ORIGINAL ARTICLE

Prognostic Value of Longitudinal Strain by Velocity Vector Imaging in Asymptomatic Severe Aortic Stenosis with Preserved Ejection Fraction

Valor pronóstico del strain longitudinal, medido por velocity vector imaging, en la estenosis aórtica grave asintomática con fracción de eyección conservada

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ABSTRACT

Background: Longitudinal systolic strain (LSS) abnormalitiess have been described in patients with preserved ejection fraction (EF). The prognostic value of LSS in asymptomatic severe aortic stenosis (AoS) is under discussion.
Objetive: The aim of this study was to assess whether LSS assessment using velocity vector imaging (VVI) predicts the progression and indication of aortic valve replacement (AVR) in asymptomatic patients with severe AoS and preserved EF.
Methods: The study included patients with severe AoS and preserved EF who were considered asymptomatic and without initial indication for AVR. They underwent two, three and four-chamber echocardiography that evaluated LSS of each segment and global longitudinal strain (GLS) by VVI, as well as NT-proBNP assessment. The primary endpoint was need for AVR.
Results: A total of 57 patients with mean age 69±8 years, 49% women, were included in the study. After two years of follow-up, 13 patients (22.8%) required AVR. This group had lower GLS (-15.5±3.4 vs.-18.9±3.1, p=0.03) and two-chamber LSS (-12.8±5.5 vs.-16.3±5.6, p=0.04). In univariate analysis, GLS, NT-proBNP and the E/e' ratio were predictors of the endpoint, while in the multivariate analysis, only GLS was an independent predictor of need for AVR (HR: 1.28 (95% CI 1.04-1.58), p=0.01).
Conclusions: Global longitudinal strain measured by VVI was an independent predictor of need for AVR.

Key words: Aortic Valve Stenosis - Diagnostic imaging - Echocardiography - Blood Flow Velocity - Asymptomatic Diseases – Prognosis

RESUMEN

Introducción: Se han descripto alteraciones en el strain longitudinal sistólico (SLS) en pacientes con fracción de eyección (FE) conservada. El valor pronóstico del SLS en la estenosis aórtica (EAO) grave asintomática está en discusión.
Objetivos: Evaluar si la medición de SLS mediante velocity vector imaging (VVI) predice la progresión y la indicación de reemplazo valvular aórtico (RVA) en pacientes asintomáticos con EAO grave y FE conservada, inicialmente asintomáticos.
Material y métodos: Se seleccionaron pacientes con EAO grave y FE conservada que fueron considerados asintomáticos sin indicación inicial de RVA. A todos los pacientes se les realizó un ecocardiograma que evaluó el SLS de cada segmento en dos y tres y cuatro cámaras y el SLS global por el método VVI. Además, se realizó la medición del NT-proBNP. Se consideró como punto final el requerimiento de RVA.
Resultados: Se evaluaron 57 pacientes con una edad de 69 ± 8 años, 49% mujeres. Luego de dos años de seguimiento 13 pacientes (22,8%) requirieron RVA. El grupo que requirió RVA presentó menor SLS global (-15,5 ± 3,4 versus -18,9 ± 3,1, p = 0,03) y SLS en dos cámaras (-12,8 ± 5,5 versus -16,3 ± 5,6, p = 0,04). En el análisis univariado, el SLS global, en NT-proBNP y la relación E/e´ fueron predictores del punto final, mientras que, en el multivariado, solo el SLS global se comportó como predictor independiente de requerimiento de RVA (HR: 1,28 (IC 95% 1,04-1,58), p = 0,01).
Conclusiones: El SLS global medido por VVI fue predictor independiente de requerimiento de RVA.

Palabras clave: Estenosis de la válvula aórtica - Diagnóstico por imagen - Ecocardiografía - Velocidad del flujo sanguíneo - Enfermedades asintomáticas - Pronóstico

INTRODUCTION

Aortic stenosis (AoS) is the most common valve disease requiring surgical resolution in Western countries. Its prevalence increases with age and is estimated to be between 2.5% and 7% in persons over 65 years of age. (1) It is a chronic, progressive disease with significant morbidity and mortality that deserves to be considered due to its clinical relevance and growing socioeconomic impact. During the natural progression of the disease the development of symptoms and ventricular

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function impairment indicate the prognosis and, consequently, the indication of aortic valve replacement (AVR) is clear. (2-4) Conversely, in asymptomatic patients, surgical opportunity is not completely defined.

Aortic stenosis is characterized by left ventricular (LV) pressure overload with ensuing hypertrophy as compensatory response and, later, fibrosis that modifies the myocardial structure. These findings appear early in disease progression and have prognostic implications. (5)

Ejection fraction (EF) is the most used parameter for the evaluation of ventricular function; however, it has some limitations since it is a parameter of chamber function, echocardiographically derived from endocardial motion which is influenced by ventricular geometry. (6) It has been documented that many patients with preserved EF have altered longitudinal fiber function evaluated both by tissue Doppler (7) and strain and strain rate technique (8, 9). The implication of these alterations in risk stratification is currently under discussion in asymptomatic patients.

The aim of this work was to evaluate whether longitudinal strain assessment, using velocity vector imaging (VVI) technique, predicts the development of symptoms and the indication of AVR in initially asymptomatic patients with severe AoS with preserved EF.

METHODS

A prospective, observational, single-center study was performed in patients with severe AoS and preserved EF who were considered asymptomatic and without initial indication for AVR. These patients were followed-up in the outpatient clinic between July 2015 and December 2017. The definition of severe AoS was carried out according to current guidelines. (2, 3, 4) Preserved ventricular function was considered as EF>55%.

Exclusion criteria consisted in patients who were symptomatic in the interrogation or who on physical examination presented clinical signs of heart failure. Patients with uncertain symptoms underwent an ergometry under the Naugthon protocol. In case of presenting symptoms or flat systolic pressure curve during the exercise test, they were considered symptomatic and, therefore, excluded. Patients with LV function impairment were those with EF ≤55% and LV dilation, defined as diastolic diameter >60 mm.

Echocardiographic parameters

All patients underwent an echocardiogram with a MyLab Seven ©-Esaote ultrasound machine (Florence, Italy) with multi-frequency probe (1.5 MHz to 2.6 MHz). The following parameters were evaluated: aortic valve peak velocity (Vmax.), mean gradient (MG), aortic valve area (AVA) by the continuity equation, left ventricular diastolic and systolic diameters (LVDD and LVSD, respectively), left ventricular mass index (LVMI), pulmonary artery systolic pressure (PASP) and EF using the biplane Simpson method. In addition, lateral wall S tissue wave (S lat) and E/e' ratio were recorded.

In each segment, longitudinal systolic strain (LSS) was measured from two, three and four chamber views and global longitudinal strain (GLS) by the VVI method. Following the manufacturer's instructions, the endocardial border was marked on the two-dimensional echocardiographic images using the aided heart segmentation (AHS) option of the trace control, which suggests the semi-automatic selection of myocardial reference points. Subsequently, longitudinal strain parameters were recorded after visual confirmation of the best wall motion tracing (by subjective visual evaluation of the operator).

The images were collected in the echocardiography laboratory, and the analysis was subsequently carried out at the workstation, using the MyLab Desk v 8.0 software, Esaote©. To reduce intra and inter-observer variability, three different measurements from each patient were averaged.

NT-proBNP

NT-proBNP assessment was performed in the institution's laboratory, using a Vitros 5600 machine after the first consultation.

End-point

Follow-up was done through medical or telephone interview. The primary end-point was need for AVR.

Statistical analysis

Continuous variables are expressed as mean±standard deviation, and categorical variables as percentages. Comparisons of continuous variables between the groups that required and did not require AVR were performed using Student's t test for normal distribution and the Mann-Whitney test for non-normal distribution, and categorical variables were compared using Fisher's chi-square or exact test, if any variable had a frequency <5.

Cox regression analysis was used for univariate analysis with surgery requirement as dependent variable, and the different echocardiographic parameters and NT-proBNP as continuous variables. The variables that were significant in the univariate analysis (with $p < 0.05$), were analyzed in a multivariate model using the proportional hazards regression method to evaluate the variables that were independently associated with surgery requirement.

Subsequently, Receiver Operating Characteristic (ROC) curves were built, with the corresponding area under the curve (AUC) and the cut-off point of independent predictive variables.

Finally, an event-free survival analysis was performed using the Kaplan-Meier method. Statistix 7 and Epidat 3.1 software packages were used for the statistical analyses.

Ethical considerations

The study was evaluated and approved by the institutional Ethics Committee. An informed consent, authorized by a relative or person responsible was requested for each patient included in the study.

RESULTS

Among a total of 85 patients evaluated, 28 were excluded: 15 were considered symptomatic (10 during the initial interview and 5 after undergoing an ergometric test), 5 had impaired ventricular function and 8 presented with poor ultrasound window that did not allow strain measurements.

Thus, 57 patients were finally evaluated in the study, with mean age of 69±8 years and 49% women. The most frequent cause of AoS was sclerodegenerative aortic valve lesions (70%, n=40), followed by bicuspid aortic (26.3%, n=15) and rheumatic (3.7%, n=2) valves. Table 1 shows patient clinical and echocardiographic characteristics.

Mean follow-up was 536±155 days; 22.8% of the patients required AVR during follow-up (n=13), the majority because of symptom onset. No patient died during follow-up. The group of patients who required AVR had lower GLS (-15.5±3.4 vs.-18.9±3.1, p=0.03) and two-chamber LSS (-12.8±5.5 vs.-16.3±5.6, p=0.04) compared with patients who did not require valve replacement.

In addition, a tendency to lower LSS was observed in the 4-chamber view (-16.5±3.2 vs.-19.9±4.1, p=0.07), together with lower tissue S wave (0.07±0.01 versus 0.08±0.01, p=0.09), higher E/e´ ratio (8.2±2 vs. 7.1±1.3, p=0.07) and higher NT-proBNP (500±130 vs. 310±150, p=0.09) (Table 1).

In the univariate analysis, GLS [HR 1.21 (95% CI 1.05-1.42), p=0.01], E/e' ratio [HR 1.49 (95% CI 1.22-2.32), p=0.01] and NT-proBNP [HR 1.03 (95% CI 1.01-1.06, p=0.04] were associated with need for AVR, while the 4-chamber LSS presented a borderline association [HR 1.10 (95% CI 1.00-1.22), p=0.05]. In the multivariate analysis, only GLS was an independent predictor of the need for AVR [HR 1.28 (95% CI 1.04-1.58), p=0.01]. Table 2 shows the univariate and multivariate analyses.

Figure 1 shows the ROC curve for GLS which presented an AUC of 0.72 (95% CI 0.56–0.89) and a cut-off point < -15%. In 26.3% of cases the patients presented GLS < -15% (n=15), which was associated with need for AVR (unadjusted HR of 4.8 (95% CI 2.5–7.4, p=0.01). Figure 2 shows the Kaplan-Meier curve for GLS.

DISCUSSION

Myocardial deformation by means of longitudinal strain is a method that provides additional information on left ventricular function, as it reflects with

Table 1. Baseline population characteristics

	Total (n=57)	With need for AVR (n=13)	Without need for AVR (n = 44)	p
Age	69 ± 12	68 ± 11	69 ± 13	0.42
Female gender; n (%)	28 (49.1)	6 (46.1)	22 (50)	0.33
SBP	130 ± 28	128 ± 32	130 ± 27	0.31
Echocardiogram				
EF (%)	64 ± 4	65 ± 3	64 ± 3	0.23
LVDD(mm)	49 ± 5	49 ± 8	49 ± 7	0.85
IVS (mm)	12 ±3	13 ± 3	12 ± 4	0.15
LVMI (gr/m2)	98 ± 38	99 ± 41	97 ± 39	0.43
Doppler				
Vmax (m/s)	4.2 ± 0.4	4.5 ± 0.8	4.2 ± 0.5	0.11
AVA index (cm2/m2)	0.58± 0.09	0.57 ± 0.1	0.58 ± 0.09	0.63
MG (mmHg)	45 ± 5	46± 4	45 ± 4	0.31
Tissue				
Lateral S wave (m/S)	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.09
E/e´ ratio	7.3 ± 1.5	8.2 ± 2	7.1 ± 1.3	0.07
Strain				
GLS	-18.0 ±3.8	-15.5 ± 3.4	-18.9 ±3.1	0.03
2-chamber LSS	-15.6 ± 6.1	-12.8 ±5.5	-16.3 ± 5.6	0.04
3-chamber LSS	-19.2 ± 3.9	-17.2 ± 3.4	-19.8 ± 4.1	0.11
4-chamber LSS	-19.3 ± 4.8	-16.5 ± 3.2	-19.9± 4.1	0.07
NT-proBNP (pg/ml)	420 ± 180	500 ± 130	310 ± 150	0.09

AVR: Aortic valve replacement. SBP: Systolic blood pressure. EF: Ejection fraction. LVDD: Left ventricular diastolic diameter. IVS: Interventricular septum. LVMI: Left ventricular mass index. Vmax: Aortic valve peak velocity. AVA: Aortic valve area. MG: Mean gradient. GLS: Global Longitudinal Strain. LSS: Longitudinal systolic strain

Table 2. Univariate and multivariate analysis

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
GLS	1.21	1.05-1.42	0.01	1.28	1.04-1.58	0.01
2-chamber LSS	1.08	0.99-1.12	0.12	--	--	--
3-chamber LSS	1.10	1.00-1.22	0.05	1.12	0.98-1.43	0.11
Tissue S wave	1.02	0.85-2.1	0.15	--	--	--
E/e´ ratio	1.49	1.22-2.32	0.01	1.4	0.99-1.82	0.06
NT-proBNP	1.03	1.01-1.06	0.04	1.00	0.99-1.02	0.07

greater sensitivity than EF the shortening capacity of the myocardial fiber, and allows the early detection of subclinical contractility abnormalities. (10) These abnormalities have been described in severe AoS in asymptomatic patients with preserved EF. (11) Nq et al. studied 420 patients with mild, moderate and severe AoS with preserved EF, and found a direct relationship between impaired longitudinal, radial and circumferential strain and the severity of AoS. (12) It has also been reported that asymptomatic patients with severe AoS and preserved EF have lower GLS compared with control subjects. (13)

In our work we found that GLS in initially asymptomatic patients with severe AoS with preserved EF was an independent predictor of the onset of symptoms and need for AVR. Similar results have been described in numerous studies. Kerney et al. (14) evaluated 122 patients with more than moderate AoS and preserved EF, and found that GLS was an independent predictor of mortality at 2-year follow-up. The cut-off point of GLS <-15% showed a thirty-fold higher risk of mortality. In addition, GLS was an independent predictor of the composite endpoint of major cardiovascular events, where AVR was the main event (in 57% of patients). Therefore, the authors suggest that GLS is a parameter that could help indicate an earlier invasive approach, as it identifies a group of high-risk patients.

In that sense, Lancellotti et al. (15) conducted a prospective study analyzing the prognostic stratification of numerous echocardiographic variables in 163 patients with more than moderate AoS. During an average follow-up of 20 months, the primary endpoint of symptoms, need for AVR and cardiovascular mortality were evaluated. Global longitudinal strain was found to be an independent predictor of worse prognosis, with a cut-off point < -15.9%.

In addition, indexed left atrial diameter, Vmax and valvulo-arterial impedance were also associated with worse outcome in the multivariate analysis. On the other hand, Fries et al. (16) in 2017 analyzed a retrospective cohort of more than 500 patients with severe AoS and preserved EF. Global longitudinal strain was an independent predictor of mortality both in patients who underwent AVR as in those in whom a conservative behavior was adopted. A study conducted in Japan by Nagata et al. (17), with 104 patients, showed that GLS performed by 3D echocardiography was an independent predictor of events at 2-year follow-up. Conversely, the study by Carstensen et al. (18), showed that baseline LSS, but not GLS was an independent predictor of AVR requirement.

The above studies show differences with respect to ours. On the one hand, our patients presented a lower event rate. Only 22% of patients required AVR and none died during follow-up. In most studies, need for AVR exceeded 50% with a similar follow-up time. This could be due to patient selection. In our work, patients with uncertain symptoms were evaluated by a stress

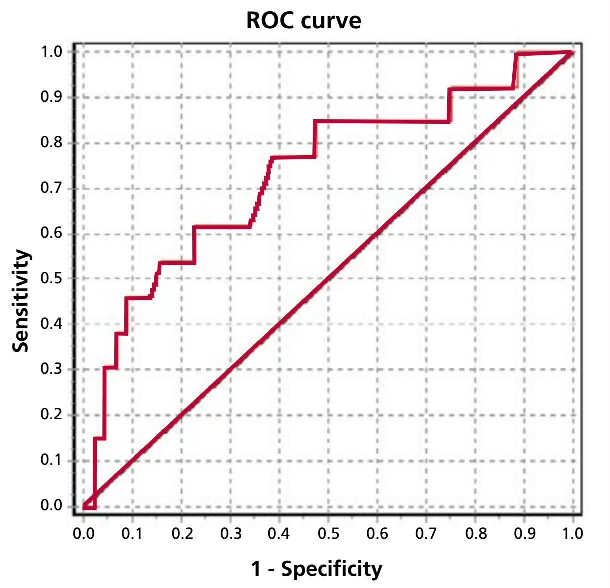
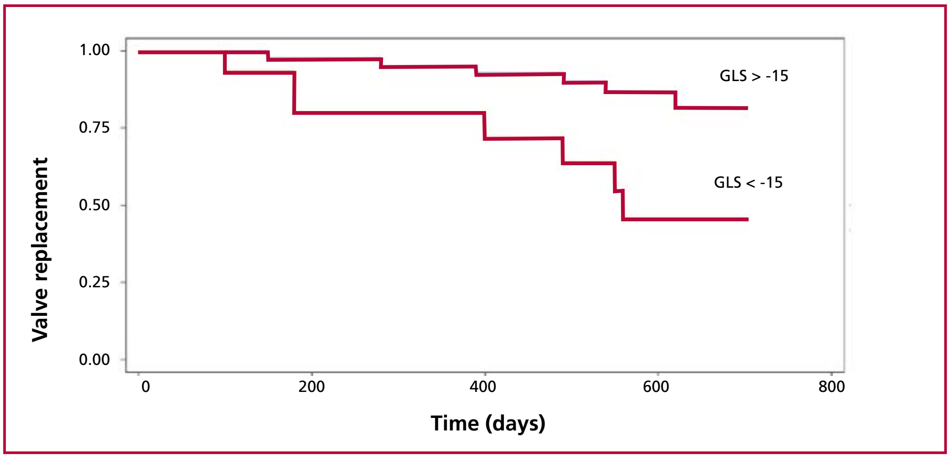


Fig. 1. ROC curve of global longitudinal strain to predict need for surgery

Fig. 2. Kaplan-Meier curve. Global longitudinal strain cut-off point >-15



test to identify the onset of symptoms; therefore, oligosymptomatic patients were excluded. Some studies, such as the one by Fries et al., also included symptomatic patients. Yet, the study by Lancelotti et al. presented similar inclusion criteria as our work, and the rate of need for AVR was higher than in our patients.

However, the main difference is that all the studies mentioned used speckle tracking to measure LSS, which is the most widespread technique. In our work, VVI was used to quantify LSS. This technique used two-dimensional echocardiography to measure strain by means of an algorithm that allows monitoring the endocardial border. The deformation of each segment guided automatically by the endocardial contour becomes a vector, whose direction represents the direction in which the myocardial tissue moves, and the length indicates the magnitude of tissue velocity (19). This method has been validated for measurement of longitudinal and radial strain (19, 20) and ventricular torsion. (21) Moreover, it has been documented that this method is useful for assessing intraventricular dyssynchrony and predicting the response to resynchronization therapy in patients with heart failure. (22, 23)

We have not found studies that evaluate the role of LSS using the VVI technique in patients with asymptomatic AoS, with preserved EF. In our work we found that GLS was an independent predictor of symptom development and need for AVR, with a cut-off point similar to that found in other studies with speckle tracking technique (< -15%), with a modest capacity of discrimination (ABC: 0.72). Therefore, this technique can be useful for the prognostic evaluation of this group of patients.

On the other hand, we found that NT-proBNP was a predictor of AVR in the univariate but not in the multivariate analysis. Numerous studies have shown that elevated natriuretic peptides are related to the appearance and development of AoS symptoms (24, 26). In this regard, the guidelines suggest that in asymptomatic patients, serial evaluation of natriuretic peptides (BNP or NT-proBNP) may be useful for risk stratification and for deciding the most appropriate time for intervention. (3, 4) It is possible that in our work we have not found NT-proBNP as an independent predictor of AVR due to the small number of study patients.

However, in a French cohort of elderly patients with severe AoS (27), it was seen that NT-proBNP in the asymptomatic subgroup was not an independent predictor of symptom progression and AVR requirement when adjusting for age, gender and AVA. Larger studies are needed to evaluate the role of LSS associated with NT-proBNP in asymptomatic patients with severe AoS.

Limitations

The main limitation of our study was its single center nature. In addition, LSS data in the different views/observations were taken by a single operator, without being corroborated by two different operators, a circumstance that could increase the risk of bias.

CONCLUSIONS

In the univariate analysis, GLS, NT-ProBNP and E/e' ratio were predictors of the primary endpoint. However, in the multivariate analysis, only GLS evaluated by VVI was an independent predictor of need for aortic valve replacement.

Conflicts of interest

All the authors of this work have contributed to the study and accepted the Editorial Committee conditions, confirming no direct or indirect conflicts of interest.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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