.7	<0.01

EF: Ejection fraction. eFS: Endocardial fractional shortening. mFS: Midwall fractional shortening. ESS: End-systolic stress. ESP: End-systolic pressure. MASD: Mitral annulus systolic displacement.

Relationship between coronary artery disease and ejection fraction <50% (Table 3)

Coronary artery disease in this group was evident in 23% of patients (11/47). Ejection fraction, presence of heart failure (dyspnea III-IV), MASD and S wave tissue Doppler were similar in both groups with and without coronary artery disease. The CL was higher in patients with coronary artery disease, although the difference between the two groups was not significant (2.3±3.2 vs.4.8±0.25; p=0.06), suggesting higher proportion of mismatch in patients with coronary artery disease. Due to the low proportion of coronary artery disease in patients with EF ≥50% (3/54), no comparison was made between the two groups. It should be kept in mind that in the group with EF ≥50%, 50% of patients (28/54) were asymptomatic and had no indication for coronary angiography.

DISCUSSION

The main finding of this work is that the decrease

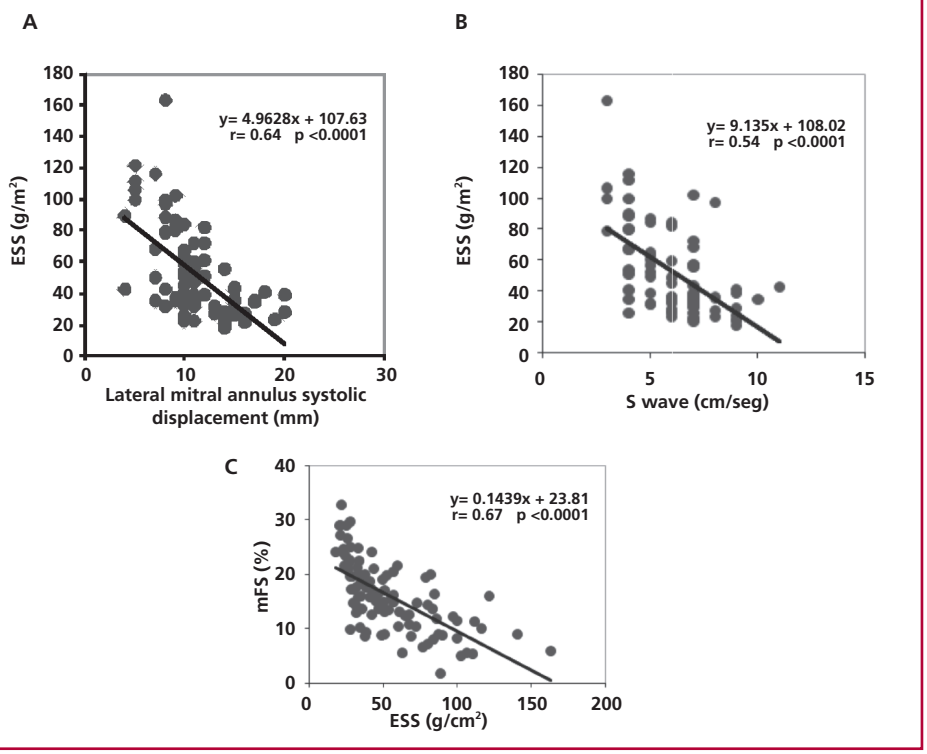

Fig. 2. Correlation between end systolic stress (ESS) and lateral mitral annulus systolic displacement (A), ESS and S wave (B) andmidwall fractional shortening (mFS) and ESS (C).

in left ventricular SLF in severe AS correlates with increased afterload and that only a third of patients presented with reduced contractility. Various publications have reported that SLF may be decreased in the presence of preserved EF, an alteration that would precede the decrease in EF. (25-27) It is generally assumed that this finding would imply a reduction of "myocardial function," which could be interpreted as loss of contractility. (28-30) In ventricular hypertrophy accompanying AS, subendocardial fiber ischemia may result in decreased longitudinal shortening. But it must be kept in mind that in these patients overall LV afterload expressed through valvuloarterial impedance is also increased, (31) implying a higher LV systolic pressure, and therefore higher myocardial oxygen consumption with subsequent subendocardial ischemia. In ventricular hypertrophy without epicardial coronary artery obstruction, the coronary circulatory autoregulation curve is shifted to the right increasing myocardial compression by increased systolic pressure, thus determining the development of subendocardial ischemia. (32, 33) Systolic longitudinal function indexes such as MASD and S wave tissue Doppler correlated inversely with afterload evaluated through ESS, as other indexes related to shortening, such as

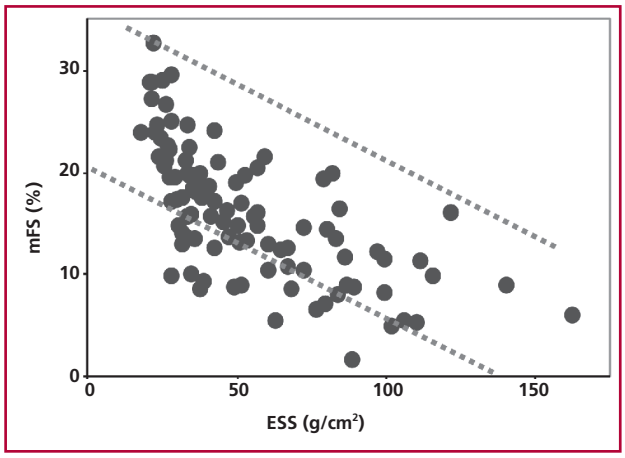

Fig. 3. Correlation between midwall fractional shortening (mFS) and end systolic stress (ESS) in patients with severe aortic stenosis

Table 2. Clinical characteristics and echocardiographic parameters in patients with aortic stenosis with ejection fraction <50% and ≥50%

	EF <50% n=47	EF ≥50% n=54	p
Coronary artery disease, n (%)	15 (32)	3 (5.5)	<0001
Symptoms			
Dyspnea III-IV, n	33	9	<0.01
Dyspnea I-II, n	9	6	ns
Angina, n	5	7	ns
Syncope, n	0	4	<0.05
Asymptomatic, n	0	28	<0.001
EF, %	33 ± 10	66 ± 8	<0.0001
EDV, ml	164 ± 62	91±35	<0.0001
ESV, ml	112 ± 53	32 ±18	<0.0001
SV index, ml/m²	30 ±11	37 ± 11	<0.01
mFS, %	13 ± 5	19 ± 5	<0.0001
ESS, g/cm²	67 ± 29	36 ±19	<0.0001
ESP, mmHg	92 ±15	96 ± 15	ns
CL	0.74 ± 4.55	3 ± 4.7	<0.004
Decreased contractility, n (%)	22 (46.8)	10 (18.5)	<0.001
MI, g/m2	179 ± 51	147 ± 39	<0.0001
RWT	0.42 ± 0.11	0.52 ± 0.11	<0.0001
Geometry			
Normal, n	0	1	ns
Concentric remodeling, n	1	9	<0.05
Concentric hypertrophy, n	16	40	<0.01
Eccentric hypertrophy, n	30	4	<0.01
MASD, mm	9.7 ± 2.77	14 ± 2.96	<0.0001
Peak S wave velocity tissue Doppler, cm/sec.	5.73 ± 1.65	7 ± 1.38	<0.0001

EF: Ejection fraction. EDS: End-diastolic volume. ESV: End-systolic volume. SV: Stroke volume. mFS: midwall fractional shortening. ESS: End-systolic stress. ESP: End-systolic pressure. CL: Contractility level. MI: Mass index. RWT: Relative wall thickness. MASD: Mitral annulus systolic displacement.

	EF <50% and coronary artery disease (n=11)	EF <50% and absence of coronary artery disease (n=36)	p
EF, %	34.7 ± 9.6	33.2 ±10.8	ns
CL	2.3 ±3.2	0.25 ±4.8	0.06
CF (dyspnea III-IV), n (%)	8 (73)	25 (69)	ns
MASD, mm	9.6 ± 2.3	9.7 ± 2.8	ns
S wave, cm/sec.	5.9 ± 1.6	5.7 ± 1.7	ns

EF: Ejection fraction.CL: Contractility level. CF: Cardiac failure. MASD: Mitral annulus systolic displacement

Table 3. Clinical characteristics and echocardiographic parameters in patients with ejection fraction <50% with and without coronary artery disease

mFS and the EF. In multivariate analysis, afterload represented by EF and ESS were the only predictors of SLF parameters; conversely, CL was not a predictor. It is worth emphasizing that shortening indexes should be related to afterload in order to infer that their decline is secondary to a contractility deficit. (34) In this work, the lower limit of contractility was the value resulting from deducing two SEE from the mFS value corresponding to a given ESS. Using this methodology, only a third of patients had decreased contractility.

The SLF was assessed with S wave peak velocity and MASD, the latter described over 25 years ago (20) proving to be useful in evaluating patients with AS. (7, 11) While this parameter could be considered "old" in the face of new technologies such as strain, it should be taken into account that in SLF assessment it is not inferior to strain, as supported by Luzcsak et al. (35) who emphasize the feasibility of M mode and tissue Doppler evaluation in all patients, even with poor ultrasound window.

The most significant finding was that 53.2% of patients with EF <50% had preserved contractility despite having ventricular remodeling (predominance of eccentric hypertrophy, increased EDV and ESV), indicating that the decrease in EF was due to afterload mismatch, as evidenced by the increased ESS. Conversely, CL was normal in 81.5% of patients with EF ≥50%, while only 18.5% had decreased contractility, suggesting that while preserved EF does not ensure normal contractility in all patients, this finding would probably be related to differences in the degree of fibrosis. (36) A finding to consider in the group with EF ≥50% is that SLF and mFS indexes were decreased compared to the C group, although ESS was lower (36±19 g/cm2 vs. 52±12 g/cm2; p <0.05). Therefore, ESS should be considered a simplification of the total stress supported by the LV from the beginning to the end of the ejection with different effects at initiation, half and end systole, (37, 38) thus being a limitation of the study. However, the decrease in SLF in this group is in agreement with reports of decreased strain in patients with preserved EF, in whom CL was not analyzed. (11, 12) The inverse correlation of mFS-EES and SLF -ESS in patients with EF <50% or ≥50% was similar to that observed in the total group of patients with AS. Considering the influence that coronary artery disease could have in patients with EF <50%, no significant differences in EF, development of heart failure, and SLF and CL indexes were found, although this last parameter had a tendency to be lower without reaching significant values in patients without coronary artery disease, probably because they had a longer evolution of their valve disease with the consequent development of fibrosis.

Limitations

Data on the presence of coronary artery disease could be evaluated by coronary angiography in 39% of patients; although 28% were asymptomatic, with EF ≥50%, and therefore had no study indication, it cannot be ruled out in the remaining 33%. Strain was not performed as it was not available in the equipment used in the study.

CONCLUSIONS

In patients with severe AS, SLF was inversely related to afterload (ESS). The presence of decreased MASD or S wave was not associated with LV contractile abnormalities. Decreased contractility was observed in one third of all patients with AS and in 46.8% of patients with EF <50%, suggesting the presence of afterload mismatch in the remaining 53.2%.

Conflicts of interest

None declared
(See author´s conflicts of interest forms in the web / Supplementary Material)

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