



Decreased reservoir function of the left atrium is associated with pre-clinical diastolic dysfunction, analysis by sex. A 2D speckle tracking study

La disminución de la función reservoria de la aurícula izquierda se asocia con disfunción diastólica preclínica, análisis por sexo. Un estudio de rastreo de manchas (2D-STE)

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ABSTRACT. Heart failure with preserved ejection fraction, characterized by the presence of diastolic dysfunction, affects more women than men. A decrease in the phasic function of the left atrium has been found in individuals with diastolic dysfunction in pre-clinical stages. It is unknown if such deterioration is greater in women. **Objective:** To determine if there are differences in the phasic function of the left atrium obtained by «strain» analysis by speckle-tracking technique (2D-STE), in individuals with preclinical diastolic dysfunction in relation to sex. **Material and methods:** This is an observational, cross-sectional and analytical study which included 53 subjects of both sexes (62% men) with ejection fraction greater than 50% in stage I of NYHA. **Results:** In individuals with diastolic dysfunction, left atrial reservoir function determined by 2D-STE, was lower compared with individuals with normal diastolic function (37.6% vs 30.3%, $p<0.0001$). However, no significant differences were found between men and women. **Conclusion:** The decrease in reservoir function was similar for individuals of both sexes, in preclinical stages of diastolic dysfunction. Sex does not seem to be a determining factor for the development of alterations in left atrial function, at least in the reservoir phase.

Key words: Diastolic dysfunction, left atrial phasic function, left atrial strain, 2D-STE.

RESUMEN. La insuficiencia cardiaca con fracción de expulsión preservada, caracterizada por la presencia de disfunción diastólica afecta más a mujeres que a hombres. Se ha encontrado disminución en la función fásica de la aurícula izquierda en individuos con disfunción diastólica en etapas preclínicas. Se desconoce si tal deterioro es mayor en mujeres. **Objetivo:** Determinar si existen diferencias en la función fásica de la aurícula izquierda obtenida por análisis de esfuerzo (strain) por técnica de rastreo de manchas (ECO 2D-STE), en individuos con disfunción diastólica preclínica en relación al sexo. **Material y métodos:** Se trata de un estudio observacional, transversal y analítico, que incluyó a 53 sujetos de ambos sexos (62% hombres) con fracción de expulsión mayor al 50% en etapa I de la NYHA. **Resultados:** En individuos con disfunción diastólica, la función de reservorio de la aurícula izquierda, determinada por ECO 2D-STE fue menor comparada con individuos con función diastólica normal (37.6% vs 30.3%; $p<0.0001$). Sin embargo, no se encontraron diferencias entre hombres y mujeres. **Conclusión:** La disminución en la función de reservorio fue similar para individuos de ambos sexos, en etapas preclínicas de disfunción diastólica. El sexo no parece ser un factor determinante para el desarrollo de alteraciones en la función auricular izquierda, al menos en la fase de reservorio.

Palabras clave: Disfunción diastólica, función fásica de aurícula izquierda, esfuerzo de aurícula izquierda, 2D-STE.

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INTRODUCTION

Diastolic dysfunction (DD) early diagnosis is essential due to the risk of progression to heart failure with preserved ejection fraction (HFpEF), because once that symptoms develop, the 5-year mortality is greater than 70%¹ and no treatment to date has shown benefits in prevention of adverse outcomes. It is well known that HFpEF is more prevalent in women, implying that gender may play an important role in its development.² Left atrial enlargement is one of the four echocardiographic criteria used to define DD.³ However, studies suggest that left atrial (LA) phasic function (reservoir, conduit and pump functions) obtained by 2D speckle tracking strain analysis (2D-STE), are more sensitive tool for the detection of DD in early stages.^{4,5}

Many echocardiographic reference values are sex related⁶ and even though previous studies have not demonstrated differences in left atrial strain (LAS) between men and women,⁷ these have been performed in specific populations and therefore cannot be generalized. The aim of this study is to determine if there is a difference in LA phasic function, obtained by 2D-STE, in individuals with preclinical DD in relation to sex. This would allow us to understand if LA dysfunction is more prevalent in women with DD⁶ and according to this establish gender specific cut-off points.

MATERIAL AND METHODS

Study population: This is an observational, cross-sectional and analytical study, carried out in individuals of both sexes, aged 18 years or older, with a left ventricular ejection fraction (LVEF) $\geq 50\%$ determined by transthoracic echocardiography (TTE) and New York Heart Association (NYHA) functional class I. This study was conducted at Hospital Español de México, from May to December 2017. It was a convenience, non-probability and sequential sampling. Patients with decompensated chronic heart failure, significant valvular disease (moderate or severe aortic stenosis, any degree of mitral stenosis, moderate to severe regurgitation), previously diagnosed cardiomyopathies, prevalent or corrected congenital heart diseases, pericardial diseases,

cardiac stimulation devices, atrial flutter or fibrillation and poor image quality were excluded. Data was collected in a capture sheet, created by the investigator, with patient identification, clinical and echocardiographic data. The protocol was approved by the local ethics and research committees, follows the guidelines of the Helsinki agreement and all participants gave informed written consent.

Echocardiography measurements:

Standard echocardiography was performed using a Philips Epiq 7 ultrasound system with a 1-5 MHz transducer. LV function analysis was assessed by Simpson's modified rule.⁶ LA volume index (LAVI) was obtained automatically using the biplane disk summation technique. Diastolic function was analyzed acquiring peak transmitral inflow velocities in early diastole (E), atrial systole (A) and E wave deceleration time (DTE) with pulsed Doppler. Tissue Doppler analysis of mitral annular septal and lateral velocities in early diastole (e'), their average and the average E/e' ratio were used for estimation of LV filling pressures. Maximum velocity of the tricuspid regurgitation (TR) jet was obtained in the apical four chamber, right ventricle entrance chamber or parasternal short axis at the level of the great vessels views, recording the highest value. DD was diagnosed based on guideline recommendations.³ For 2D speckle-tracking LAS analysis images were acquired at 60-80 frames per second with manual tracing of atrial endocardial borders. An average of 3 measurements from 2 cardiac cycles in the apical 2 and 4 chamber axis views was used, for a total of six measurements per each atrial function. Strain curve analysis was QRS-triggered. Reservoir function was obtained from peak systolic deformation of the plotted curve, conduit function during passive LV filling and pump function at peak of atrial contraction. Images were processed with QLAB Cardiac software (Philips Healthcare).

Statistical analysis: Normality's assessment was based on kurtosis and skewness values. Data are expressed as mean \pm SD for continuous variables or interquartile ranges according to distribution and percentages for categorical variables. The primary objective was evaluated with Student's T test for parametric variables or Mann-Whitney U test for nonparametric

ones. Proportion differences were evaluated with the χ^2 test. A ROC curve analysis was used to compare sensitivity and specificity of atrial function against. P values < 0.05 at two tails were considered significant.

RESULTS

Clinical and echocardiographic characteristics

Were included 53 patients, 34 (64%) with normal diastolic function and 19 (35%) with diastolic dysfunction. Amongst the known risk factors for DD, we observed that 61% of the subjects with systemic arterial hypertension presented with some degree of DD ($p=0.008$) and prevalence was higher in older individuals ($p<0.001$). Individuals with DD had lower LVEF ($p=0.005$) and higher LAVI (22.6 mL/m^2 vs 30.9 mL/m^2 , $p=0.002$). The average e' velocity was significantly lower in individuals with DD ($p<0.0001$). However, no difference was found between the E/e' ratio and the presence or absence of DD ($p=0.151$). There were no significant differences in DD between men and women ($p=0.279$). Only in five cases had evidence of increased LV filling pressures

determined by E/e' ratio or significant dilatation of the LA was found ($\text{LAVI} > 42\text{ mL/m}^2$) (Table 1).

Left atrial function and diastolic dysfunction

Reservoir function was significantly lower in subjects with DD (37.6 vs 30.3%, $p<0.0001$). However, we found no significant differences between men and women ($p=0.298$). There was no deterioration in conduit and pump functions in individuals with DD compared with those with normal diastolic function ($p=0.383$ y $p=0.439$, respectively) (Table 1).

ROC curve analysis of LA reservoir function and LAVI

We assessed sensibility and specificity for DD diagnosis by ROC curve analysis. Reservoir function showed better performance with an area under the curve (AUC) of 0.83 compared to LAVI ($\text{AUC}=0.77$, $p<0.001$).

DISCUSSION

Our results were consistent with previously published studies in which a decrease in LA

Table 1: Echocardiographic variables in total population and group differences.

	Total population (n = 53)	Normal diastolic function (n = 34)	Diastolic dysfunction (n = 19)	p
LVEF (%)**	63.1 (60-65)	65 (61.9-66.9)	60.7 (59.8-63.8)	0.005
LAVI (mL/m^2)*	25.6 ± 7.8	22.6 ± 4.5	30.9 ± 9.6	< 0.0001
Em (cm/s)**	76 ± 22.7	79.1 (68.6-94.6)	65.5 (49.5-82)	0.047
Am (cm/s)**	66.4 ± 23.7	59.9 ± 20.2	78 ± 25.5	0.009
DT (ms)*	226.7 ± 65.6	195.8 ± 43.6	282.1 ± 62.5	< 0.0001
Septal e' (cm/s)**	8.9 ± 2.6	9.8 ± 2.2	7.3 ± 2.6	< 0.0001
Lateral e' (cm/s)*	11 ± 3.3	12.4 ± 2.6	8.5 ± 2.7	< 0.0001
Average e' (cm/s)**	9.9 ± 2.7	10.9 (9.8-12.3)	8.16 (6.6-9.2)	< 0.0001
E/e' *	8.2 ± 3.1	7.6 ± 2	9.2 ± 4.4	0.077
TR jet velocity (m/s)**	2.1 ± 1.2	2.06 (1.8-2.4)	2.34 (1.3-2.6)	0.409
Reservoir function (%)*	35 ± 6.6	37.6 ± 5.5	30.3 ± 5.9	< 0.0001
Conduit function (%)**	16.1 (14.3-18.5)	16.7 (14.7-18.5)	16 (13.8-18.6)	0.860
Pump function (%)*	-2.5 (-3.5, -1.2)	-2.4 (-4.1, -1.6)	-1.6 (-3.1, -1.04)	0.084

LVEF = left ventricle ejection fraction; LAVI = left atrium index volume; Em = mitral E velocity; Am = mitral A velocity; TR = tricuspid regurgitation; DT = mitral deceleration time.

* Student's T test. ** Mann-Whitney U test.

reservoir function is observed in patients in preclinical stages of DD, who may not even present LA structural changes or other data suggesting elevated LV filling pressures.^{4,5} Reservoir function decline was similar for both men and women, which suggests that sex does not seem to be an independent risk factor for the development of LA dysfunction, at least not in the reservoir phase. The foregoing should be considered when analyzing traditional risk factors for DD since male individuals may present with the same subclinical alterations as women. Similarly, ROC curve analysis suggests that LA dysfunction alterations, in this case reservoir function, could be a more sensitive and specific tool for DD detection in early stages compared with volumetric analysis, which has been previously reported.⁸ Therefore, its routine evaluation in patients with known risk factors, the definition of cut-off points and echocardiographic surveillance could result in early diagnosis, allowing for a more efficient prevention strategy. Unlike data reported in other studies, no significant decrease was found in conduit and pump functions, which could be due to the number of subjects included in our study, or to the lack of standardization of measurement techniques and cut-off points. Furthermore, this may be explained because of maintenance of conduit and pump functions until a greater degree of DD develops. Limitations of the present study were our sample size, the lack of established cut-off points and the absence of software specifically dedicated to LA strain analysis.

CONCLUSIONS

Left atrial reservoir function declines in individuals with pre-clinical diastolic

dysfunction. However, sex does not seem to be an independent variable for the development of LA dysfunction. LA function strain analysis could be a diagnostic tool with better performance than LAVI for the detection of diastolic dysfunction in preclinical stages. Further studies are needed in our population to establish specific cut-off points and an association with LA dysfunction and clinical adverse outcomes.

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