Original Article

Diastolic Function Assessment with Doppler Echocardiography and Two-Dimensional Strain

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Summary

Background: **The evaluation of left ventricular (LV) diastolic dysfunction presents a significant number of indeterminate dysfunctions, especially when ejection fraction (EF) is preserved. Global longitudinal strain (GLS) and systolic strain rate (SSR) and early diastolic strain rate (EDSR) may be useful for reclassifying diagnosed patients.**

Objective: **To evaluate, using GLS, SSR and EDSR, patients with diastolic dysfunction, compare with healthy individuals, and determine the additive value of the method.**

Methods: **The study included 149 patients (age 62.2 ± 10.6) with diastolic dysfunction (49.7% grade 1; 15.4% grade 2; 18.1% grade 3 and 16.8% unspecified) and 189 healthy individuals (age 44.5 ± 13.3). Left ventricular (LV) and left atrial (LA) dimensions and function, mitral and tissue Doppler velocities and their ratios, GLS, SSR and EDSR have been determined. Data evaluation using the Kolmogorov-Smirnoff, Kruskal-Wallis tests, multiple regression analysis and area under the ROC curve. Data were considered significant when $p < 0.05$.**

Results: **In diastolic dysfunction, LV dimensions and thickness were increased and EF was lower. Mitral and tissue Doppler revealed abnormalities and LA volume and tricuspid regurgitation velocity were increased. GLS and EDSR were decreased in dysfunction grade 2 and 3 and EDSR was decreased in dysfunction grade 1, correlating better with diastolic dysfunction. The ROC cutoff value for the EDSR was 1.0 s^{-1}.**

Conclusion: **Diastolic dysfunction supplemented with myocardial strain rate seems to add sensitivity and specificity where the diastolic function is indeterminate and may be used for reclassifying these patients. (Arq Bras Cardiol: Imagem cardiovasc. 2017;30(2):46-53)**

Keywords: **Ventricular Dysfunction, Left; Compliance/physiology; Echocardiography, Doppler; Coronary Artery Disease; Echocardiography, Stress.**

Introduction

Diastolic function determines the filling of ventricular cavities by two main mechanisms: an active mechanism, resulting from the contraction of the ascending apical band of the helical myocardium which, by a mechanism of counter-rotation, causes the rapid ventricular filling, and a passive mechanism resulting from myocardial distensibility or compliance.[1] These mechanisms depend on the myocardial functional state and its changes occur early in all conditions that alter the ventricular cavities function. Its determination is therefore very important for the identification of heart failure and clinical stratification of patients.

The evaluation of left ventricular (LV) diastolic function performed by Doppler echocardiography is based on a set of data that can translate the left cavities hemodynamic and load conditions, the ventricular contraction and relaxation dynamics and the ventricular, atrial and pulmonary circulatory system filling pressures.[2] For this reason, many parameters are used together to provide an overview of the dynamics and pressure conditions of the cavities, allowing to classify the diastolic function.

The main parameters are mitral flow, with the measurement of E and A waves and their ratio, mitral valve lateral and septal annulus velocities obtained from tissue Doppler (TD) and their relationship with the mitral E wave, left atrial (LA) indexed volume and tricuspid valve (TRV) regurgitation velocity. Analysis of patients with normal or reduced LV function allows to classify them into normal diastolic function (NDF), diastolic dysfunction with abnormal relaxation, grade 1 (DD-1) with normal LA pressure, diastolic dysfunction with pseudonormal pattern, grade 2 (DD-2) with increased LA pressure and restrictive dysfunction, grade 3 (DD-3). Mitral flow A-wave duration, reverse atrial flow duration and the ratio between the pulmonary veins systolic and diastolic waves, the Valsalva maneuver and isovolumetric relaxation time can be used as supplementary analysis tools. When some of the conditions are not fulfilled, diastolic dysfunction is classified as indeterminate (DD-i).

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Manuscript received September 27, 2016; revised October 13, 2016; accepted February 6, 2017.

DOI: 10.5935/2318-8219.20170012

Although the methods of systolic myocardial strain (global longitudinal strain and systolic strain rate) and diastolic myocardial strain (early diastolic strain rate) are mentioned as supplementary methods, they are not employed in the systematic assessment of diastolic dysfunction due to variability in equipment and analysis software. However, recent agreements have been forged echocardiography societies and the leading manufacturers of equipment and software,[3] resulting in improved standardization of these analyses to obtain more reproducible data.

Objective

The objective of this study is to analyze, using speckle tracking with global longitudinal strain (GLS), systolic strain rate (SSR) and early strain diastolic rate (EDSR), the diastolic function in patients previously classified by Doppler echocardiography, for the purposes of determining the additive value of the method in the stratification of healthy patients and individuals, and use these parameters to evaluate patients with DD-i.

Method

Retrospective analysis was conducted on 338 echocardiography scans, of which 189 were from healthy individuals with mean age 44.5 ± 13.3, 108 women (57%), and 149 from patients with varying degrees of diastolic dysfunction with mean age 62.2 ± 10.6, of which 90 were women (60%). The patients presented the following distribution: 25 with DD-i (16.8%), 74 with DD-1 (49.7%), 23 with DD-2 (15.4%) and 27 with DD-3 (18.1%).

All patients and healthy individuals were in sinus rhythm with no evidence of mitral annulus calcification or pericardial disease. Left ventricular (EF) ejection fraction was normal in most healthy individuals (≥ 54% for females and ≥ 52% for males),[4] but in some cases it was slightly decreased, as well as in patients with DD-i and DD-1. EF was low in most patients with DD-2 and DD-3. The echocardiography scan was of satisfactory quality, allowing the registration of at least 15 LV segments for analysis of myocardial strain.[5]

All healthy patients and individuals had conventional echocardiography scans done to determine LV dimensions (diastolic and systolic diameters, septal and wall thickness), aorta and LA diameter, EF through two-dimensional (2D) echo and indexed LA volume. LV mass index and relative wall thickness were calculated. Doppler was used to determine E wave and mitral A wave velocities and their ratios and, if any, TRV. Tissue Doppler measured e' wave velocity in the mitral valve lateral annulus (e'_{lat}) and the E/e' ratio. Because most of the scans retrospectively analyzed have no record of septal e' wave velocity with tissue Doppler, its ratio with mitral flow E wave or the mean E/e' was not calculated. With 2D echocardiography using speckle tracking, LV GLS was calculated using apical four, two and three-chamber views, as well as SSR and EDSR (Figures 1 and 2).

For the Doppler analysis of diastolic function, the most recent recommendations were followed.[2] DD-1 was considered, as well as abnormal relaxation with normal LA pressure, which had mitral E-wave velocity ≤ 50 cm/s and E/A ≤ 0.8 ratio with e'_{lat} wave ≤ 10 cm and E/e'_{lat} <15. Pseudonormal DD-2 was diagnosed when the E/A ratio was ≤ 0.8 with E wave velocity > 50 cm/s or when the E/A ratio > 0.8 and < 2.0 with signs of increased LA pressure. Restrictive DD-3 was diagnosed when the mitral flow E/A ratio was ≥ 2.0 with signs of increased LA pressure. The parameters that indicate increased LA pressure were: E/e'_{lat} ratio ≥ 15, indexed LA volume > 34 ml/m² and TRV > 2.8 m/s. In cases where the three parameters were evaluated, LA pressure was higher when two of them met the criteria. When only two parameters were evaluated, both positive parameters indicated higher LA

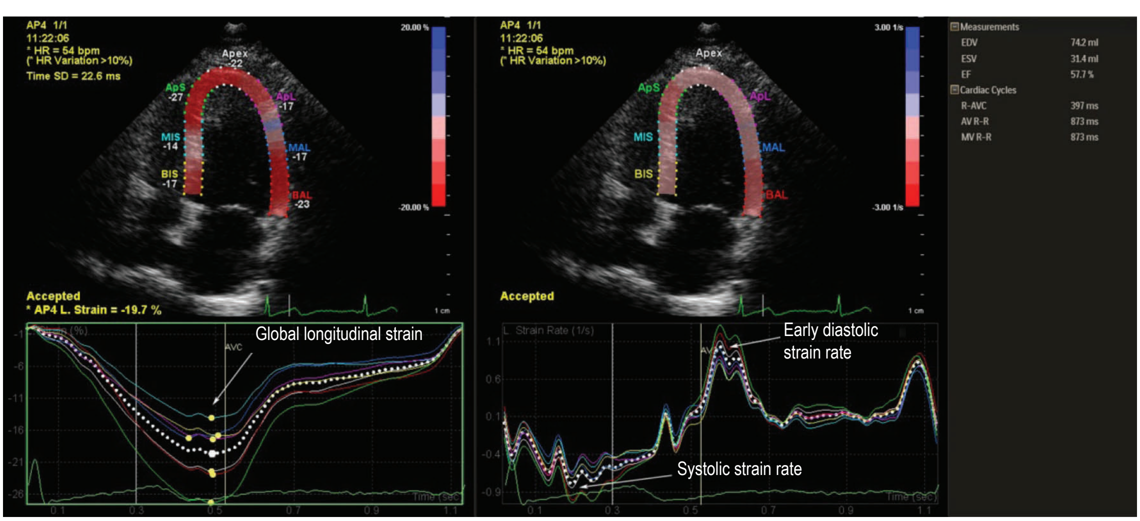

Figure 1 – *Longitudinal strain obtained from the longitudinal apical position and systolic strain rate and early diastolic strain rate obtained from the same position, evaluated with software Qlab 10®.*

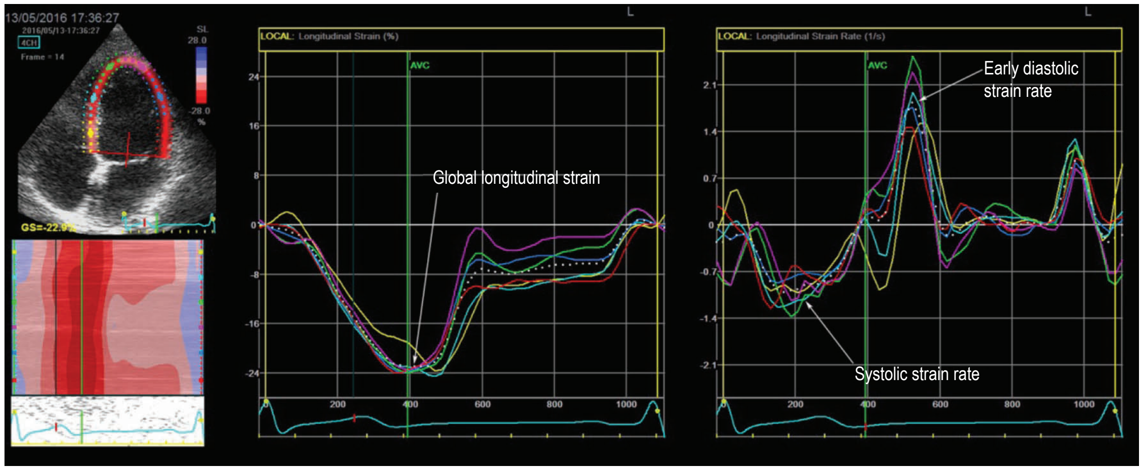

Figure 2 – *Longitudinal strain obtained from the apical four-chamber position and systolic strain rate and early diastolic obtained from the same position, evaluated with software Echopac 201®.*

pressure, both negative parameters indicated normal LA pressure, and one positive and one negative parameter indicated DD-i.

The scans were conducted on the devices HD15, CX50 and IE33 (Philips Healthcare, Andover, MA, USA) and were analyzed using the software Qlab 10® and Vivid T8 (General Electric Healthcare, Horten, Norway), analyzed with Echopac 201®.

Mean and standard deviation of all the data were calculated. Demographic data, dimensions and function parameters were compared using the Kolmogorov-Smirnoff test. Reproducibility of demographics between the groups with diastolic dysfunction and healthy individuals was tested by the intraclass correlation coefficient. To compare the parameters that evaluate diastolic function (mitral Doppler, tissue Doppler, indexed LA volume and TRV) and the myocardial strain parameters (GLS, SSR and EDSR), the Kruskal-Wallis analysis of variance was used to compare the individual values using the Dunn method. Multiple regression analysis was used to determine how the speckle tracking parameters correlated with diastolic dysfunction. The sensitivity and specificity of speckle tracking parameters were determined using the area under the ROC curve. Differences were considered significant when $p < 0.05$.

Results

Demographic data showed significant differences in age and height between healthy individuals and patients with diastolic dysfunction. (Table 1). To test whether the groups were comparable, the intraclass correlation coefficient was used and it showed high reproducibility index ($F = 12.8183$; $ICC = 0.8854$, $p < 0.0001$).

Among individuals with NDF, one hundred sixty-eight showed no abnormalities on the echocardiography scan, thirty-eight were hypertensive and were under clinical treatment and seventeen were compensated diabetics. Five individuals had mild mitral regurgitation with no hemodynamic repercussions; four had been under chemotherapy; four had moderate obesity;[6]three had mild left ventricular hypertrophy; three had atrial septal aneurysm; one had coronary artery disease treated with stent, with no segmental contractility abnormality and one had mitral valve prolapse (fibro-elastic dysplasia) with mild regurgitation.

Among patients with diastolic dysfunction, thirty-four had no echocardiographic abnormalities (except for diastolic abnormalities); thirty-four were hypertensive; sixteen were compensated diabetics; thirty had Chagas' heart disease; fifteen had mild mitral regurgitation or aortic regurgitation; ten had LV hypertrophy; seven had dilated cardiomyopathy; seven had coronary artery disease; five were on chemotherapy; two had scans compatible with myocarditis; two patients had mitral valve prolapse; one had non-compacted cardiomyopathy; one had atrial septal aneurysm and one had restrictive cardiomyopathy.

Compared to healthy individuals, it was found that the LV dimensions, wall thickness and mass index were higher in individuals with diastolic dysfunction, while these had lower EF (Table 2).

The parameters that determined diastolic function, mitral Doppler, tissue Doppler, indexed LA volume and TRV were analyzed in groups classified according to the methodology recommended by the echocardiography societies[2] in NDF, DD-i, DD-1, DD-2 and DD-3. Compared with individuals with FDN, using the Kruskal-Wallis analysis of variance, all diastolic function parameters presented significant difference ($p < 0.0001$). The individual comparison between the parameters of each group using the Dunn's methodology showed a decreasing E wave velocity in groups DD-i and DD-I ($p < 0.05$) with no significant change in groups DD-2 and DD-3. The mitral flow E/A ratio was lower in the groups DD-i, DD-1 and DD-2 ($p < 0.05$) and higher in group DD-3 ($p < 0.05$). The e'_{lat} wave was smaller in groups DD-i, DD-1, DD-2 and DD-3 ($p < 0.05$). There was a higher indexed LA volume in groups DD-2 and DD-3 ($p < 0.05$) and TRV in groups in DD-1, DD-2 and DD-3 ($p < 0.05$) (Table 3).

Table 1 – Demographic data of healthy individuals and patients with diastolic dysfunction

Group	N	Sex	Age (years)	Weight (kg)	Height (cm)	BS (m^2)
Healthy individuals	189	108 females 81 males	44.56 ± 13.35	72.27 ± 15.06	165.83 ± 8.11	1.78 ± 0.21
Diastolic dysfunction	149	90 females 59 males	62.19 ± 10.64	69.43 ± 13.94	161.82 ± 9.94	1.71 ± 0.22
Statistical analysis			P < 0.01	Ns	P < 0.01	ns

Values expressed as mean and standard deviation. BS: body surface.

Table 2 – LV dimensions, body mass index, indexed LA volume and FE in healthy individuals and patients with diastolic dysfunction

Group	LVDd (mm) (mm)	LVSd (mm)	DST (mm)	DWT (mm)	Mass index (g/m^2)	Relative Thickness	EF (%)
Healthy individuals	47.14 ± 4.52	29.74 ± 3.14	7.95 ± 1.14	7.76 ± 1.10	71.18 ± 16.90	0.33 ± 0.04	56.99 ± 3.58
Diastolic dysfunction	52.01 ± 9.54	35.85 ± 11.64	8.46 ± 1.45	8.30 ± 1.38	89.98 ± 31.64	0.33 ± 0.08	51.03 ± 12.33
Statistical analysis	p < 0.01	p < 0.01	p < 0.05	p < 0.05	p < 0.01	ns	p < 0.01

LVDd: left ventricular diastolic diameter; LVSd: left ventricular systolic diameter; DST: diastolic septal thickness; SST: systolic septal thickness; EF: ejection fraction. Values expressed as mean and standard deviation.

LV SSR gradually and significantly decreased as the diastolic dysfunction degree increased. EDSR significantly decreased in all groups with diastolic dysfunction when compared to the healthy group, but there was no difference between the groups with dysfunction (Table 4).

The multiple correlation coefficient, used to compare the diastolic strain parameters among healthy individuals and different degrees of diastolic dysfunction, showed a global correlation with r^2 of 0.65 and $p < 0.0001$. In the evaluation of partial factors, GLS showed no significant correlation ($t = 1.7892$ and $p = 0.076$), SSR proved significant ($t = 2.2687$ and $p = 0.025$) and EDSR was highly significant ($t = -8.115$ and $p < 0.0001$).

Determination of sensitivity and specificity by the area under the ROC curve revealed the following data: for the GLS, the cutoff value was -17%. Lower values would indicate LV diastolic dysfunction with 44.35% sensitivity and 97.35% specificity. For the SSR, the cutoff value was -0.94 s^{-1}. Lower values would indicate 72.67% sensitivity and 91.51% specificity. For the EDSR, the cutoff value was 1.0 s^{-1}. Lower values would indicate diastolic dysfunction with 83.9% sensitivity and 100% specificity (Chart 1).

Mean values of strain parameters (GLS, SSR and EDSR) in healthy individuals with NDF were normal. However, five cases (2.6%) showed isolated GLS <-17% and nine (4.8%) SSR <- 0.94 s^{-1}. No healthy individual presented EDSR < 1.0 s^{-1}. Among patients with DD-i, mean GLS and SSR were normal, but three (12%) had GLS < -17% and six (24%), SSR < -0.94 s^{-1}. The mean EDSR value was low and in ten patients (40%), EDSR was < 1.0 s^{-1}. In patients with DD-1, mean GLS values were normal and twelve patients (18%) had GLS < -17%, ten patients (13.5%), SSR < -0.94 s^{-1} and seventeen (23%), EDSR < 1.0 s^{-1}. In patients with DD-2, mean GLS, SSR and EDSR were lower and fifteen (65%) had GLS < -17%, sixteen (69.5%) had EDSR < -0.94 s^{-1} and twenty-one (91%) had EDSR < 1.0 s^{-1}. Among patients with DD-3, the mean values of all strain parameters were lower and GLS was < 17% and SSR was < -0.94 s^{-1} on all patients (100%). EDSR was < 1.0 s^{-1} on twenty-six patients (96%) (Table 4).

Using the area under the ROC curve cutoff value for EDSR < 1.0 s^{-1} (AUC 0.95, p <0.0001) in patients with DD-i, ten of the twenty-five patients (40%) could be ranked as DD-1 with no increased LA pressure, twelve (48%) as with NDF, two (8%) would remain as DD-i and one patient (4%) would be considered DD-2 (Table 5).

Discussion

Detection of diastolic dysfunction is of fundamental importance for stratification, drug treatment and follow-up of patients, with important prognostic implications, since diastolic dysfunction, even in cases with preserved systolic function, is associated with increased morbidity and mortality, as seen in cases of heart failure with systolic dysfunction.[7]

Conventional analysis parameters, with mitral flow velocities, mitral annulus tissue Doppler, indexed LA volume and TRV, possibly associated with additional maneuvers or measurements, as recommended by the guidelines, classify some patients as DD-i, producing a degree of confusion, mainly for the clinical cardiologists who receive the test results and need to set a course for their patients. Although there is no clear picture of the impact that this classification would produce on the evaluation of patients, we believe that about 10–20% of DD-1 diagnoses delivered according to the old guideline would now be considered indeterminate. Further tools able to reclassify these patients would be of great clinical importance.

Table 3 - Mitral Doppler, tissue Doppler, indexed left atrial (LA) volume and tricuspid regurgitation velocity (TRV) in healthy individuals and patients with indeterminate diastolic dysfunction (DD-I), grade 1 (DD-1), grade 2 (DD-2) and grade 3 (DD-3)

Group		E mitral velocity (cm/s)	E/A ratio	e' lateral velocity (cm/s)	E/e' ratio	Indexed LA volume (ml/m²)	TRV (m/s)
Healthy individuals	M SD	80.94 13.78	1.38 0.44	14.68 3.39	5.76 1.20	20.15 5.06	2.42 0.18
DD-i	M SD	64.39 11.78	0.84 0.19	9.38 1.06	7.09 1.67	22.49 11.08	2,67 0.25
DD-1	M SD	38.03 2.42	0.64 0.11	8.50 1.28	4.61 0,93	20.78 7.68	2.72 0,30
DD-2	M SD	79.37 18.52	0.99 0.25	5.45 1.20	14.56 0.97	36.49 12.61	3.10 0.35
DD-3	M SD	96.49 29.45	2.77 1.00	5.96 1.62	16.54 3.93	54.02 18.90	3.45 0.56
Analysis of variance	M SD	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001

M: median; SD: standard deviation; p: p significance.

Table 4 – Myocardial strain in healthy individuals with normal diastolic function (NDF) and patients with indeterminate diastolic dysfunction (DD-i), grade 1 (DD-1), grade 2 (DD-2) and grade 3 (DD-3)

Group	GLS (%)	SSR (s^{-1})	EDSR (s^{-1})
NDF	-20.92 ± 2.54	-1.14 ± 0.15	1.40 ± 0.22
DD-i	-19.72 ± 2.76	-0.99 ± 0.15	0.96 ± 0.30
DD-1	-19.07 ± 2.77	-0.97 ± 0.17	0.87 ± 0.29
DD-2	-15.96 ± 4.41	-0.81 ± 0.20	0.79 ± 0.25
DD-3	-9.52 ± 2.84	-0.58 ± 0.16	0.67 ± 0.25
Multivariate analysis	t = 1.7892 p = 0.076	t = 2.2687 p = 0.025	t = -8.115 p < 0.0001

Values expressed as mean and standard deviation. GLS: LV global longitudinal strain; SSR: LV systolic strain rate; EDSR: LV early diastolic strain rate; t: t test value; p: p significance.

The methods of myocardial strain, GLS, SSR and EDSR, as mentioned in the supplementary recommendations after consensus with the industry[3] must provide more robust and comparable results. These parameters may be important aids to detect diastolic dysfunction, especially early diastolic strain rate (EDSR), measured at the e′ wave level (Figures 1 and 2). The strain rate is the time over which the strain occurs, measuring, in general terms, the efficiency of this strain, be it systolic or diastolic.[8] Myocardial strain parameters gradually change in diastolic dysfunction.[9-11] GLS is lower in diastolic dysfunction in patients with preserved systolic function with decreased exercising capacity.[12] In this study, we observed a lower GLS in DD-2 and DD-3, when there was an increase in LA pressure (Chart 2A). The SSR was also more sharply decreased in DD-2 and DD-3 (Chart 2B). EDSR was smaller in all forms of diastolic dysfunction (Chart 2C).

As the cutoff value obtained through the areas under the ROC curves for EDSR < 1.0 s^{-1} (AUC 0.95, p <0.0001) would indicate diastolic dysfunction, with good sensitivity and high specificity, this strain parameter could be used to reclassify cases of DD-i. By doing so, ten of the twenty-five patients with DD-i (40%) would be classified as DD-1 with no LA pressure increase.

Limitations

The main limitations are due to the methodology employed to separate patients into types of diastolic dysfunction. Due to the uncertainty degree provided by the analysis with mitral flow Doppler and tissue Doppler, a significant number of patients is classified as with indeterminate diastolic dysfunction. The most severe diastolic dysfunctions are more easily diagnosed, as they show signs of increased LA pressure (E/e′ > 15, indexed LA volume > 34 ml/m² and tricuspid regurgitation velocity > 2.8 m/s).

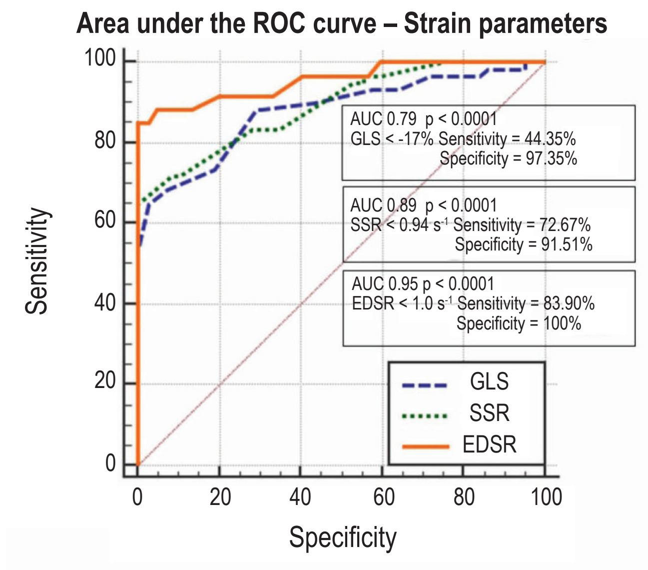

Chart 1 – *Area under the ROC curve of myocardial strain parameters between healthy individuals and patients with varying degrees of diastolic dysfunction.*

Table 5 – Reclassification of patients with indeterminate diastolic dysfunction (DD-i) analyzed using strain parameters in normal diastolic function (NDF), diastolic dysfunction grade 1 (DD-1) and diastolic dysfunction grade 2 (DD-2)

	Age (years)	EF (%)	LAVol (ml/m²)	E wave (cm/s)	E/A ratio	E' wave (cm/s)	E/e' ratio	GLS (%)	SSR (s-1)	EDSR (s-1)	TRV (m/s)
NDF	57.00 6.63	58.50 2.81	19.81 4.96	65.53 12.45	0.78 0.08	9.63 1.00	6.89 1.56	- 20.50 2.07	- 1.11 0.07	1.13 0.12	2.40 0.10
DD-i	65.33 10.69	56.67 3.21	18.69 2.94	58.53 5.10	0.80 0.06	9.09 1.30	6.51 0.91	- 18.67 2,52	-1.03 0.06	1.13 0.50	3.00 0.20
DD-1	67.20 8.27	57.70 4.14	26.85 16.12	68.11 15.96	0.77 0.05	9.17 1.11	7.51 1.97	- 19.10 3.48	-0.90 0.12	0.77 0.11	2.76 0.19
DD-2	66.00	51.00	46.00	97.80	1.08	8.43	11.60	- 16.00	-0.80	0.60	3.00

EF: ejection fraction; LAVol: LA indexed volume; E wave: mitral E wave velocity; E/A ratio: ratio of mitral E and A waves; e' wave: lateral mitral annulus e' wave velocity; E/e' ratio: ratio of mitral E wave and e' tissue wave; GLS: LV global longitudinal strain; SSR: LV systolic strain rate; EDSR: LV early diastolic strain rate; TRV: tricuspid regurgitation velocity.

The parameters that assess myocardial strain are easily accessible. Only apical views are enough, but the results depend on the quality of two-dimensional images and heart rate, as an adequate frame acquisition speed is required and it may be impaired by tachycardia.by The mean measurements obtained in the three views should be calculated.

The tests were performed on devices of two different manufacturers and by three operators, but there were no significant differences in the test results. We conducted another study to test compatibility,[13] evaluating healthy patients and individuals, obtaining a good correlation between the devices (Pearson correlation, r = 0.89 for GLS and SSR) and good interobserver correlation (Pearson, r = 0.81).

Conclusion

Echocardiographic diagnosis of diastolic function using mitral flow Doppler and mitral annulus tissue Doppler associated with indexed LA volume and tricuspid regurgitation velocity may have ambiguous results in some patients with mild dysfunction and preserved systolic function. These cases are categorized as indeterminate diastolic dysfunction. The methods that assess myocardial strain, especially early diastolic strain rate, seem to add sensitivity and especially specificity to the conventional method, allowing for reclassifying some patients into diastolic dysfunction grade 1 or grade 2. Nevertheless, more extensive studies are needed to further cement the method, which seems to be quite useful to fill the gap left by conventional Doppler. It will be greatly important to combine these findings with the results of clinical treatment in reclassified patients and in patients with diastolic dysfunction to determine the additive value of strain parameters, treatment effectiveness and improvement of dysfunction parameters.

Acknowledgements

To Dr. José Sebastião de Abreu and Dr. André Cerqueira de Almeida for their invaluable assistance in reviewing the manuscript. Their comments and suggestions were of fundamental importance to the results and conclusions of the study.

Authors' contributions

Research creation and design: Del Castillo JM; Data acquisition: Del Castillo JM, Albuquerque ES, Silveira CAM; Data analysis and interpretation: Del Castillo JM; Statistical analysis: Del Castillo JM; Manuscript drafting: Del Castillo JM; Critical revision of the manuscript as for important intellectual content: Del Castillo JM, Albuquerque ES, Silveira CAM, Lamprea DP, Sena ADM.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

Sources of Funding

This study had no external funding sources.

Academic Association

This study is not associated with any graduate program.

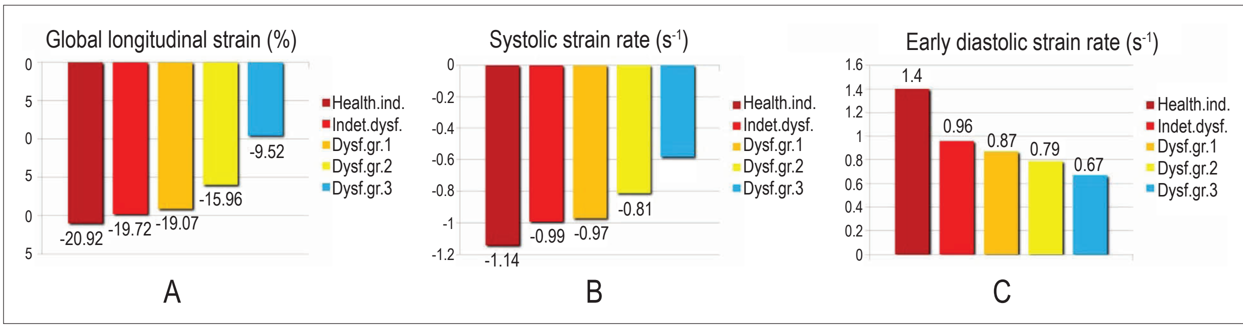

Chart 2 – *Myocardial strain parameters distributed among healthy individuals and patients with LV diastolic dysfunction. A: global longitudinal strain; B: systolic strain rate; C: early diastolic strain rate; Health.ind: healthy individuals; Indet.Dysf.: indeterminate diastolic dysfunction; Dysf.Grad. 1 to 3: diastolic dysfunction grade 1 to 3.*

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