Original article

Left Atrial Reserve Function in Assessing Indeterminate Diastolic Function

Função de Reserva do Átrio Esquerdo na Avaliação da Função Diastólica Indeterminada

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Abstract

Background: Elevation of left ventricular filling pressures secondary to diastolic dysfunction plays a central role in the pathophysiology of heart failure. However, international guidelines still fail to diagnose diastolic dysfunction in some cases.

Objective: To evaluate left atrial reservoir function in indeterminate diastolic function

Method: Observational study with individuals in sinus rhythm and preserved left ventricular ejection fraction, submitted to echocardiogram and divided into three groups according to the combined analysis of E/e´ ratio and indexed left atrium volume: Group 1, if normal left ventricular filling pressures; Group 2, if increased left ventricular filling pressures and Group 3, if indeterminate left ventricular filling pressures. Two-dimensional speckle tracking was used to measure peak left atrial strain (LAS). Analysis of variance, Student's t test and receiver-operator curve (ROC) were used in the statistical analysis.

Results: We included 58 patients who had 61 ± 14 years old, 57% of whom were women, and had average left ventricular ejection fraction 62 ± 7%. Groups 2 and 3 had lower LAS than Group 1 (20 ± 5% versus 22 ± 6% versus 30 ± 8%, respectively, p = 0.004), but did not differ between them (p = 0.93). LAS was a good predictor of elevated left ventricular filling pressures (p = 0.026; area under the curve = 0.80), obtaining sensitivity of 60% and specificity of 80% with a cut-off value ≤ 20%.

Conclusion: The findings suggest that the left atrial reservoir function of individuals with indeterminate diastolic function is similar to that of individuals with advanced diastolic dysfunction, rendering LAS the potential to support the reclassification of indeterminate diastolic function.

Keywords: Diastolic function; Left atrium; Heart failure; Echocardiography.

Resumo

Fundamento: *A elevação das pressões de enchimento secundária à disfunção diastólica do ventrículo esquerdo ocupa papel central na fisiopatologia da insuficiência cardíaca. Mesmo assim, as diretrizes internacionais falham em detectar a disfunção diastólica em uma parte dos casos.*

Objetivo: *Avaliar a função de reserva do átrio esquerdo, estimada pelo strain longitudinal de pico do átrio esquerdo, nos casos de função diastólica indeterminada.*

Método: *Estudo observacional com indivíduos em ritmo sinusal e fração de ejeção do ventrículo esquerdo preservada, submetidos ao ecocardiograma e divididos em três grupos conforme a análise conjunta da relação E/e´ e do volume de átrio esquerdo indexado: Grupo 1, se pressões de enchimento normais; Grupo 2, se pressões de enchimento elevadas e Grupo 3, se pressões de enchimento indeterminadas. Speckle tracking bidimensional foi empregado para medir o strain longitudinal de pico do átrio esquerdo. Análise de variância, teste t Student e curva receptor-operador (ROC) foram empregados na análise estatística.*

Resultado: *Foram incluídos 58 pacientes, com 61 ± 14 anos, sendo 57% mulheres, com fração de ejeção do ventrículo esquerdo de 62 ± 7%. Os Grupos 2 e 3 tiveram strain longitudinal de pico do átrio esquerdo menor que o Grupo 1 (20 ± 5% versus 22 ± 6% versus 30 ± 8%, respectivamente, p=0,004), mas não diferiram entre si (p=0,93). O strain longitudinal de pico do átrio esquerdo foi preditor de pressões de enchimento elevadas (p=0,026, área sob a curva=0,80), obtendo-se sensibilidade de 60% e especificidade de 80% com valor de corte ≤ 20%.*

Conclusão: *A função de reserva do átrio esquerdo dos indivíduos com função diastólica indeterminada é similar à dos indivíduos com disfunção diastólica avançada, conferindo ao strain longitudinal de pico do átrio esquerdo o potencial de auxiliar na reclassificação da função diastólica indeterminada.*

Palavras-chave: *Função Diastólica; Átrios do coração; Insuficiência cardíaca; Ecocardiografia.*

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Introduction

Increased filling pressures (FP) secondary to left ventricular (LV) diastolic dysfunction (DD) is the main hemodynamic determinant of the onset of heart failure (HF).[1] Thus, in cardiology practice, it is essential to determine whether there is underlying DD in patients with dyspnea of unknown origin and/or suspected HF, especially in those with a preserved ejection fraction (EF). Echocardiography provides essential noninvasive information about cardiac structure, function, and hemodynamics and should be performed on all patients with clinically suspected HF.

The American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/ EACVI) guideline recommends that the noninvasive analysis of increased FP adopt an integrated approach to the following echocardiographic parameters: E/e' ratio (ratio between early diastolic mitral inflow velocity on pulsed Doppler (E) and early diastolic mitral annular velocity on tissue Doppler [e']),tricuspid regurgitation velocity (TRV), and left atrial volume indexed (LAVI) for body surface area.[2] When more than half of the parameters are changed, FP is considered abnormal. However, the definitive criteria are not completely met in all cases; thus, DD presence and/or degree can be indeterminate.[2] This often occurs when it is impossible to determine the tricuspid regurgitation curve (due to the absence of regurgitation or inadequate tracing) and the other two parameters are conflicting.

The left atrium (LA) plays an important physiological role in LV filling dynamics, improving reserve function and atrial conduit and contraction. A decreased reserve function prior to chamber dilation can occur in the early stages of LVDD, when only the LV end-diastolic pressure is elevated and this increase is transmitted to the LA.[3] Two-dimensional speckle tracking echocardiography can measure LA deformation in the reserve phase, like the peak LA longitudinal strain (LAS), for example, which has the potential to be a subclinical DD marker.[1,3]

This study compared LAS in cases of indeterminate diastolic function versus cases with a normal or increased FP.

Methods

This cross-sectional observational study included a random sample of patients in sinus rhythm with an LVEF ≥ 50% who were referred to the echocardiography service by their attending physician for testing. The exclusion criteria were significant valvular heart disease (moderate- or severe-degree regurgitation, stenosis degree [if any], and presence of prosthetic valve), congenital heart disease, or pericardiopathy. Basic demographic and clinical data were collected from a form completed by all patients before the test. All patients signed a consent form.

The participants underwent complete transthoracic echocardiography using a commercially available echocardiography machine (EPIQ7; Philips Medical Systems). LVEF was calculated of part of the sample by the two-dimensional Simpson's method in all patients and the three-dimensional method. Myocardial hypertrophy was diagnosed when the LV mass index was >95 g/m² in women or >115 g/m² in men. Diastolic function analysis included the following parameters: mitral flow E and A waves on pulsatile Doppler, E/A ratio, e' velocity on tissue Doppler, E/e' ratio, TRV, and LAVI. The cutoff values used to distinguish the presence or absence of increased FP were E/e' ratio ≥ 15 (mean of the septal and lateral annulus) and LAVI > 34 mL/m².[2] The cases were then divided into three groups with FP defined according to the combined analysis of these two parameters. Group 1, normal FP with normal E/e' and LAVI ratios; Group 2, high FP with increased E/e' and LAVI ratios; and Group 3, indeterminate FP with one normal and one increased parameter.

Values of TRV > 2.8 m/s were excluded from this analysis for often being unfeasible (absent or inadequate tricuspid regurgitation curve) in clinical practice and resulting in indeterminate diastolic function. Concomitantly, a traditional secondary LV diastolic function analysis was performed according to the specific algorithms recommended in the ASE/ EACVI guideline (including the E/e', LAVI, and TRV ratios).[2] DD was classified in ascending order of severity as: grade I, decreased ventricular relaxation without increased FP; grade II, decreased relaxation with increased FP; and grade III, highly increased FP with restrictive mitral flow pattern.

Two-dimensional speckle tracking echocardiography was used to measure the LAS using a zoomed-in apical four-chamber view LA image and analysis by a commercially available semi-automatic software (Cardiac Motion Quantification, QLAB 9.0; Philips Medical Systems). The start of the QRS complex was used as a zero-reference point and resulted in a positive strain by convention (Figure 1).[4] The frame rate used was 50–70 frames per second. The atrial endocardial border was identified manually by clicking on three points for the software to generate the region of interest. Subsequently, the images were manually optimized by exclusion of the pulmonary veins and the left atrial appendage. The region of interest was adjusted to include the atrial wall (generally 3 mm). Visual inspection of the moving image ensured myocardial tracking adequacy. The LA was divided into six segments, and the mean peak positive LAS (maximum) of the segments, which represents the reserve function, was recorded.[4] The LV LAS was calculated from the analysis of the three usual apical sections.

Continuous variables are expressed as mean and standard deviation and categorical variables as percentages and absolute numbers. The statistical analyses were performed using SPSS Statistics 22 software (IBM) and included analysis of variance, Student's t-test, chi-square test, receiver operating characteristic curve, and multivariate logistic regression analysis. Statistical significance was defined as values of $p < 0.05$.

Results

A total of 58 patients with a mean age of 61 ± 14 years were included; 57% were women, 50% hypertensive, 22% diabetic, 12% smokers, and 36% dyslipidemic. Table 1 shows the main demographic and clinical characteristics of the study population. The mean two-dimensional EF was 62 ± 7%. Myocardial hypertrophy was found in 21% of the sample (12 patients, of

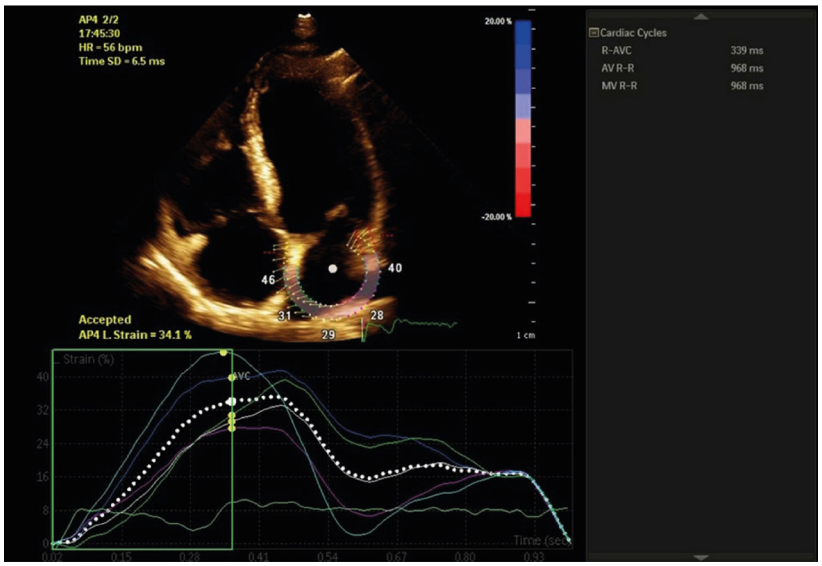


Figure 1 – *Left atrium in the apical four-chamber view with atrial deformation analysis performed by semi-automatic software. The beginning of the QRS complex was used as a zero-reference point by convention, resulting in a positive strain.*

whom eight had concentric and four had eccentric hypertrophy). The mean LA dimension was 34 ± 5 mm, while the mean LAVI was 28 ± 7 mL/m². Table 2 shows the main echocardiographic characteristics of the studied population. The patients with an increased FP were older (74 ± 8 *vs.* 59 ± 14 years; p = 0.023) and had a higher proportion of arterial hypertension (100% *vs.* 45%; p = 0.026) than those with a normal FP. There were no differences in sex, body mass index, LVEF, or LV global LAS.

The combined analysis of the E/e' and LAVI ratios showed that the FP was normal in 66% (Group 1), increased in 5% (Group 2), and indeterminate in 29% (Group 3) of the studied population. Groups 2 and 3 had lower mean LAS strains than Group 1 (20 ± 5% *vs.* 22 ± 6% *vs.* 30 ± 8%, respectively; p = 0.004), but the values did not differ from one another (p = 0.93). Figure 2 compares the mean LAS between groups. LAS was a predictor of a high FP (p = 0.026, area under the curve [AUC], 0.80) with 60% sensitivity, 80% specificity, and a cutoff value of ≤20% (Figure 3). Age-adjusted multivariate logistic regression analysis and LAVI showed that LAS was an independent predictor of an increased FP according to the criteria.

According to the ASE/EACVI guideline, DD was diagnosed in 55% of the patients (46% grade I, 9% grade II). There was a gradual LAS decrease with increased DD degree (normal = 35 ± 6%; degree I = 23 ± 7%; degree II = 18 ± 6%; p < 0.001). It was not possible to obtain a tricuspid reflux curve to measure TRV in 14 patients (24%); the other patients had a mean TRV of 2.4 ± 0.4 m/s.

Discussion

The findings of this study suggest that the LA reserve function (estimated by LAS) in patients with indeterminate diastolic function is similar to that of patients with DD and that LAS progressively decreases with DD severity.

Table 1 - Main demographic and clinical characteristics of the study population.

Variable	n=58
Age, years	61±14
Male sex	43 (25)
Body mass index	26±37
Systolic blood pressure, mmHg	134 ± 24
Diastolic blood pressure, mmHg	79 ± 19
Heart rate, bpm	68 ± 11
Dyspnea	28 (16)
Arterial hypertension	50 (29)
Diabetes	22 (13)
Dyslipidemia	36 (21)
Smoking	12 (7)
Sedentary lifestyle	38 (22)
Previous myocardial infarction	7 (4)
Angina pectoris	7 (4)
Family history of coronary artery disease	21 (12)
ARB	31 (18)
ACEI	9 (5)
Calcium channel blocker	9 (5)
Beta-blocker	34 (20)
Diuretic	17 (10)
Statin	36 (21)
Acetylsalicylic acid	26 (15)

Results expressed as mean ± standard deviation or n (%). ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Several studies and clinical experiences indicate that the noninvasive LV FP estimation provided by echocardiography is useful in clinical decision-making, but some problems persist regarding sensitivity and positive predictive value, notably in patients with a preserved EF (>50%) and in some specific clinical conditions.[1] The ASE/EACVI guideline, based on a tripartite approach (E/e' ratio, LAVI, and TRV), increases the specificity of increased FP findings but fails to detect DD in approximately 8–15% of cases.[5-7] Much of the problem lies in the fact that some patients have no tricuspid regurgitation and that an appropriate TRV measurement is not always feasible in some who do. It may not be possible to obtain an adequate Doppler signal from the tricuspid regurgitation curve in up to 40% of patients.[8] In this situation, an essential portion of the algorithm becomes absent and, if the other two parameters (E/e' and LAVI) are conflicting, the diastolic function becomes indeterminate, making it impossible to determinate the FP.

Table 2 - Main echocardiographic characteristics of the studied population.

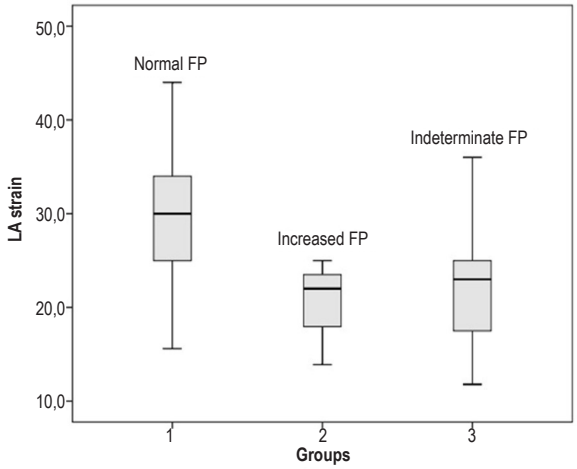
Variable	n = 58
Percentage of two-dimensional EF	62 ± 6
Percentage of three-dimensional EF*	61 ± 8
LVDD, mm	48 ± 5
LV mass index, g/m²	88 ± 26
LAD, mm	34 ± 5
LAVI, mL/m²	28 ± 7
E wave, cm/s	78 ± 17
A wave, cm/s	80 ± 24
E/A ratio	1.0 ± 0.4
Mean e', cm/s	7.6 ± 2.6
E/e' ratio	12 ± 3
TRV, m/s	2.4 ± 0.4
Percentage of LV GLS†	-18.9 ± 1.9
Percentage of LAS in the reserve phase	26.2 ± 8.1

*Results expressed as mean ± standard deviation. *n = 27; †n = 44; A, mitral flow velocity at atrial contraction; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular velocity; EF, ejection fraction; GLS, global longitudinal strain; LAD, left atrium dimension; LAS, left atrial strain; LAVI, left atrial volume index; LV, left ventricle; LVDD, left ventricular diastolic dimension; TRV, tricuspid regurgitation velocity.*

In the past decade, pioneering studies on LA deformation using the speckle tracking technique proposed that a decreased reserve function estimated by LAS measurement would be a subclinical DD marker.[3] Within this scope, Singh et al. evidenced the relationship between DD severity and LAS. The authors demonstrated that LAS has an inverse correlation with DD severity and the New York Heart Association functional class.[5] The best diagnostic performance seems to be achieved with a cutoff value of <19%, which separates grade III DD from the other grades.[5] A subsequent invasive study by the same group showed that an LAS < 20% is more accurate than the ASE/EACVI guideline algorithm for predicting a high FP.[9] This study, despite using a different group stratification method and not considering invasive hemodynamic data, also found an LAS cutoff value of <20% as a predictor of high FP.

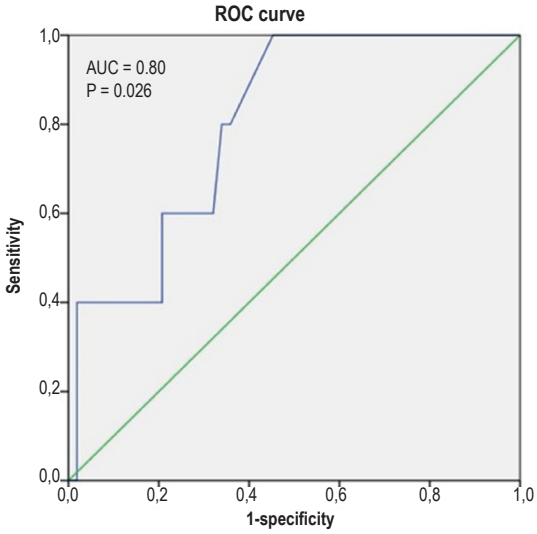
It is worth mentioning that the definition of normal LAS values remains open since the LA reserve function is influenced by several factors, such as age, LV systolic function, one- or two-dimension LA image acquisition, and software version used. A meta-analysis by Pathan et al. reported that the mean normal LAS value was 39% with a minimum expected value of 27.6%.[10] In contrast, the NORRE study reported a mean normal LAS value of 42% with a minimum expected value of 26%.[11] Consequently, the definitive LAS cutoff value to be used as a high FP marker has not yet been fully defined.

LA remodeling and dysfunction secondary to an increased LV pressure is associated with more clinical symptoms, lower exercise capacity, and adverse clinical outcomes. Morris et al. demonstrated that LAS was a predictor of hospitalization and mortality in HF patients with a preserved EF, highlighting the potential clinical application of echocardiographic determination of atrial reserve function.[12] This study showed that LA reserve function may be decreased in indeterminate



FP, filling pressure; LA, left atrium.

Figure 2 – *Intergroup comparison of the mean peak LA longitudinal strain.*



AUC, area under the curve; ROC, receiver operating characteristic curve .

Figure 3 – *ROC of peak LA longitudinal strain used to detect high filling pressure.*

diastolic function in a way similar to that found in patients with severe DD, which should make cardiologists establish more rigorous clinical follow-up for these patients.

This study has limitations that should be highlighted. First, it was a small study that included a select group of outpatients without arrhythmia, LV systolic dysfunction, heart valve disease, or pericardial disorders. Second, the presence of an increased FP was not confirmed through an invasive assessment. Third, the LAS cutoff values presented here cannot be generalized since different commercial brands of echocardiography machines present significantly varied estimates for the same patient. In addition, the semi-automatic software detection of myocardial deformation used in this study, originally designed for LV use, was adapted to assess the LA.

Conclusion

These study findings suggest that the LA reserve function of patients with indeterminate diastolic function is similar to that of patients with severe DD. In practical terms, LAS shows great potential to improve the reclassification of indeterminate diastolic function cases obtained using current algorithms. Larger-scale prospective studies are needed to validate normal LAS values in the general population and cutoff values indicative of increased LV diastolic pressure in populations with cardiovascular diseases before this technique becomes part of the clinical evaluation of DD. It seems reasonable to assume that LAS will be incorporated into future guidelines to decrease indeterminate diastolic function rates.

Authors' contributions

Research creation and design: Barberato SH; Data acquisition: Barberato SH, Borsoi R; Data analysis and interpretation: Barberato SH, Borsoi R; Statistical analysis: Barberato SH; Obtaining financing: Barberato SH; Manuscript writing: Barberato SH; Critical revision of the manuscript for important intellectual content: Barberato SH, Borsoi R.

Conflict of interest

The authors have declared that they have no conflict of interest.

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