ORIGINAL ARTICLE

Relationship Between Strain Rate and Myocardial Structure in Severe Aortic Stenosis

Relación entre el strain rate y la estructura miocárdica en la estenosis aórtica severa

ALEJANDRO HITA[MTSAC], SERGIO J. BARATTA[MTSAC], DEMIAN CHEJTMAN, ALEJANDRO BENTICUAGA, RICARDO COSTANTINI, GUILLERMO VACCARINO[MTSAC], MARTÍN DONATO[MTSAC], RICARDO GELPI[MTSAC], MIRIAM MATOSO, CELINA MORALES

ABSTRACT

Background: In severe symptomatic aortic stenosis (SSAS) altered global longitudinal systolic strain (GLSS) would correlate with changes in myocardial histological architecture and could identify early contractile involvement in patients with preserved ejection fraction (PEF).
Objective: The aim of this study was to analyze GLSS, collagen volume (CV), myocyte area (MyAr) and contractile involvement in patients with SSAS and PEF.
Methods: Twenty six patients with SSAS and PEF (67±11 years old, 53% male) were included in the study. A preoperative hemodynamic study and an intraoperative endomyocardial biopsy were performed to determine CV and MyAr. Three groups of patients were identified: G1: compensated left ventricular hypertrophy (LVH) without coronary disease (n=8); G2: decompensated LVH without coronary disease (n=7) and G3: decompensated LVH with coronary disease (n=11). GLSS was normalized by stroke volume, meridional end-systolic wall stress (8) and end-diastolic diameter (EDD).
Results: No significant differences in stroke volume, ± and EDD were observed between groups G1, G2 and G3. Differences between groups were observed in: CV (%) (G1: 4.7 ± 1.2, G2: 8.4 ± 1.2, G3: 11.0 ± 3.0; p < 0.01), MyAr (μm2) (G1: 328.7 ± 66.2, G2: 376.7 ± 21.9, G3: 385.0 ± 13.0; p = 0.01), LVEDP (mm Hg) (G1: 13.1 ± 1.5, G2: 19.0 ± 3.8, G3: 23.6 ± 5.8; p < 0.01), $+dP/dt_{max}$ (mm Hg/sec / LVEDP, mm Hg) (G1: 176.4 ± 45.5, G2: 89.6 ± 20.1, G3: 113.1 ± 43.7; p < 0.01), and GLSS (%) (G1: -17.9 ± 4.2, G2: -13.5 ± 2.5, G3: -13.6 ± 3; p = 0.021). GLSS correlated with CV and LVEDP and it evidenced a trend to correlate with a contractility index ($+dP/dt_{max}$ mm Hg/s / LVEDP, mm Hg).
Conclusions: Altered GLSS in patients with SSAS and PEF expresses myocardial structural changes related to increase in CV, which is associated with enhanced LVEDP and probable myocardial contractile failure.

Key words: Severe Aortic Stenosis - Myocardium - Doppler Echocardiography - Strain Rate - Myocardial Biopsy

RESUMEN

Introducción: En la estenosis aórtica sintomática grave (EASG), la alteración del strain global longitudinal sistólico (SGLS) tendría correlación con las modificaciones de la histoarquitectura y podría identificar compromiso contráctil temprano en pacientes con fracción de eyección conservada (FEyC).
Objetivo: Analizar el SGLS, el volumen de colágeno (VC), el área miocitaria (ArMi) y el compromiso contráctil en pacientes con EASG y FEyC.
Material y métodos: Se incorporaron 26 pacientes con EASG y FEyC (edad 67 ± 11 años, 53% hombres). Se realizaron un estudio hemodinámico preoperatorio y una biopsia endomiocárdica intraoperatoria para determinar el VC y el ArMi. Se identificaron tres grupos de pacientes: G1, hipertrofia ventricular izquierda (HVI) compensada sin enfermedad coronaria (n = 8); G2, HVI descompensada sin enfermedad coronaria (n = 7) y G3, HVI descompensada con enfermedad coronaria (n = 11). El SGLS se normalizó por volumen sistólico, estrés meridional de fin de sístole (8) y diámetro de fin de diástole (DFD).
Resultados: G1, G2 y G3, sin diferencias en volumen sistólico, 8 y DFD y con diferencias en VC (%) (G1: 4,7 ± 1,2; G2: 8,4 ± 1,2; G3: 11,0 ± 3,0; p < 0,01), ArMi (μm2) (G1: 328,7 ± 66,2; G2: 376,7 ± 21,9; G3: 385,0 ± 13,0; p = 0,01), PFDVI (mm Hg) (G1: 13,1 ± 1,5; G2: 19,0 ± 3,8; G3: 23,6 ± 5,8; p < 0,01), $+dP/dt_{máx}$ (mm Hg/seg / PFDVI, mm Hg) (G1: 176,4 ± 45,5; G2: 89,6 ± 20,1; G3: 113,1 ± 43,7; p < 0,01), SGLS (%) (G1: -17,9 ± 4,2; G2: -13,5 ± 2,5; G3: -13,6 ± 3; p = 0,021). El SGLS se correlacionó con VC y PFDVI y hubo tendencia con un índice de contractilidad ($+dP/dt_{máx}$ mm Hg/seg / PFDVI, mm Hg).
Conclusiones: Las alteraciones del SGLS en pacientes con EASG y FEyC son expresión de alteraciones estructurales del miocardio relacionadas con incremento del VC, asociado con un aumento de la PFDVI y con probable falla miocárdica contráctil.

Palabras clave: Estenosis aórtica grave - Miocardio - Ecocardiografía Doppler - Strain rate - Biopsia miocárdica

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Address for reprints: Dr. Alejandro Hita - Hospital Universitario Austral, Instituto de Cardiología - Juan Domingo Perón 1500 - (1629) Derqui, Pilar, Pcia. de Buenos Aires, Argentina - Tel. 54 11 4795-5299 - e-mail: ahita@cas.austral.edu.ar

Department of Cardiology, Hospital Universitario Austral. Institute of Cardiovascular Physiopathology, Universidad de Buenos Aires
[MTSAC] Full Member of the Argentine Society of Cardiology

Abbreviations

CC	Correlation coefficient
CV	Collagen volume
+dP/dt$_{max}$	Positive first derivative of left ventricular pressure
-dP/dt$_{max}$	Negative first derivative of left ventricular pressure
EF	Ejection fraction
G1	Group 1
G2	Group 2
G3	Group 3
GLSS	Global longitudinal systolic strain
LV	Left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MFS	Midwall fractional shortening
PEF	Preserved ejection fraction
SSAS	Severe symptomatic aortic stenosis
t_{50}	Time taken for pressure to fall to 50% its initial value

INTRODUCTION

Aortic stenosis is the most prevalent valve disease in developed countries. In patients suffering from this disease, surgery is indicated based on two parameters: symptoms and ventricular function expressed by ejection fraction (EF). Patients with symptomatic severe aortic stenosis (SSAS) are at greater risk of mortality and require immediate valve replacement surgery. (1) Ejection fraction is a limited parameter to assess left ventricular (LV) function, (2-4) as many patients with preserved EF (PEF) present altered longitudinal fiber function assessed by tissue Doppler. (5)

The "speckle tracking" technique to study myocardial fibers has shown to be useful to evaluate LV function, even in the presence of left ventricular hypertrophy (LVH). (6) The adaptive process of LVH in valve disease presents myocardial structure modifications, as development of fibrosis, which appear early in the evolution of the disease and condition the long-term outcome. (7, 8)

We hypothesize that global longitudinal systolic strain (GLSS) correlates with changes in myocardial histological architecture, and could detect early contractile involvement in patients with PEF.

METHODS

Population

The study included 26 consecutive patients (mean age ± standard deviation: 67.7 ± 11 years, 53% men). They presented with symptomatic aortic stenosis, defined by angina, syncope or dyspnea at rest and/or exercise, and severe aortic stenosis, defined by Doppler echocardiography (valve area < 1 cm2, mean gradient > 40 mm Hg) with EF > 50%, and were referred to Hospital Universitario Austral for aortic valve replacement. All patients underwent preoperative hemodynamic and Doppler echocardiographic studies. During surgery, a LV anterolateral wall biopsy sample was taken.

Patients with associated cardiomyopathies or other valve diseases were excluded from the study.

Three groups of patients were identified according to left ventricular end-diastolic pressure (LVEDP) < 15 mmHg or ≥ 15 mm Hg (9) assessed in the hemodynamic study, and presence of coronary disease (every main coronary vessel lesion with ≥ 50% obstruction): group 1 (G1, n = 8; LVEDP < 15 mm Hg), defined as compensated LVH without coronary lesion; group 2 (G2, n = 7; LVEDP ≥ 15 mm Hg) described as decompensated LVH without coronary lesion and group 3 (G3, n = 11) termed decompensated LVH with coronary lesion.

Study protocol

Echocardiographic study: An echocardiography and GLSS analysis with speckle tracking using Vingmed VIVID 7 equipment (GE Vingmed, Milwaukee, WT, USA) and 3.5 MHz transducer were performed following the American Echocardiography Society recommendations. (10)

Left ventricular fractional shortening, LV volume and EF (Simpson´s method) were calculated. (10). Midwall fractional shortening (MFS) (11) was determined and normalized by meridional end-systolic wall stress. (12) Aortic valve area was calculated by the continuity equation and gradients according to the modified Bernouilli equation (4V2).

Left ventricular mass was estimated according to the American Echocardiography Society and the LV mass index (LVMI) was obtained, considering that increased values were ≥ 115 g/m2 in men and ≥ 95 g/m2 in women. (13)

Two-dimensional echocardiography with gray-scale speckle tracking images, in 2, 3 and 4 chamber long axis apical views with frame rate > 50 frames/s (14) was used to evaluate GLSS. (14) The Lagrange formulation (L2L0/L0) was applied to calculate strain (15) using GE (EchoPAC version 7.0.0, General Electric-Vingmed) software. The end-systolic endocardial contour was manually traced according to the literature, and then the software concentrically defined the region of interest automatically. (16)

To analyze strain each apical image was divided into six segments and GLSS was calculated from the average of 18 segments.

Hemodynamic study

A hemodynamic study was performed prior to surgery registering left intraventricular pressure and aorta/LV gradient. Pressures were recorded on a computerized Philips Polygraph system (Xper Information System XIMs Version 1.2.01474) connected to an Edwards LifeScience pressure transducer. Aortic pressure, LV systolic pressure (mm Hg) and LVEDP (mm Hg) were measured. In addition, maximum velocity of LV pressure rise (+dP/dt$_{max}$, mm Hg/s), the inverse of the linear slope originating from applying the natural logarithm to the exponential fall of LV pressure during the period of isovolumic relaxation (lin tau, ms), and the time of LV pressure fall to 50% its initial value (t_{50}), taking as initial LV value the one corresponding to -dP/dt$_{max}$, were obtained.

The contractile state was calculated as the ratio between +dP/dt$_{max}$ and LVEDP. (17)

The two components of diastolic function were evaluated: relaxation and myocardial stiffness. Isovolumic relaxation was assessed as the time taken for pressure to fall to 50% its initial value (t_{50}), taking as initial pressure the value corresponding to the time of –dP/dt$_{max}$. Myocardial stiffness

was evaluated as the ratio between LV end-diastolic pressure and diameter.

Collagen content and morphometry

Left ventricular anterolateral biopsies were taken during surgery, fixed in 10% formaldehyde buffer at room temperature and included in paraffin. Serial 5 μm sections were then stained with hematoxylin-eosin and Picrosirius red to quantify interstitial collagen and with rhodamine to calculate myocyte area (WGA no.RL-1022, Vector Laboratories, Burlingame,CA).

Myocyte images were obtained using a fluorescence microscope (Olympus BX61) attached to a digital camera and myocyte cross-sectional areas stained with rhodamine-lectin were measured with an image analyzer (Image Pro Plus 6.0, Media Cybernetics, Inc, Silver Spring, Md). At least 80 myocyte cross-sectional areas were routinely measured. (18)

In the sections stained with the Pricosirus red technique, interstitial collagen deposition was measured using the same digital imaging system. The percent collagen volume (CV) of each region was calculated adding the corresponding collagen areas and dividing by the total myocyte areas plus the areas of collagen tissue, as previously described. (18)

Statistical analysis

Intraobserver and interobserver variability of GLSS calculation was assessed using the coefficient of variation, resulting in 5.4% and 6.2% variation, respectively. Measurements of three consecutive beats were averaged. Discrete variables were expressed as frequencies and percentages and continuous variables as means and standard deviations. Qualitative variables were analyzed using the chi-square test with Yates correction or Fisher´s exact test. Continuous independent variables were analyzed using Student´s t test for non-paired data or the Wilcoxon rank-sum test, as appropriate. Spearman´s correlation coefficient was used to analyze correlation between continuous variables. A p value < 0.05 was considered as statically significant. A ROC curve analysis was used to establish the longitudinal systolic strain cut-off point to predict the presence of decompensated hypertrophy.

Ethical considerations

All patients signed an informed consent (Hospital Universitario Austral Ethics Committee, in accordance with the Helsinki Declaration of 1975, revised in 1983).

RESULTS

Cardiac structure and function

Endomyocardial biopsy

The histologic structure presented differences between groups both in myocyte area as in CV ($p < 0.01$). All groups has an equivalent LVMI (quantitative concept for hypertrophy); however, the morphometric analysis revealed that compensated hypertrophy (G1) had a smaller myocyte area than decompensated G2 and G3 groups ($p < 0.05$) (Figure 1A). Decompensated groups showed greater increase of CV compared to the compensated group despite an equivalent LVMI ($p < 0.05$), supporting the qualitative concept of hypertrophy due to structural difference for a comparable mass index (Fig. 1B).

Diastolic function

The LVEDP was used as cut-off point to separate compensated versus decompensated hypertrophy populations according to Peterson et al. (9) The pressure difference between groups in the absence of changes in diastolic diameter would express an increase in myocardial stiffness in patients with decompensated LVH (G2 and G3, $p < 0.02$).

Increased LVEDP was associated with structural changes, correlating with increased CV [correlation coefficient (CC) 0.97, $p < 0.001$]. All patients had impaired myocardial relaxation, expressed by a change in tau50, without differences between groups (Table 1).

Systolic function

All groups presented EF within the normal range (see Table 1), without differences in LVMI, basal and normalized by wall stress MFS, or hemodynamically-assessed LV end-systolic pressure, suggesting absence of systolic dysfunction based on these variables.

Two sensitive parameters used to detect systolic function impairment: a hemodynamic parameter [$+dP/dt_{max}$ (mm Hg /s) normalized by LVEDP (mm Hg)] normalized in turn by preload due to its dependence on this variable), and an echocardiographic parameter (GLSS), evidenced more marked involvement in G2 and G3 decompensated hypertrophy groups compared

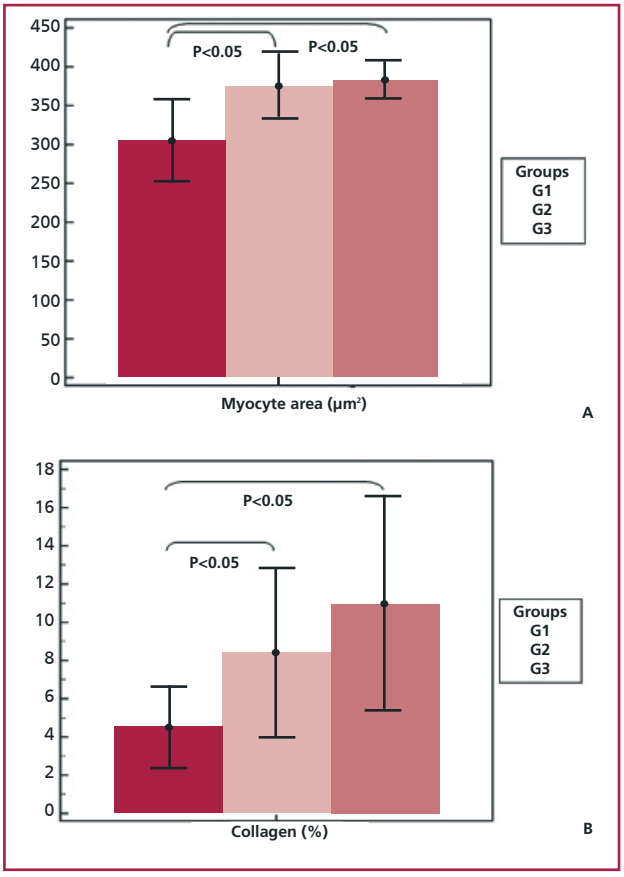

Fig. 1. Myocyte area differences between groups. B. Percent differences of collagen volume between groups (*$p < 0.05$ G1 vs. G2 and G3).

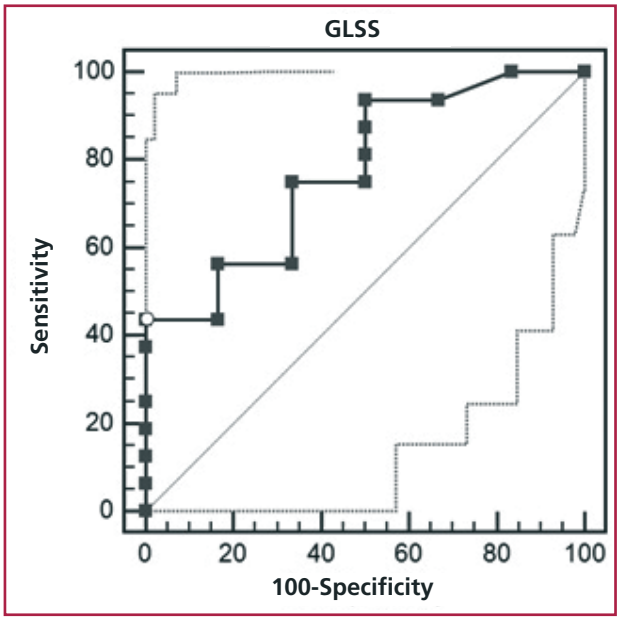

Fig. 2. Area under the ROC curve showing sensitivity and specificity of global longitudinal systolic strain cut-off point of -13.2%

to the G1 compensated group ($p < 0.05$).

Global longitudinal systolic strain was normalized in all groups by preload (end-diastolic diameter), afterload (meridional end-systolic wall stress) and LV stroke volume, which can modify GLSS without being evidence of contractile impairment. (19-21) As shown in Table 1, absence of significant differences between groups for the three variables, suggests that GLSS abnormalities would be secondary to myocardial structural and functional modifications.

Absolute GLSS changes correlated with LVEDP (CC – 0.59, $p < 0.05$) and with CV (CC -0.44, $p < 0.05$). In addition, a trend was observed in the correlation between GLSS and $+dP/dt_{max}$ (mm Hg/s) normalized by LVEDP (mm Hg) with CC of -0.71 ($p = 0.06$), which did not attain statistical significance probably due to the small number of patients.

A GLSS value < -13.2% discriminated compensated versus decompensated LVH with an area under the ROC curve of 0.77 ($p = 0.01$), with 43.75% sensitivity and 100% specificity (Figure 2).

DISCUSSION

The increase in wall stress triggers LVH as compensating response. This hypertrophy progresses with quantitative changes (mass increase) and qualitative changes (structural modifications). In our work, qualitative changes were produced without LVMI differences between groups; as expressed by Karl Weber "it is not the quantity, but rather the quality of myocardium that distinguishes hypertensive cardiomyopathy from adaptive hypertrophy of the athlete". (22)

Among these changes, fibrosis is usually an early finding in symptomatic aortic stenosis even with preserved EF and contributes to the progression from compensated hypertrophy to heart failure, (7) with significant impact on the clinical condition as well as in the long-term survival after aortic valve replacement. (8)

Our patients had normal EF, but it is known that this index is subject to changes depending, among other variables, on chamber geometry, afterload and mass increase. (1-3) Ejection fraction is more accurate to assess chamber function than ventricular function, as it predominantly expresses myocardial radial function and is less affected by subendocardial abnormalities. (23) Midwall fractional shortening, a more specific index of ventricular function evaluation in hypertrophy, (24) was normal in all the groups, even after normalizing by wall stress. This behavior could be attributed to its application in a population of patients with normal EF and end-systolic stress ≤ 120 kdynes/cm2, a cut-off point deemed inadequate to consider LVH by some authors (12), and suggests that myocardial dysfunction should not be ruled out in these patients based only on normal EF and even MFS.

Another two parameters detecting myocardial contractile failure, even in aortic stenosis, (6) one hemodynamic ($+dP/dt_{max}$ (25) normalized by LVEDP), and the other echocardiographic (GLSS) (26) confirmed systolic function involvement, especially in decompensated groups, and would be useful tools to characterize subtle functional changes.

Myocardial involvement and structural changes initially and mainly affect the subendocardium, (27) altering longitudinal function that is not accurately evaluated by EF but by other indexes, as mitral annulus lateral displacement by M mode echocardiography and/or tissue Doppler, or systolic longitudinal strain. (28)

Other studies have described altered strain in both asymptomatic and symptomatic severe aortic stenosis with PEF, (5, 6, 29) but we believe the most important concept is demonstrating that such a GLSS alteration represents myocardial structural involvement correlated with changes of systo-diastolic function. In this sense, it is necessary to point out that other variables that might alter GLSS behavior, other than myocardial contractility and fibrosis, are not responsible for its changes. We have shown that the most important factors influencing strain changes: preload, afterload and stroke volume do not account for its modification, indicating the responsibility of myocardial structural and contractile involvement.

The relationship between structural and functional changes showed linear correlation between strain alterations and CV, suggesting that structural transformations condition functional modifications (even in patients with PEF). Global longitudinal systolic strain changes, (after excluding confounding

Clinical variables	G1	G2	G3	p
Age	68±12	64.14±9,92	71±11.59	ns
Male/Female gender	2 / 5	3 / 4	9 / 3	
SBP	119.71±22.84	125.14±5.87	132±9.03	ns
NYHA functional class for angina				
II	3	3	1	
III	1		2	
IV		1		
NYHA functional class for dyspnea				
II	3	6	4	
III	3		3	
IV				
Angina	4	4	3	ns
Dyspnea	6	6	7	ns
Syncope	0	1	1	ns
Cardiac catheterization				
LVESP	202.5±19.46	211.28±40.47	193.16±24.37	ns
LVEDP	13.17±1.5	19±3.89	23.7±5.8	<0.01
$+dP/dt_{max}$, mm Hg/s	2230.75±493.03	1830.28±346.98	22316.5±313.02	0.07
$+dP/dt_{max}$, mm Hg/s normalized by LVEDP mmHg	176.4±45	89.64±20	113.17±41	<0.01
t50	24.99±2.41	32.66±5.96	32.52±8.85	ns
Myocardial histology				
Myocyte area, µm2	328.7±66	376.7±21.9	385.05±13	<0.01
Collagen volume, %	4.77±1.27	8.40±1.27	11.05±3.08	<0.01
Echocardiography				
Ejection fraction, %	75.71±5.93	64±6.03	66.72±10.65	0.04
End-systolic diameter, mm	29.74±6.26	26.33±5.39	33.37±8.06	ns
End-diastolic diameter, mm	49.31±5.29	48.16±5.15	52.75±4.15	ns
End-diastolic pressure, mmHg/end-diastolic diameter, mm	0.27±0.01	0.39±0.06	0.44±0.11	<0.02
Myocardial mass index, gm/m^2	198±85	162±43	209±42	ns
Meridional end-systolic stress, $kdynes/cm^2$	42.54±22.03	37.7±14.98	51.67±24.15	ns
MFS, %	14.15±3.95	14.96±2.7	13.48±4.35	ns
MFS/stress	18.68±0.83	18.86±0.56	18.05±1.04	ns
Aortic valve área, cm^2	0.77±0.26	0.45±0.07	0.74±0.15	ns
Mean aortic gradient, mmHg	52.74±18.,87	66.83±10.83	48.36±9.42	<0,05
Peak aortic gradient, mmHg	89.28±26.,32	103.66±15.06	80.09±16.1	0,07
Preoperative peak global longitudinal strain, %	-17.73±4.57	-13.4±3.04	-13.58±3.13	<0.05
Stroke volume	42.49±9.91	38.98±8.50	41.76±9.03	ns

G1: Group 1. G2: Group 2. G3: Group 3. NYHA: New York Heart Association. SBP: Systolic blood pressure. LVESP: Left ventricular end-systolic pressure. LVEDP: Left ventricular end-diastolic pressure. +dP/dt: Positive first derivative of left ventricular pressure. t50: Time taken for pressure to fall to 50% its initial value. MFS: Midwall fractional shortening. ns: Not significant.

Table 1. Clinical, hemodynamic, echocardiographic and myocardial histological characteristics in the 26 patients included in the three groups

variables) and its correlation with LVEDP and CV, together with the trend to correlate with $+dP/dt_{max}$ (mm Hg/s) normalized by LVEDP (mm Hg), indicate that the observed alterations would have a structural basis associated with increased CV and a functional behavior related to end-diastolic pressure and contractile state.

Different studies have described the association between altered strain in patients with symptomatic aortic stenosis and its impact on increased long-

term risk and clinical events. (5) Lancellotti et al. studied patients with asymptomatic aortic stenosis and observed that GLSS < -15.9% (30) was a prognostic marker of adverse outcome. In our patients, the group with compensated LVH presented higher values than the cut-off point, whereas in the decompensated groups with or without coronary disease, values were -13.5% and -13.6%, respectively, with a cut-off point of -13.2% separating with high specificity patients with compensated LVH from those with decompensated LVH. Lafitte et al. (5) described a population of patients with severe aortic stenosis in which the cut-off point of longitudinal basal septum strain < -13% identified a subpopulation of patients with adverse outcome and greater event rate.

Global longitudinal systolic stress normalization in the postoperative long-term follow-up after valve replacement has been shown by several authors (31) and in our experience this behavior one year after valve replacement was only observed in the compensated LVH group. Finally, the correlation between de degree of fibrosis and strain alterations has been described by other authors (32) and by our group (33), as well as its normalization after aortic valve replacement. (34)

Clinical impact

Since symptomatic aortic stenosis is the most prevalent valve disease involving elderly patients (9% mortality in octogenarian patients with pure aortic valve replacement in the best world centers) (35) in whom it is difficult to categorize symptoms, (36) and EF presents limitations in myocardial function evaluation, it is important to identify other risk markers to improve stratification and decision-making.

CONCLUSIONS

Altered GLSS in patients with SSAS and PEF expresses myocardial structural alterations related to increased CV, which is associated with higher end-diastolic pressure and probably myocardial contractile failure.

Conflicts of interest

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

REFERENCES

1. Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. J Am Coll Cardiol 2006;47:2141-e51. http://doi.org/c7ncbf

2. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195-202. http://doi.org/ffkqr6

3. Donal E, Bergerot C, Thibault H, Ernande L, Loufoua J, Augeul L, et al. Influence of afterload on left ventricular radial and longitudinal systolic functions: a two-dimensional strain imaging study. Eur J Echocardiogr 2009;10:914-21. http://doi.org/ffkqr6

4. Palmon LC, Reichek N, Yeon SB, Clark NR, Brownson D, Hoffman E, et al. Intramural myocardial shortening in hypertensive left ventricular hypertrophy with normal pump function. Circulation 1994;89:122-31. http://doi.org/xsk

5. Lafitte S, Perlant M, Reant P, Serri K, Douard H, De Maria A, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. Eur J Echocardiogr 2009;10:414-9. http://doi.org/cr83pv

6. Delgado V, Tops LF, van Bommel RJ, van der Kley F, Marsan NA, Klautz RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30:3037-47. http://doi.org/cpwvg9

7. Hein S, Arnon E, Kostin S, Schönburg M, Elsässer A, Polyakova V, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart structural deterioration and compensatory mechanisms. Circulation 2003;107:984-91. http://doi.org/bvxstf

8. Milano AD, Faggian G, Dodonov M, Golia G, Tomezzoli A, Bortolotti U, et al. Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. J Thorac Cardiovasc Surg 2012;144:830-7. http://doi.org/fzd789

9. Peterson KL, Tsuji J, Johnson A, Di Donna J, LeWinter M. Diastolic left ventricular pressure-volume and stress-strain relations in patients with valvular aortic stenosis and left ventricular hypertrophy. Circulation 1978;58:77-89. http://doi.org/xsm

10. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67. http://doi.org/xsn

11. Shimizu G, Zile MR, Blaustein AS, Gaasch WH. Left ventricular chamber filling and midwall fiber lengthening in patients with left ventricular hypertrophy: overestimation of fiber velocities by conventional midwall measurements. Circulation 1985;71:266-72. http://doi.org/bw83fh

12. Serneri GG, Modesti PA, Boddi M, Cecioni I, Paniccia R, Coppo M, et al. Cardiac growth factors in human hypertrophy: relations with myocardial contractility and wall stress. Circ Res 1999;85:57-67. http://doi.org/xsp

13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63. http://doi.org/b92m9w

14. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, et al. Two-dimensional strain a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. J Am Soc Echocardiogr 2005;18:1247-53. http://doi.org/d727q3

15. Langeland S, D'Hooge J, Wouters PF, Leather HA, Claus P, Bijnens B, et al. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. Circulation 2005;112:2157-62. http://doi.org/d6wnf5

16. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography from technical considerations to clinical applications. J Am Soc Echocardiogr 2007;20:234-43. http://doi.org/c66bxd

17. Little WC. The left ventricular +dP/dtmax in diastolic volume relation in closed-chest dogs. Circ Res 1985;56:808. http://doi.org/xsq

18. González GE, Seropian IM, Krieger ML, Palleiro J, López Verrilli MA, Gironacci MM, et al. Effect of early versus late AT1 receptor blockade with losartan on postmyocardial infarction ventricular remodeling in rabbits. Am J Physiol Heart Circ Physiol 2009;297:H375-86. http://doi.org/b5s4kn

19. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, et al. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol 2002;283:H792-9.

20. Iida N, Seo Y, Ishizu T, Nakajima H, Atsumi A, Yamamoto M, et al. Transmural compensation of myocardial deformation to preserve left ventricular ejection performance in chronic aortic regurgitation. J Am Soc Echocardiogr 2012;25:620-8.

21. Marciniak A, Sutherland GR, Marciniak M, Claus P, Bijnens B, Jahangiri M. Myocardial deformation abnormalities in patients with aortic regurgitation: a strain rate imaging study. Eur J Echocardiogr 2009;10:112-9. http://doi.org/fkpts3
22. Weber KT. Cardioreparation in hypertensive heart disease. Hypertension 2001;38(part 2):588-91. http://doi.org/xst
23. Maciver DH, Townsend M. A novel mechanism of heart failure with normal ejection fraction. Heart 2008;94:446-9. http://doi.org/d82kbm
24. Ballo P, Mondillo S, Guerrini F, Barbati R, Picchi A, Focardi M. Midwall mechanics in physiologic and hypertensive concentric hypertrophy. J Am Soc Echocardiogr 2004;17:418-27. http://doi.org/b98wjm
25. Katz AM. Regulation of myocardial contractility 1958-1983: An odyssey. J Am Coll Cardiol 1983;1:42-51. http://doi.org/bfgq4c
26. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, et al. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol 2002;283:H792-9.
27. Heymans S, Schroen B, Vermeersch P, Milting H, Gao F, Kassner A, et al. Inhibitor of metalloproteinase-2 is related to cardiac fibrosis and dysfunction in the increased cardiac expression of tissue inhibitor of metalloproteinase-1 and tissue chronic pressure-overloaded human heart. Circulation 2005;112:1136-44. http://doi.org/ckpvvn
28. Takeda S, Rimington H, Smeeton N. Chambers long axis excursion in aortic stenosis. Heart 2001;86:52-6. http://doi.org/fm8hkq
29. Dal Bianco JP, Khanderia BK, Mookadam F, Gentile F, Sengupta PP. Management of asymptomatic severe aortic stenosis. J Am Coll Cardiol 2008;52:1279-92. http://doi.org/dmft9f
30. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, et al. A risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364e1371.
31. Rost C, Korder S, Wasmeier G, Wu M, Klinghammer L, Flachskampf FA, et al. Sequential changes in myocardial function after valve replacement for aortic stenosis by speckle tracking echocardiography. Eur J Echocardiogr 2010;11:584-9. http://doi.org/dgbt2m
32. Weidemann F, Herrmann S, Störk S, Niemann M, Frantz S, Lange V, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009;120:577-84. http://doi.org/dg5td5
33. Hita A, Baratta SJ, Donato M, Chejtman D, Morales C, Costantini R, et al. Study of the ventricular function and its correlation with morphometry in patients with severe symptomatic aortic stenosis. Eur Heart J 2012;33(Abstract Suppl):569.
34. Poulsen SH, Søgaard P, Nielsen-Kudsk JE, Egeblad H. Recovery of left ventricular systolic longitudinal strain after valve replacement in aortic stenosis and relation to natriuretic peptides. J Am Soc Echocardiogr 2007;20:877-84.
35. Varadarajan P, Kapoor N, Bansal R, Pai R. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. Ann Thorac Surg 2006;82:2111-5. http://doi.org/cg76zs
36. Malouf J, Le Tourneau T, Pellikka P, Sundt T, Scott C, Schaff H, et al. Aortic valve stenosis in community medical practice: Determinants of outcome and implications for aortic valve replacement. J Thorac Cardiovasc Surg 2012;144:1421-7. http://doi.org/xsw