ORIGINAL ARTICLE

Two-dimensional Strain Echocardiography Differentiates Cardiac Amyloidosis from Hypertrophic Cardiomyopathy with Preserved Ejection Fraction

Perfiles ecocardiográficos del strain 2D permiten diferenciar a la amiloidosis cardíaca de la miocardiopatía hipertrófica con fracción de eyección conservada

ARIEL SAAD[1], ROSINA ARBUCCI[1], GRACIELA ROUSSE[1], VICTOR DARÚ[1], PABLO MERLO[1], ELENA ROMERO[2], IDELFONSO ROLDÁN[2], VICENTE MORA[2], JORGE LOWENSTEIN[1]

ABSTRACT

Background: Ejection fraction is a poor parameter to assess left ventricular function in ventricular hypertrophy. It is highly important to analyze aspects of ventricular mechanics that could differentiate cardiac amyloidosis from hypertrophic cardiomyopathy.
Objective: The aim of this study was to compare longitudinal strain and other ventricular mechanical parameters between patients with hypertrophic cardiomyopathy and cardiac amyloidosis, both with preserved ejection fraction.
Methods: A comparative, prospective study was conducted in 15 patients with cardiac amyloidosis [Group (G) 1] and 15 patients with hypertrophic cardiomyopathy (G2), both presenting preserved ejection fraction (>50%). Patients were analyzed with speckle tracking echocardiography and strain and left ventricular (LV) rotational parameters. Longitudinal strain was obtained from apical 4-, 3- and 2-chamber planes. Circumferential strain and ventricular rotation were obtained from LV transverse planes. Twist: algebraic sum of apical and basal rotation (°), torsion [twist/LV base-apex distance (º/cm)] and the new parameters: deformation product (global longitudinal strain × apical circumferential strain); deformation index: [twist/ longitudinal strain (º/%)] and ejection fraction/global longitudinal strain ratio were calculated.
Results: Patients with cardiac amyloidosis presented significantly lower ejection fraction (58.08%±6.16 vs. 67.15%±8.09; p=0.012) and global longitudinal strain values (–12.61%±4.32 vs. –17.15%±3.95; p=0.008) at the expense of basal segments. No significant differences were found for twist, torsion, and circumferential and radial strain. The product between longitudinal strain and apical circumferential strain decreased, while the ejection fraction/global longitudinal strain ratio was significantly increased in patients with cardiac amyloidosis.
Conclusions: The product of longitudinal strain × apical circumferential strain and the ejection fraction/global longitudinal strain ratio are useful parameters that allow differentiating cardiac amyloidosis from hypertrophic cardiomyopathy patients.

Key Words: Echocardiography/methods - Cardiomyopathy, Hypertrophic/diagnosis imaging – Amyloidosis - Ventricular Dysfunction, Left

RESUMEN

Introducción: La fracción de eyección es un parámetro débil para evaluar la función ventricular en la hipertrofia ventricular. Es de fundamental importancia analizar aspectos de la mecánica ventricular que podrían diferenciar una amiloidosis cardiaca de una miocardiopatía hipertrófica.
Objetivo: Comparar el comportamiento del strain longitudinal y otros parámetros de la mecánica ventricular entre pacientes con miocardiopatía hipertrófica y amiloidosis cardíaca ambos con fracción de eyección conservada.
Material y métodos: Estudio comparativo, prospectivo realizado en 15 pacientes con amiloidosis cardíaca (Grupo [G] 1) y 15 pacientes con miocardiopatía hipertrófica (G 2), ambos con fracción de eyección conservada (>50%). Fueron analizados con ecocardiografía por seguimiento de marcas (speckle tracking), parámetros de strain y rotacionales del VI. El strain longitudinal se obtuvo a partir de planos apicales de 4, 3 y 2 cámaras. El strain circunferencial y la rotación ventricular a partir de planos transversales del VI. Se calculó el giro: suma algebraica de rotación apical y basal (º), torsión (giro / distancia base-ápex del VI (°/cm)) y los nuevos parámetros: producto de deformación (multiplicación entre el strain longitudinal global y el strain circunferencial apical); índice de deformación (°/%): (giro / strain longitudinal) y el cociente fracción de eyección / strain longitudinal global
Resultados: Los pacientes con amiloidosis cardíaca presentaron valores significativamente menores de fracción de eyección (58,08% ± 6,16 vs. 67,15% ± 8,09; p = 0,012) y de strain longitudinal global (–12,61% ± 4,32 vs. –17,15% ± 3,95; p = 0,008) a expensas de los segmentos basales. No se constataron diferencias significativas con el giro, la torsión, el strain circunferencial y el radial. El producto entre strain longitudinal y el circunferencial apical resultó disminuido mientras que el cociente fracción de eyección / strain longitudinal global se encontró aumentado de manera significativa.
Conclusiones: El producto strain longitudinal x strain circunferencial apical y el cociente fracción de eyección / strain longitudinal global son parámetros útiles que permiten diferenciar pacientes con amiloidosis cardíaca de pacientes con miocardiopatía hipertrófica.

Palabras clave: Ecocardiografía/métodos - Cardiomiopatía Hipertrófica/diágnostico por imágenes – Amiloidosis - Disfunción Ventricular Izquierda

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Address for reprints: Ariel K. Saad - Av. Córdoba 2351 - (C1120AAF) Ciudad Autónoma de Buenos Aires, República Argentina - e-mail: aksaad@arnet.com.ar

[1] Echocardiography Laboratory. Investigaciones Médicas. Buenos Aires, Argentina.
[2] Division of Cardiology. Hospital Universitario Dr. Peset. Valencia.

Abbreviations

ACS	Apical circumferential strain	**GLS**	Global longitudinal strain
AL	Light chain amyloidosis	**HCM**	Hypertrophic cardiomyopathy
CA	Cardiac amyloidosis	**MRI**	Magnetic resonance imaging
CT	Computed tomography	**RS**	Radial strain
EF	Ejection fraction	**TTR**	Transthyretin

INTRODUCTION

Amyloidosis is characterized by the extracellular deposit of insoluble protein fibrils, resulting in the abnormal functioning of the affected organ. In the heart, light chain immunoglobulins (AL) and transthyretin (TTR) are the most common types of hereditary or age-related "wild-type" amyloidosis. The progressive accumulation of amyloid material in the cardiac tissue generates myocyte separation, cellular toxicity, apoptosis and tissue stiffness, leading to various degrees of heart failure due to mechanical, biochemical and electrical dysfunction. (1)

Given the unspecific nature of signs and symptoms, the diagnosis of cardiac amyloidosis (CA) is often a true challenge. Although the final diagnosis is made by anatomical pathology, imaging techniques, and specially, echocardiography, are very useful tools when this disease is suspected in the clinical evaluation. One of the most frequent findings is a diffuse increase of left ventricular wall thickness, and consequently, one of the main differential diagnoses is with hypertrophic cardiomyopathy (HCM). The distinction between both diseases has relevant prognostic and therapeutic implications. (2)

Left ventricular (LV) function results from the interaction of a complex myocardial fiber architecture composed of two helical fiber geometries, one subendocardial and another subepicardial, which rotate almost simultaneously in opposite directions during the cardiac cycle. The contraction of these fibers produces changes in the size and form of the left ventricle, resulting in longitudinal shortening, circumferential rotation and myocardial radial thickening.

In the last years, speckle tracking echocardiography has emerged as an advanced tool of relatively easy operation, enabling the more detailed study of ventricular mechanics beyond the classical ejection fraction assessment. (3-5)

Some diseases usually have a characteristic pattern of myocardial disorder and consequently lead to different degrees of abnormal contractility that can be detected through the selective analysis of different types of deformation. A double gradient myocardial involvement has been described in CA, extending from base to apex and from the subendocardium to the subepicardium. (6)

The aim of the present study was to compare the behavior of two-dimensional longitudinal strain and other myocardial deformation parameters related with ventricular mechanics between patients with CA and HCM, both with preserved ejection fraction (EF).

METHODS

Population

This was a descriptive, comparative, prospective study of speckle tracking echocardiography in 15 patients with CA [3 with light chain CA (AL CA) and 12 with transthyretin CA (TTR CA)] and 15 patients with diagnosis of HCM, all with preserved ejection fraction (EF >50%), according to the analysis of the diagnoses reported in their respective clinical histories between August 2015 and March 2018.

The diagnosis of amyloidosis was confirmed by one of the following methods: biopsies, magnetic resonance imaging (MRI), 99m technetium-pyrophosphate cardiac scintigraphy or anatomical pathology.

Wall thickness >15 mm, assessed by echocardiography, MRI or CT scan, not explained by hemodynamic causes (hypertension, aortic stenosis, etc.) was considered a positive diagnosis for HCM.

All patients signed the corresponding informed consent before entering the study. Carriers of structural heart disease of another known etiology, such as ischemic heart disease or heart valve disease, as well as patients presenting history of complete left bundle branch block or inadequate ultrasound window, were excluded from the study.

Echocardiogram

A Vivid E 9 or E 95 (GE Healthcare) ultrasound system was used with 5 MHz Matrix array transducer for two-dimensional image acquisition with a frame rate of 60 and 70 frames per second. Evaluation of chamber diameters and thickness and left atrial area, as well as transvalvular flows with the respective systolic and diastolic function assessments were performed according to the American Society of Echocardiography guidelines.

Systolic parameters were obtained from the analysis of the automated EF. Diastolic function was analyzed by pulsed wave Doppler E wave (cm/s) and A wave (cm/s) velocities corresponding to transmitral flow, and the E/A ratio. Tissue Doppler imaging was used to calculate peak septal e', lateral e' (cm/s), a' wave (cm/s) and s´ wave (cm/s) velocities and the E wave ratio of mitral filling with the average of two e' velocities (E/average e'). In addition to conventional echocardiographic assessment, longitudinal strain (LS), circumferential strain (CS) and radial strain (RS) were analyzed. Longitudinal strain was obtained from 4-, 3- and 2-chamber apical views. Apical CS (ACS) and the parameters of ventricular rotation were obtained from the analysis of LV basal and apical short-axis views. Twist (°) was calculated as the algebraic sum of basal and apical rotation, and torsion (°/cm) as the ratio between twist and the LV base-apex distance. We also evaluated the following new parameters, which integrate the values of different types of deformation:

- Deformation product: Global LS (GLS) multiplied by ACS.
- Deformation index (°/%): The ratio between twist and GLS.
- The ratio between EF and GLS.

Image processing of 2D strain was later performed in a workstation (GE EchoPac 201-201).

Statistical analysis

IBM SPSS® Statistics 20 software was used to perform the analyses. Nominal variables were expressed as percentages relative to the total number of cases and quantitative variables as mean and standard deviation or median and interquartile range, as appropriate. Kolmogorov-Smirnov or Shapiro-Wilk tests were used to analyze distribution normality. Student's t test, a non-parametric test, the chi-square test or Fischer's exact test were used to compare between groups, according to the type of variable and data distribution. A p value <0.05 was considered to be significant.

Ethical considerations

The study was approved by the Institutional Ethics Committee.

RESULTS

Population characteristics

No significant differences were found for sex, age and blood pressure values between groups. Patients with CA presented higher heart rate. Results are shown in Table 1.

Two-dimensional and Doppler echocardiography

In the conventional echocardiographic analysis, patients with CA exhibited lower interventricular septal (IVS) thickness compared with HCM patients (16±3.2 vs. 20±6.2 mm; p=0.017), though no significant differences were observed between both groups with respect to LV mass. The group with CA exhibited significantly lower values of EF (58.08±6.16 vs. 67.15±8.09%; p=0.004) and the same was observed with mitral annular plane systolic excursion (MAPSE) (9.83±3.18 vs. 15.15±2.51 mm; p=0.01). Diastolic function also evidenced greater involvement in patients with CA, taking into consideration the E/A ratio (2.28±1.02 vs. 1.25±0.52; p=0.027). The complete analysis is illustrated in Table 2.

Ventricular mechanical assessment

Patients with CA had significantly lower EF (58.08 %±6.16 vs. 67.15%±8.09; p=0.012) and global LS (–12.61%±4.32 vs. –17.15%±3.95; p=0.008) (Table 3), the latter at the expense of basal segments (–8.42%±4.24 vs. –12.74%±4.40); p=0.014). No differences were observed for twist, torsion, CS and RS. As a consequence of the differences observed, the GLS

Table 1. General characteristics of the two study groups

	CA (n = 15)	HCM (n = 15)	p
Age (years)	67.11 ± 11.5	58.92 ± 13.97	NS
Male gender (%)	11 (73%)	10 (66%)	NS
Body surface area (m2)	1.94 ± 0.19	1.93 ± 0.27	NS
Systolic BP (mmHg)	116.67 ± 5.1	118.24 ± 3.9	NS
Diastolic BP (mmHg)	68.83 ± 4.1	72.24 ± 7.7	NS
HR (bpm)	76.40 ± 14.34	65.07 ± 5.78	0.010

CA: Cardiac amyloidosis; HCM: Hypertrophic cardiomyopathy; BP: Blood pressure; HR: Heart rate.

Table 2. Two-dimensional echocardiography and Doppler assessments

	CA (n = 15)	HCM (n = 15)	P
LVDD (mm)	44.00 ± 4.76	41.12 ± 4.18	NS
IVS (mm)	16 ± 3.2	20.2 ± 6.2	0.017
PW (mm)	14.67 ± 4.8	12.0 ± 2.01	NS
LAA (cm2)	28 ± 8.2	24.24 ± 5.1	NS
EF (%)	58.08 ± 6.16	67.15 ± 8.09	0.004
Mitral E wave (cm/s)	95.95 ± 19.46	77.17 ± 18.70	0.012
Mitral A wave (cm/s)	51.07 ± 27.96	71.11 ± 19.95	0.027
E/A	2.28 ± 1.02	1.25 ± 0.52	0.03
Mitral deceleration time (ms)	250.43 ± 85.8	233.79 ± 53.2	NS
Tissue Doppler E wave (cm/s)	5.75 ± 0.88	6.0 ± 2.59	0.07
Tissue Doppler A wave (cm/s)	5.05 ± 2.1	7.70 ± 2.03	0.001
E/e´	16.97 ± 4.5	14.59 ± 6.4	NS
MAPSE (mm)	9.83 ± 3.18	15.15 ± 2.51	0.01
Ventricular mass (g/m2)	141.13 ± 46.63	129.71 ± 17.94	NS

CA: Cardiac amyloidosis; HCM: Hypertrophic cardiomyopathy; LVDD: Left ventricular diastolic diameter; IVS: Interventricular septum; PW: Posterior wall; LAA: Left atrial area; EF: Ejection fraction; MAPSE: Mitral annular plane systolic excursion.

× ACS product and the EF/LS ratio were different from a statistical point of view. The GLS × ACS product was lower (316.59±172.59 vs. 519.61±192.64; p=0,007) and the EF/GLS ratio was higher (–5.21±1.86 vs. –4.07±0.82; p=0.03) in CA patients (Figure 1).

DISCUSSION

An interesting finding in the present work is that both the GLS × ACS product and the EF/GLS ratio are easily obtained parameters that allow differentiating CA from HCM.

In general, the various types of CA share the same physiopathological mechanism leading to heart failure, consisting in extracellular matrix expansion and increased myocardial stiffness which produces a restrictive physiology in both ventricles. Amyloid deposit also involves the atria, heart valves and conduction tissue. (7)

However, there are some differences between AL and TTR types of CA. From a histological point of view, amyloid deposits in AL are more diffuse in the endocardium and with arterial and arteriolar involve-

	CA (n = 15)	HCM (n = 15)	P
EF (%)	58.08 ± 6.16	67.15 ± 8.09	0.012
Global longitudinal strain (%)	–12.61 ± 4.32	–17.15 ± 3.95	0.008
Apical longitudinal strain (%)	–18.27 ± 4.64	–21.25 ± 6.69	NS
Medial longitudinal strain (%)	–14.75 ± 4.43	–15.46 ± 4.05	NS
Basal longitudinal strain (%)	–8.42 ± 4.24	–12.74 ± 4.4	0.014
Circumferential strain (%)	–18.17 ± 4.64	–19.85 ± 5.95	NS
Apical circumferential strain (%)	–24.23 ± 7.12	–27.60 ± 6.89	NS
Radial strain (%)	21.55 ± 7.60	23.98 ± 8.95	NS
Basal rotation(°)	–7.38 ± 3.25	–8.46 ± 5.28	NS
Apical rotation(°)	12.88 ± 6.56	15.23 ± 5.55	NS
Twist (°)	20.67 ± 8.48	23.79 ± 8.48	NS
Torsion (°/cm)	2.57 ± 1.14	2.58 ± 1.29	NS
Twist/GLS	1.73 ± 0.96	1.75 ± 0.53	NS
GLS × ACS	316.59 ± 172.59	519.61 ± 192.64	0.007
EF/GLS	–5.21 ± 1.86	–4.07 ± 0.82	0.03

Table 3. Speckle tracking echocardiographic parameters

CA: Cardiac amyloidosis; HCM: Hypertrophic cardiomyopathy; EF: Ejection fraction; GLS: Global longitudinal strain; ACS: Apical circumferential strain.

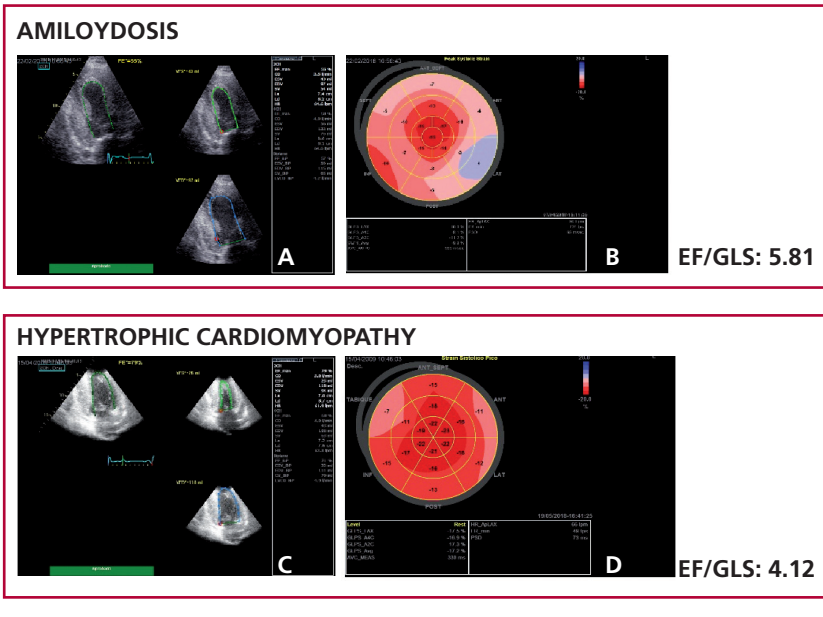

Fig. 1 A. Automated EF. **B.** GLS polar map. **C.** Automated EF. **D** GLS polar map

EF: Ejection fraction; GLS; Global longitudinal strain.

ment. Conversely, amyloid deposits in TTR are more nodular. (8) Also clinically, the AL type produces more severe signs and symptoms of heart failure (HF) despite the ventricular mass is more reduced than in TTR, suggesting that in some cases of AL amyloidosis, direct light chain cardiotoxicity may represent an additional physiopathological mechanism. Deleterious cellular effects produced by different mechanisms, such as free radicals, lysosomal and mitochondrial dysfunction, abnormal calcium homeostasis, arteriolar reactivity, etc. have been found, leading to myocyte apoptosis and necrosis. (9)

Consequently, CA associated to light immunoglobulin chains has a more aggressive course and definitely poorer prognosis.

Transthyretin CA may be a hereditary, dominant autosomal disorder, caused by this protein's mutation (of which there are more than 120 described), or a wild type TTR deposit, formerly known as senile amyloidosis. Its precise prevalence is uncertain, but continuously growing. Its presence has been reported in 13% of HF patients with preserved EF, in 16% of aortic stenoses treated with percutaneous valve replacement and in 5% of HCM. (10)

Magnetic resonance imaging studies have shown that in the case of the AL type, the most frequent late enhancement pattern is a diffuse subendocardium, whereas in TTR CA there is more transmural involvement, which is probably a continuum in the progression of amyloid accumulation from the subendocardium to the subepicardium. In AL CA, the diagnosis is usually earlier due to the severe cardiac or underlying disease symptoms. However, due to the more evasive TTR course, the disease is detected later and in a more advanced deposition phase. In any event, the more the transmural infiltration, the worse the prognosis and the greater the EF involvement. (11)

Similarly to specifying the type of CA, establishing a differential diagnosis between CA and HCM has mainly prognostic and therapeutic relevance.

The study of myocardial deformation by speckle tracking echocardiography consists of a semiautomatic technique whose growing use in the last decades has demonstrated its usefulness in different clinical scenarios, even in cardiomyopathies. It allows the analysis of regional function of all the myocardial segments in different planes and independently of the ultrasound angle because the analysis is based on the two-dimensional image (acoustic marker tracking, i.e. speckle tracking) and not on a Doppler effect. (12)

A study of GLS by 2D echocardiography in 79 patients who, in most cases, also underwent gadolinium MRI, evidenced a base to apex gradient of myocardial involvement. It additionally showed a good correlation between strain and late enhancement, and an apical LS below -14.5% had prognostic value. This gradient might be explained by the greater basal segment wall stress, and hence, more remodeling and apoptosis. In this sense, the greatest wall thickness is found in basal and medial segments. (6, 13) Phelan et al. observed that the ratio between apical strain and the rest of the segments allowed differentiating cardiomyopathy by amyloid deposition from other cardiomyopathies with similar phenotype. A value ≥1 had 93% sensitivity and 82% specificity to diagnose CA. This work also showed a significant difference between AL apical LS (-17.5%±5.2) and TTR apical strain (-14.5%±4.8), though the population size should be taken into account to draw definitive conclusions. (14)

Another interesting study by Baccouche et al. using three-dimensional echocardiography, showed that the analysis of the base-to-apex RS gradient could differentiate CA from HCM. In the case of CA, apical segments presented greater deformation values, whereas HCM and controls showed the opposite. (15)

When we compared deformation in CA and HCM patients, we detected in our patients a marked global decrease in LS at the expense of basal segments, but we did not observe differences in radial and circumferential deformation. This result is in agreement with the gradient of myocardial involvement manifest in this disease: from base to apex and from the subendocardium to the subepicardium. The innermost myocardial fibers are responsible for longitudinal deformation and those situated in the external sectors are more implicated in circumferential deformation. The delayed involvement of subepicardial portions somehow explains the dissociation observed between a greatly decreased GLS in the early stages of the disease and a preserved EF until more advanced stages.

It could be assumed that the early and marked fall of longitudinal deformation would be compensated by the less affected circumferential movement. Consequently, the value of twist within normal parameters observed in these patients would be one of the main mechanisms of EF preservation during prolonged periods of disease progress. In this work, we have not observed significant differences in torsion or twist between the two study groups.

The fact that not all deformation parameters are similarly altered leads us to assume that certain indices forming part of the information in some of them could be useful to express in a reproducible and comprehensible way the degree of ventricular contractile dysfunction and, in turn, orient the diagnosis of the underlying pathology. As an example, the usefulness of the GLS × torsion product has been shown in the risk prediction of myocardial toxicity with anthracyclines (17) and in the degree of HF with reduced EF, demonstrating a good correlation of this index with serum NT-proBNP levels. (18)

In the present work, the deformation product (LS × ACS) evidenced a significant difference due to greater involvement of both parameters in CA, while the EF/GLS ratio was significantly higher in CA due to greater longitudinal deformation.

Recently, Pagourelias et al. published a descriptive study in 40 patients with CA, 40 with HCM and 20

with hypertension. The purpose of the study was to compare the diagnostic precision of several echocardiographic parameters described as associated with myocardial involvement for amyloidosis. The authors concluded that the best echocardiographic parameter for the diagnosis of CA was the EF/GLS ratio, with an area under the ROC curve of 0.95 (95% CI 0.89-0.98) and a cut-off value of 4.1. No parameter resulted useful to differentiate between the two types of CA. (19)

Similarly, in the present study we have observed that the ratio between EF/GLS is useful to discriminate between both entities and we believe that this parameter should be considered and routinely incorporated in the echocardiographic report when there is suspicion of any of these diseases.

We consider that the GLS × ACS product (equivalent to the 3D echocardiographic strain area) is also useful, although its practical implementation is more difficult due to the need of obtaining a good apical minor axis which is not always easy, in contrast with the fast and easy acquisition of the already mentioned parameter.

Limitations

The main limitation is the reduced number of patients included in the study. For the same reason, differences among the various types of CA were not evaluated. Nevertheless, we do not know any study with a large number of patient that has found different strain patterns.

Moreover, we consider that the conclusions of the work are only valid for patients with CA and HCM with EF >50%.

CONCLUSIONS

Patients with CA presented lower LS than those with HCM as a consequence of regional basal strain behavior. Furthermore, lower values were observed for the GLS × ACS product. Finally, the ratio between EF and GLS was significantly higher in patients with amyloidosis.

Conflicts of interest

None declared.

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

REFERENCES

1. Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy Genetics, Pathogenesis, Clinical Manifestations, Diagnosis and Therapy. Circ Res 2017;121:819-37. http://doi.org/gbw6js

2. Popovic Z, Collier P, Griffin B, Thomas JD, Marwick TH. Application of a parametric display of two-dimensional speckle-tracking longitudinal strain to improve the etiologic diagnosis of mild to moderate left ventricular hypertrophy. J Am SocEchocardiogr2014;27:888-95. http://doi.org/f6gxfs

3. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr2004;17:1. http://doi.org/bg2g6q

4. Delgado V, Mollema SA, Ypenburg C, Tops LF, van der Wall EE, Schalij MJ, et al. Relation between global left ventricular longitudinal strain Assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiograph 2008;21:1244-50. http://doi.org/bn87sf

5. Kocabay G, Muraru D, Peluso D, Cucchini U, Mihaila S, Padayattil-Jose S, et al. Mecánica ventricular izquierda normal mediante ecocardiografía speckle tracking bidimensional. Valores de referencia para adultos sanos. Rev Esp. Cardiol 2014;67:651-8. http://doi.org/f2rd8v

6. Ternacle J, Bodez D, Guellich D, Audureau E, Rappeneau S, Lim P, et al. Causes and Consequences of Longitudinal LV Dysfunction Assessed by 2D Strain Echocardiography in Cardiac Amyloidosis. J Am Coll Cardiol Imaging 2016;9:126-38. http://doi.org/cwg3

7. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light Chain) Cardiac Amyloidosis. A Review of Diagnosis and Therapy. J Am Coll Cardiol 2016;68:1323-41. http://doi.org/crss

8. Larsen BT, Mereuta OM, Dasari S, Fayyaz AU, Theis JD, Vrana JA, et al. Correlation of histomorphological pattern of cardiac amyloid deposition with amyloid type: a histological and proteomic analysis of 108 cases. Histopathology 2016;68:648-56. http://doi.org/cwg4

9. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res 2004;94:1008-10. http://doi.org/cbst3f

10. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Eng J Med 2018;379:1007-16. http://doi.org/gd9tj3

11. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015;132:1570-9. http://doi.org/f7vp48ñ

12. D'Andrea A, Radmilovic J, Ballo P, Mele D, Agricola E, Cameli M, et al. Left ventricular hypertrophy or storage disease? The incremental value of speckle tracking strain bull's eye. Echocardiography 2017;34:746-59. http://doi.org/cwg5

13. Jiang L, Huang Y, Hunyor S, dos Remedios CG. Cardiomyocyte apoptosis is associated with increased wall stress in chronic failing left ventricle. Eur Heart J 2003;24: 742-51. http://doi.org/bd6t8b

14. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional, speckle-tracking echocardiography in both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98:1442-8. http://doi.org/f38n6j

15. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, et al. Differentiating Cardiac Amyloidosis and Hypertrophic Cardiomyopathy by Use of Three-Dimensional Speckle Tracking Echocardiography. Echocardiography 2012;29:668-77. http://doi.org/cwg6

16. Mornos C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Can J Physiol Pharmacol 2013;91:601-7. http://doi.org/f45j9b

17. Mornos C, Ruşinaru D, Ionac A, Petrescu L, Cozma D, Pescariu S, et al. Additive value of torsion to global longitudinal left ventricular strain in patients with reduced ejection fraction. Acta Cardiol 2011;66:565-72. http://doi.org/cwg7

18. Pagourelias DE, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis. A Head-to-head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging 2017;10:e005588. http://doi.org/cwg8