



Impact of the diastolic dysfunction in the left atrial strain in patients with ischemic heart disease. A cross-sectional study

Impacto de la disfunción diastólica en el strain de la aurícula izquierda en pacientes con cardiopatía isquémica. Un estudio transversal

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Keywords:

Left atrial strain, diastolic dysfunction, ischemic heart disease, left atrial reservoir strain, left atrial conduct strain, left atrial pump strain.

Palabras clave:

Strain de aurícula izquierda, disfunción diastólica, cardiopatía isquémica, strain reservorio de la aurícula izquierda, strain conducto de la aurícula izquierda, strain bomba de la aurícula izquierda.

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ABSTRACT

Introduction: Left atrial strain (LAS) has been related to the grade of diastolic dysfunction. However, only a few reports exist about its relationship among patients with ischemic heart disease (IHD). **Objective:** To compare the LAS value among patients with normal and abnormal diastolic function. **Material and methods:** A cross-sectional, retrospective, observational, analytic, single-center study (Hospital Civil de Guadalajara). All patients with an ischemic heart disease diagnosis (acute and chronic) were included between June 2017 and July 2019. **Results:** Two hundred forty-eight patients were included. Among the study population, 58% had diastolic dysfunction. LAS was lower in the diastolic dysfunction group on the reservoir (39% vs 23%), conduit (22 vs 11%) and pump phases (16 vs 23%). As diastolic dysfunction progressed, the reservoir (39 vs 30% vs 22 vs 16%) and conduit (22 vs 12% vs 12 vs 9%) phases of left atrial strain decreased, and during the pump phase an improvement was noticed between grade 1 diastolic dysfunction compared with a normal diastolic function (16 vs 18% vs 11 vs 6%). We used the ROC curve to determine the cut-off value to predict diastolic dysfunction, and the cut-off was < 31.6%. The LAS also correlated with proBNP concentrations. **Conclusion:** As diastolic dysfunction progresses, the three phases of LAS present a linear decline in IHD.

RESUMEN

Introducción: El strain de aurícula izquierda se ha relacionado con el grado de disfunción diastólica, sin embargo, sólo pocos estudios existen de su relación en pacientes con cardiopatía isquémica. **Objetivo:** Comparar el valor del strain de aurícula izquierda en pacientes con función diastólica normal y anormal. **Material y métodos:** Estudio transversal, retrospectivo, observacional, analítico, unicéntrico (Hospital Civil de Guadalajara). Se incluyeron todos los pacientes con diagnóstico de cardiopatía isquémica aguda o crónica, en el periodo de junio 2017 a julio 2019. **Resultados:** Doscientos cuarenta y ocho pacientes fueron incluidos. El 58% de los pacientes tuvieron disfunción diastólica. El strain de aurícula izquierda fue menor en el grupo de disfunción diastólica en la fase de reservorio (39 vs 23%), conducto (22 vs 11%) y de bomba (16 vs 23%). Conforme progresó la disfunción diastólica, la fase de reservorio (39 vs 30% vs 22 vs 16%) y la de conducto (22 vs 12% vs 12 vs 9%) del strain de la aurícula izquierda fueron descendiendo; en la fase de bomba hubo un incremento en la disfunción diastólica grado 1 en comparación con función diastólica normal (16 vs 18% vs 11 vs 6%). El valor de corte del strain de reservorio para predecir disfunción diastólica fue de < 31.6%, utilizando curvas ROC. El strain de aurícula izquierda se correlacionó con las concentraciones de proBNP. **Conclusión:** Conforme la disfunción diastólica progresa, las tres fases del strain de la aurícula izquierda presentaron declive lineal en pacientes con cardiopatía isquémica.

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INTRODUCTION

Ischemic heart disease (IHD) stands as the main cause of death in the world. The World Health Organization estimates that 17 million people die every year due to this condition, and the number increases year after year.¹ Ischemic heart disease can be broadly divided into stable ischemic heart disease² and acute coronary syndromes (ACS),^{3,4} which can also be divided into unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI).

Diastolic function comprises 4 phases: isovolumetric relaxation, early rapid diastolic filling, diastasis, and atrial contraction (also called a late diastolic filling). These four phases require an active myocardial relaxation, elasticity and distensibility of the left ventricle.⁵

Currently, the diastolic function can be easily assessed with an echocardiogram, following the American Society of Echocardiography guidelines.⁶ Left atrial function has been historically related to the grade of diastolic dysfunction since, in the absence of mitral valve disease, an enlarged left atrium can be associated with an increased left ventricular diastolic pressure.⁷ Left atrial function encompasses three physiological processes. In the reservoir phase, the left atrium is filled with blood coming from the pulmonary veins; the conduit phase, the diastasis; and the contraction phase (also called the pump phase), when the left atrium contracts.⁸

Patients with ischemic heart disease have an abnormal diastolic function, and it is known that diastolic function is affected even before the appearance of systolic dysfunction on the ischemic cascade.⁹

Left atrial strain (LAS) is a relatively new echocardiographic procedure. It represents the percent change of myocardial fibers on the spatial position in each phase of the atrial cycle.¹⁰ This technique has the great advantage of non-invasively assessing all three phases of the atrial cycle, producing curves that accurately represent that function.

There have been discrepancies in the typical values of left atrial deformation (strain), with a mean reservoir strain of 40% among the larger studies.^{11,12} Its relationship with the grade of

diastolic dysfunction has been studied before, and it is proposed that a left atrial reservoir strain (LARS) below 35% can be associated with diastolic dysfunction.¹³

Among patients with IHD, the association between myocardial deformation and the degree of diastolic dysfunction has been barely studied. To our knowledge, there is only one report describing this relation.¹⁴ The study included 109 patients with a NSTEMI and found that the three components of left atrial strain correlate with the classic parameters of diastolic function. Additionally, the LAS declines as the diastolic dysfunction grade increases.

Apart from IHD, another condition in which an association with left atrial strain is well documented is atrial fibrillation, where a decreased strain predicts the development of this arrhythmia.^{15,16} After an ablation procedure can also be linked to a higher risk of recurrences.¹⁷ Furthermore, it can predict the risk of systemic embolism in patients with atrial fibrillation.^{8,10,18}

There is a broadly described linear relationship between a decline in left atrial strain and mitral valve regurgitation progression in valvular heart disease, mainly mitral valve disease. The association with survival has also been described.^{19,20} It can predict the appearance of atrial fibrillation in mitral stenosis.²¹

LAS has also been described in patients with hypertension,⁸ chronic kidney disease²² and autoimmune diseases, such as lupus²³ and rheumatoid arthritis.²⁴

This study's importance implies the relevance of diastolic function stratification, using the LAS percentage in patients with IHD. This novel technique could lead to the re-stratification of those patients with an undetermined diastolic function. It is innovative as only a few papers describe this topic.

The objective of this study is to compare the LAS value among patients with normal and abnormal diastolic function.

MATERIAL AND METHODS

A cross-sectional, retrospective, observational, analytic, single-center study was performed. All patients older than 18 years old, hospitalized at the Cardiology Department of the "Hospital

Civil de Guadalajara Fray Antonio Alcalde" between June 2017 and August 2019, with a diagnosis of IHD (including UA, STEMI, NSTEMI and stable angina) were included. Every patient had an echocardiogram during the first 72 hours of their hospitalization. Exclusion criteria were: atrial fibrillation, poor acoustic window and mitral stenosis.

This study's main objective was to compare the percentage of LAS in patients with normal and abnormal diastolic function. The specific objectives were to contrast the percentage of LAS with the grades of diastolic dysfunction. To assess the capacity of LAS to predict diastolic dysfunction and compare these findings with the classic parameters of diastolic dysfunction. Also, to determine if there is a correlation between LAS and the classic diastolic dysfunction parameters and establish an association between the LAS and proBNP blood levels.

Demographic variables of our patients were age, gender, body mass index (BMI), co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, smoking, blood analysis (HbA1c, Uric Acid, Creatinine, Cholesterol, triglycerides, proBNP). Moreover, initial diagnosis: UA, STEMI, NSTEMI and stable angina; and among the echocardiographic variables we had: left ventricle ejection fraction (LVEF), E/A ratio, e' , E/ e' ratio, left atrial indexed volume (LAVI), tricuspid regurgitation maximal velocity (TR Vmax), presence or absence of mitral regurgitation, and the severity of it.

A cardiologist performed echocardiographic studies, supervised by an echocardiographer, with a Siemens ACUSON SC2000 prime, using the 4v1c, 2.5 MHz probes. The LVEF was calculated by the biplane method (Simpson's rule). The LAVI was also calculated by a biplane method, and TR Vmax was determined using the continuous wave Doppler of the tricuspid regurgitation. E/ e' ratio was calculated with the product of the division of the mitral inflow E wave (measured by pulsed wave Doppler) and the average of the medial and lateral e' waves (measured by tissue Doppler). Diastolic function was established according to the 2016 Left ventricular diastolic function guidelines of the American Society of Echocardiography 2016.⁶

LAS was obtained using the syngo[®] Velocity Vector Imaging technology software. An apical

4-chamber view echo was predetermined to calculate myocardial strain. The left atrial endocardium was traced at end-systole, and the traced endocardial border was followed during the cardiac cycle. The R-R interval on EKG was used as the reference for strain assessment. A maximal longitudinal strain global was acquired, represented as the Left Atrial Reservoir Strain (LARS). Additionally, the other two values were obtained: The Left Atrial Conduit Strain (LACS) and the Left Atrial Pump Strain (LAPS). The maximum value represents LARS during the reservoir phase, the LAPS is the highest value in the contraction phase, and the difference between the former two is the LACS.

Qualitative variables are expressed in proportions, quantitative variables in mean (standard deviation) or median (interquartile range), according to their distribution (Kolmogorov-Smirnov). Qualitative values were compared using χ^2 , while a Student's t-test, Mann-Whitney U test, ANOVA or Kruskal-Wallis were used for quantitative variables according to their distribution. According to the LAS, a ROC curve was used to establish a precise cut-off point to diagnose diastolic dysfunction, compared with the E/A ratio, E/ e' , LAVI, and TR Vmax. Spearman's correlation was used to determine LAS relation with E/A ratio, E/ e' , LAVI, and TR Vmax, along with proBNP. The inter-observe variability was determined by the kappa coefficient. Statistical significance was determined with a $p < 0.05$. The statistical program Medcal statistical software, version 15.2, was used.

The Declaration of Helsinki ethical principles were followed.

RESULTS

During the study period, 248 patients were included. 58% of our study population (*Table 1*) had diastolic dysfunction. Among demographic features, the male gender was more prevalent. The diastolic dysfunction group had an older median age (57 vs 62 yr.), a lower BMI (27.8 vs 26.5) and a higher prevalence of diabetes mellitus (33 vs 54%). There was no significant difference in the prevalence of hypertension, dyslipidemia, and tobacco consumption. The most common diagnosis at hospital discharge was STEMI.

Table 1: Baseline characteristics of the patients. N = 248.

Parameter	Normal diastolic function n (%)	Diastolic dysfunction n (%)	p
Demographic characteristics			
N	105 (42)	143 (58)	
Age (years)	57 ± 11	62 ± 12	< 0.001
Male sex (%)	79	69	0.100
BMI (kg/m ²)	27.8 ± 4.0	26.5 ± 4.7	0.030
Hypertension (%)	48	61	0.060
Diabetes mellitus (%)	33	54	0.002
Dyslipidemia (%)	54	37	0.090
Smoker (%)	68	66	0.900
Admission diagnosis (%)			
STEMI	43	53	0.900
NSTEMI	14	22	0.900
UA	28	18	0.600
Stable angina	15	6	0.600
Laboratory data			
HbA1c (%)	7 (5-9)	7.6 (5-10)	0.100
Creatinine (mg/dL)	0.9 (0.3-1.4)	1.1 (0.5-2)	0.100
Cholesterol (mg/dL)	162 ± 37	159 ± 52	0.700
Triglycerides (mg/dL)	164 (110-190)	141 (101-182)	0.080
Uric acid (mg/dL)	6.1 ± 1.6	7 ± 2.4	0.020
Pro BNP (pg/mL)	933 (200-1530)	3432 (350-5450)	0.001
BMI = body mass index, STEMI = ST-elevation myocardial infarction, NSTEMI = Non-ST-elevation myocardial infarction; UA = unstable angina.			

As we evaluated laboratory blood analysis, we documented that patients with diastolic dysfunction had higher uric acid levels (6.1 vs 7 mg/dL) and proBNP (933 vs 3432 pg/dL), and we found no difference among HbA1c, creatinine, cholesterol and triglycerides.

Among echocardiographic parameters (Table 2), the population with diastolic dysfunction had a lower LVEF (57 vs 43%), a higher E/A ratio (1 vs 1.3), lower e' (8.1 vs 6.4 cm/s), higher E/e' ratio (9.2 vs 13.3), higher LAVI (23.4 vs 31.5 mL/m²), and a higher TR Vmax (2.2 vs 2.6 m/s). Regarding LAS (Figure 1), it was lower among the diastolic dysfunction group,

with a LARS of 39 vs 23%, a LACS of 22 vs 11% and a LAPS of 16 vs 12%.

A total of 105 patients showed a normal diastolic function, 50 patients with grade 1 diastolic dysfunction, 57 on grade 2 and 36 on grade 3. Echocardiographic parameters were divided according to the grades of diastolic dysfunction (Table 3). It was found that just as diastolic dysfunction advance, LVEF progressively declines (57 vs 46% vs 42 vs 39%), the E/A ratio increases, with the exception of grade 1 (1 vs 0.7 vs 1 vs 2.7), the e' decreases (8.1 vs 6.9 vs 6.2 vs 6 cm/s), E/e' relation worsens (9.1 vs 8.7 vs 14 vs 18.5), LAVI grows (23 vs 25 vs 32 vs 40 mL/m²), and the TR Vmax rises (2.2 vs 2.3 vs 2.6 vs 2.9 m/s).

The LAS assessment showed a progressive decline as diastolic dysfunction increased (Figure 2), in reservoir phase (39 vs 30% vs 22 vs 16%), and conduit phase (22 vs 12% vs 12 vs 9%). The pump phase on grade 1 diastolic dysfunction improved compared to a normal diastolic dysfunction (16 vs 18% vs 11 vs 6%) and decreased with higher grades of diastolic dysfunction.

When we used the ROC curve, the cut-off value to determine diastolic dysfunction was < 31.6% of LARS compared to other diastolic function parameters, and it was superior in predicting the presence of diastolic dysfunction (Figure 3).

A correlation (Figure 4) between LARS, diastolic function parameters and proBNP values was examined. A slight correlation with e', E/e', LAVI and proBNP was found.

The interobserver variability for the left atrial strain assessment documented in our study was 0.85.

DISCUSSION

Our study's main objective was to investigate a difference in LAS values among patients with and without diastolic dysfunction. We found that patients with a normal diastolic function had a LARS of 39%, while patients with diastolic dysfunction had LARS of 23%. Morris et al.²⁵ documented a mean left atrial strain of 45% (± 11) on a healthy population and a reservoir strain of 28% on patients with diastolic dysfunction (± 11). Another healthy population

study reported a mean reservoir strain of the left atrium of 40% (± 6). A Metanalysis¹¹ that included 40 studies described a mean left atrial reservoir strain of 39% for a healthy population, the same value that we found on patients with a normal diastolic dysfunction in our study.

Comparing the reservoir and pump phases on both of our study groups, both values were lower on patients with diastolic dysfunction. We reported a LACS of 22% and a LAPS of 16% on patients with a normal diastolic function, values similar to the data described by Pathan et al,¹¹ as they demonstrated 23 and 17%, respectively.

Table 2: Echocardiographic parameters according to diastolic function.

Parameter	Normal diastolic function	Diastolic dysfunction	p
LVEF (%)	57 \pm 9.0	43 \pm 11.0	< 0.001
E/A ratio	1 \pm 0.3	1.3 \pm 0.9	0.001
e' (cm/s)	8.1 \pm 1.6	6.4 \pm 1.2	< 0.001
E/e' ratio	9.2 \pm 2.7	13.3 \pm 6.9	< 0.001
LAVI (mL/m ²)	23.4 \pm 6.8	31.5 \pm 11.6	< 0.001
TR Vmax (m/s)	2.2 \pm 0.4	2.6 \pm 0.6	< 0.001
LARS (%)	38.7 \pm 12.0	23.2 \pm 9.0	< 0.001
LACS (%)	22.2 \pm 9.5	11.1 \pm 4.7	< 0.001
LAPS (%)	16.5 \pm 7.0	12.1 \pm 7.3	< 0.0001

LVEF = Left ventricle ejection fraction, LAVI = Left atrial volume index, TR Vmax = Tricuspid regurgitation velocity, LARS = Left atrial reservoir function, LACS = Left atrial conduction strain, LAPS = Left atrial pump function.

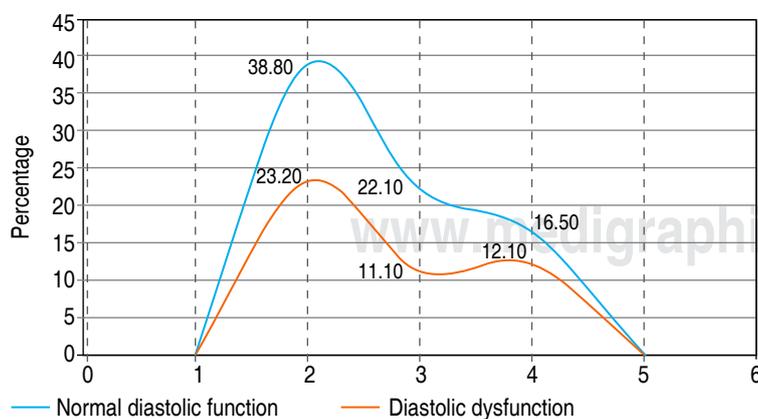


Figure 1: Left atrial reservoir strain and diastolic function.

Lower LAS values have been previously reported on patients with diastolic dysfunction and IHD.²¹

As detailed in other studies,^{26,27} we also found that as diastolic dysfunction increases, the classic diastolic dysfunction parameters worsen. The interesting finding was that the 3 phases of LAS decreased progressively, just as diastolic dysfunction evolved. Brecht et al.²⁸ observed this inverse relationship of LAS deterioration as diastolic dysfunction advances and even suggested that it could be a sign of subclinical diastolic dysfunction. He also mentioned how the LAPS increases on grade 1 diastolic dysfunction, just as our study's findings. Singh et al.¹³ and Thomas et al.²⁹ reported the same inverse relationship between LAS and systolic dysfunction. Another study on patients with an ACS¹⁴ compared the relationship between LAS and the degree of diastolic dysfunction. They described a LARS of 27.7% for DD1, 17.8% for DD2 and 9.5% on DD3; a LACS of 17.8% DD1, 6.2% DD2, 3.3% DD3; and a LAPS of 18.6% for DD1, 8.2% for DD2, and 10.5% for DD3; being the reservoir phase values similar to our findings.

Moreover, in our study, it can be appreciated how LAS turns abnormal at an early stage of diastolic dysfunction, compared with an E/e' ratio that turned abnormal until stage 2 of diastolic dysfunction, whereas LAVI came abnormal until stage 3 diastolic dysfunction. These findings have been previously described,^{13,29-31} suggesting that LAS could be a premature indicator of diastolic dysfunction, as it becomes abnormal before the appearance of classic diastolic dysfunction parameters, being even capable of reclassifying patients that could have a normal diastolic function on traditional algorithms or classifying patients on a higher diastolic dysfunction grade.

ROC curves were analyzed to determine the best parameter that could predict diastolic dysfunction. The left atrial strain was revealed to be the most significant, followed by the e' and the left atrial indexed volume. The cut-off point with the highest diagnostic accuracy was < 31.6%, with a sensitivity of 84% and a specificity of 71%. This cut-off value is similar to the value proposed by Singh et al.,¹³ who suggested a value of < 35% with a sensitivity of 90% but a specificity of 59%. Furthermore, it

Table 3: Echocardiographic findings according to diastolic dysfunction grade.

Parameter	NDF	DD 1	DD 2	DD 3	p
N	105 (42%)	50 (20%)	57 (23%)	36 (15%)	
Echocardiographic parameters					
LVEF (%)	57 ± 9.0	46 ± 9.0	42 ± 10.0	39 ± 13.0	< 0.001
E/A ratio	1 ± 0.3	0.7 ± 0.2	1 ± 0.3	2.7 ± 0.8	< 0.001
e'	8.1 ± 1.5	6.9 ± 1.7	6.2 ± 2.1	6 ± 1.8	< 0.001
E/e' ratio	9.1 ± 2.7	8.7 ± 2.7	14 ± 5.5	18.5 ± 8.7	< 0.001
LAVI	23.4 ± 6.8	25.3 ± 7.5	31.8 ± 9.6	39.8 ± 14	< 0.001
TR Vmax	2.2 ± 0.4	2.3 ± 0.5	2.6 ± 0.6	2.9 ± 0.6	< 0.001
LARS (%)	38.8 ± 12.0	29.7 ± 7.0	22.3 ± 8.0	15.7 ± 9.0	< 0.001
LACS (%)	22.1 ± 9.0	11.8 ± 5.0	11.6 ± 5.0	9.1 ± 4.0	< 0.001
LAPS (%)	16.5 ± 7.0	17.9 ± 6.0	10.7 ± 5.0	6.5 ± 6.0	< 0.001

NDF = normal diastolic function, DD = diastolic dysfunction, LVEF = left ventricle ejection fraction, LAVI = left atrial volume index, TR Vmax = tricuspid regurgitation velocity, LARS = left atrial reservoir function, LACS = left atrial conduction strain, LAPS = left atrial pump function.

showed accurate detecting an E/e' ratio higher than > 14 on ischemic heart disease patients.¹⁴

Other studies indicated that compared with the classic diastolic function parameters, LAS could be a superior and more precise predictor of increased left atrial filling pressure.³² It can also identify patients with heart failure with preserved LVEF,³³ which correlates with the pulmonary capillary wedge pressure.³⁴

Additionally, the correlation level between LAS and other diastolic function variables was

determined, with LAVI the highest correlation followed by e' and E/e' ratio. Nagueh et al.⁵ reported the correlation previously demonstrated between the LARS and left ventricular end-diastolic pressures. Degirmenci et al.³⁵ described the correlation present with the LAVI. Among patients with IHD, there is also a recognized moderate correlation with LAVI, E/e' ratio and e'.¹⁴

Finally, we attempt to identify a correlation between the LARS and proBNP concentration, displaying an inverse relation. This exact inverse correlation has been found in patients with heart failure³³ and patients with NSTEMI.³⁵

LAS evaluation demonstrated an echocardiographic technic with a straight correlation with diastolic function in patients with IHD. It can show a sudden change that can accurately categorize diastolic function, especially when the classic parameters seem unreliable or undetermined. This technic has the advantage of being unaffected by the angle of exploration and high reproducibility, even by inexperienced operators. The disadvantage is the lack of a well-defined consensus on normal values, the best imaging views, and the precise

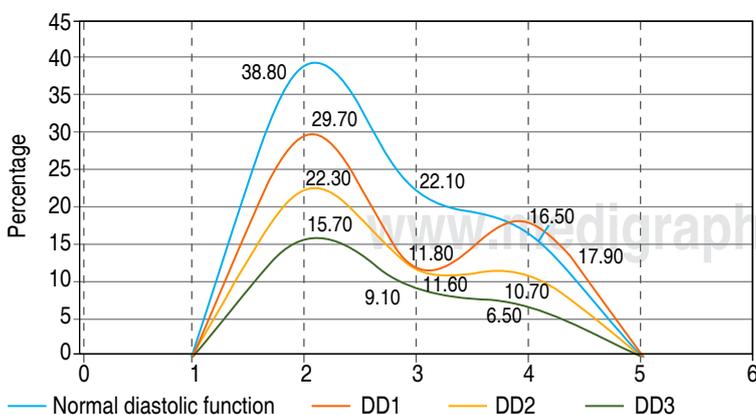


Figure 2: Left atrial strain according to the grade of diastolic dysfunction.

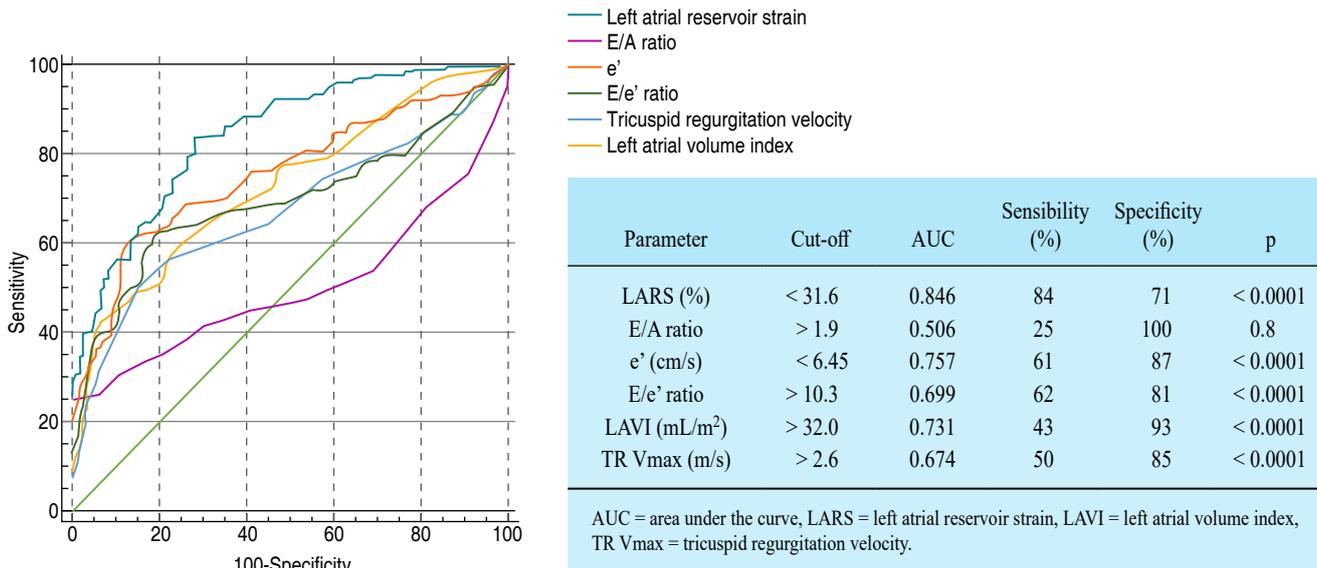


Figure 3: ROC curves of echocardiographic and diastolic function parameters.

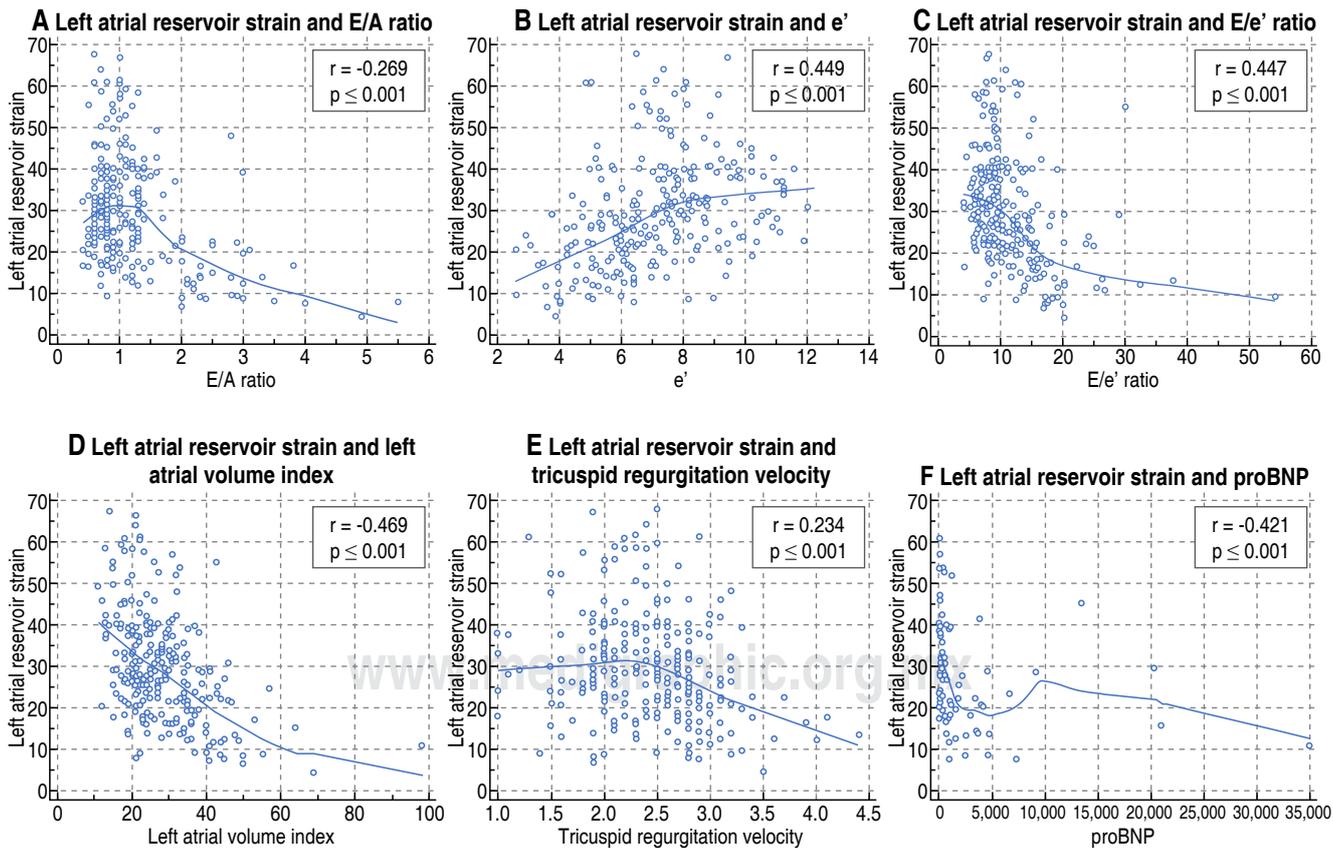


Figure 4: Correlation between left atrial strain and echocardiographic parameters.

echocardiographic reference point that should be used.

Our study's limitations are the retrospective, single-center design, exclusive to patients with IHD, and its modest sample size. However, it has the advantage of being one of the first studies in Latin America to use this technic to evaluate diastolic function. Our results encourage us to continue exploring this tool on prospective trials to estimate cardiovascular events and their performance in pathologies other than ischemic heart disease.

CONCLUSION

The left atrial strain, on its three phases, is decreased among patients with IHD and diastolic dysfunction. These three phases show a linear decline just as diastolic dysfunction progresses. Left atrial function is an important emerging entity and carries significant clinical and prognostic implications. The left atrial strain measurement is feasible, and the findings of this study suggest that left atrial strain could be a proper parameter in the evaluation con diastolic dysfunction in patients with IHD.

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