LA reservoir Strain: A Sensitive Parameter for Estimating LV Filling Pressure in Patients with Preserved EF

Turkan Seda Tan (✉ tsedatan@gmail.com)

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi <https://orcid.org/0000-0002-9349-3371>

Irem Muge Akbulut

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Ayşe İrem Demirtola

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Nazlı Turan Serifler

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Nil Ozyuncu

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Kerim Esenboga

Ankara Üniversitesi Tıp Fakültesi: Ankara Üniversitesi Tıp Fakültesi

Hacı Ali Kurklu

Lokman Hekim University: Lokman Hekim Üniversitesi

Volkan Kozluca

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Aydan Ongun

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Demet Menekşe Gerede Uludağ

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Eralp Tutar

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Irem Dincer

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

Original Article

Keywords: LV filling Pressure, left atrium, Strain, Echocardiography, Diastolic dysfunction

Posted Date: February 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-179321/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at The International Journal of Cardiovascular Imaging on April 10th, 2021. See the published version at <https://doi.org/10.1007/s10554-021-02235-x>.

Abstract

Aims: An elevated left ventricular (LV) filling pressure is the main finding in patients with heart failure with preserved ejection fraction, which is estimated with an algorithm by the recent ASE/EACVI guideline. In this study, we sought to determine the efficacy of the LA global longitudinal strain to estimate the elevated LV filling pressure.

Methods and Results: Consecutive patients who underwent left ventricular catheterization between January 2016 and December 2018 were included. Transthoracic echocardiography was performed within 24hrs before the catheterization. The LV filling pressure was estimated using echo parameters based on the 2016 ASE/EACVI algorithm. Moreover, to evaluate left atrial function, the LA GLS was measured using 2D speckle tracking echocardiography on four chamber-view (GE, Vivid E9 USA). Invasive LV pre-A pressure corresponding to mean left atrial pressure (LAP) was used as a reference, and >12 mm Hg was defined as elevated.

71 patients (mean age of 63.2 ± 9.75 , 70.4% male) underwent left heart catheterization. Invasive LV filling pressure was defined as elevated in 41 (57.8%) and normal in 30 patients (42.2%). 9(12.7%) patients of 71 were defined as indeterminate based on the 2016 algorithm. Using the ROC method, the accuracy of the algorithm was found as AUC:0.75 with 77% specificity and 70% sensitivity. The accuracy of 25.5 % cut point of LASr was found as AUC:0.79 with 77% specificity and 80% sensitivity for estimating LAP.

Conclusions: LASr with higher sensitivity may add an incremental value to estimate LV filling pressure, and hence may be used for HFpEF diagnosis.

Introduction

Prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing due to the aging population with comorbidities(1, 2). Patients with HFpEF commonly have normal LV systolic function with a normal systolic and diastolic diameter; but, often have an increased LV wall thickness and left atrial (LA) dilatation. Increased LV filling pressure is an essential finding in patients with HFpEF. Although cardiac catheterization is the gold standard method to demonstrate the elevated LV filling pressure, it is not practical(3). Therefore, estimation of LV filling pressure using transthoracic echocardiography has become a standard method due to its feasibility and reproducibility. Conventional Doppler methods such as diastolic mitral inflow measurement from the tip of mitral leaflets with pulse wave Doppler(PW) and tissue Doppler imaging were previously used to define diastolic dysfunction(4). To simplify the estimation of LV filling pressure 2016 EACVI/ASE guideline demonstrated a new algorithm (5) using similar echo parameters such as E/e', left atrium volume index(LAVi).

The left atrium (LA) has an essential role in diastole with its reservoir, conduit, and contraction functions to modulate the left ventricular (LV) filling, and both structure and mechanics of the LA change to adapt in diastolic dysfunction (DD)(6). The atrial functional parameters impair at the earliest stage of LVDD before the enlargement of LA. (7, 8) LA speckle tracking strain is the novel method to assess LA

functions. Especially peak LA strain has become an essential parameter to evaluate the LA compliance, which is highly crucial for LV filling and hence normal diastolic function(9).

In this study, we aimed to evaluate whether the LA strain is feasible and reproducible in patients with preserved EF. In addition, we sought to determine the incremental value of the LA strain for estimating LV filling pressure.

Materials And Methods

Patient Data. 78 consecutive adult patients who underwent left heart catheterization between 2016 and 2018 were reviewed. 71 of those who had been performed transthoracic echocardiography (TTE) immediately before catheterization and had feasible views for LA strain measurement included in our study. Those with ST-elevation and non-ST elevation myocardial infarction (MI), reduced EF, moderate to severe aortic and mitral regurgitation, and moderate to severe aortic and mitral stenosis were excluded. The medical histories, including all clinical and demographic data, were obtained from the electronic medical records. Laboratory results received within 24hrs before catheterization were obtained. The study protocol was reviewed and approved by the ethical committee.

Transthoracic Echocardiography. 71 patients who met the clinical criteria for study inclusion were performed two-dimensional echocardiographic imaging at Ankara University Cardiology Department. ., Two experienced physicians performed Two-dimensional, color flow, continuous-pulse wave, and tissue Doppler TTE using Vivid E9 imaging system (GE Medical Systems, Chicago, USA) within 24hrs before left heart catheterization, and measurements were obtained in a standard manner as recommended by the American Society of Echocardiography. LV dimensions were measured in the parasternal long-axis view at end-systole and end-diastole. LV ejection fraction was calculated from 4 chamber views using the modified Simpson method.

TTE parameters assessed LV diastolic function. Diastolic filling periods, including rapid filling, diastasis, and atrial contraction, were assessed by pulsed-wave Doppler. Mitral inflow at the level of mitral valve leaflet tips was used to measure the peak early (E-wave) and late (A-wave) diastolic flow velocities and calculate the E/A ratio. In addition, tissue Doppler imaging (TDI) using PW was performed with the sample volume at the lateral and septal mitral annulus to obtain lateral e' and medial e' velocities. The arithmetic mean of lateral and medial e' was defined as average e' , which was used to calculate the E/ e' ratio. Peak velocity of the tricuspid regurgitation (TR) jet was measured using continuous-wave Doppler. Left atrial volume was measured using a 4-chamber view and divided body surface area (BSA) to calculate the left atrial volume index (LAVi).

Left Atrial Global Longitudinal Strain. A four-chamber view with 50-70 fps was selected in the Echo Pack imaging workstation (Echo Pack imaging systems). Speckle tracking 2D LA strain was performed according to standardized measurements recommended by the 2018 EACVI/ASE consensus document(10). At least 3 average of 3 beats results were entered as average LA global longitudinal strain. If the LA image quality was not suitable to measure or if tracking quality could not be improved by

adjusting the region of interest (ROI), the image was not used to measure LA strain. Zero reference was defined as end-diastole. LA cycle was defined as follows:

- Reservoir strain (LASr): It comprises of the left ventricular isovolumic contraction time, ejection time, and isovolumic relaxation time. LASr is calculated as $\text{LASr} = \text{Peak systolic strain} - \text{the strain value at the end-diastole}$. This value is always positive.
- Conduit strain (LAScd): In sinus rhythm, LAScd is calculated as $\text{LAScd} = \text{the strain value at the onset of atrial contraction} - \text{the peak value of the curve}$, and this value is always negative. In patients with atrial fibrillation, LAScd has the same value as LASr, but with a negative sign.
- Contraction strain (LASct): LASct is calculated as $\text{LASct} = \text{the strain value at end-diastole (by definition zero)} - \text{the value at the onset of atrial contraction}$. LASct occurs as a result of atrial contraction; thus, it is measured only in sinus rhythm and has always a negative value(10, 11) (figure1).

LV catheterization. Left heart catheterization was performed according to the standard procedure by an interventional cardiologist. Invasive LV systolic and diastolic pressure measurements were performed using a 6-Fr pigtail catheter (Boston Scientific, Marlborough, MA) placed in the left ventricle through the femoral or radial artery before the evaluation of coronary artery visualization. The measurements were obtained after the fluid-filled transducer was balanced with the zero level at the mid-axillary line. Continuous pressure tracings were acquired at least in three consecutive respiratory cycles. As recommended by 2016 ASE/EACVI guideline LV pre-A pressure, which corresponds to the mean left atrial pressure(LAP) was defined as LV filling pressure and Pre-A pressure >12 mm Hg confirmed as elevated LV filling pressure(5).

Statistical Analysis

Baseline characteristics were presented as mean $\pm$ SD for continuous variables and compared using the Student *t*-test, or percentages for categorical variables differences compared using the chi-square test. A *p*-value < 0.05 was defined as statistically significant. Correlation between LASr and diastolic parameters were analyzed using the Pearson correlation method. Correlation of invasive LV filling pressure with echocardiographic parameters were analyzed using the Pearson correlation method as well. Sensitivity, Specificity, positive predictive value (PPV), and negative predictive value (NPV) of echocardiographic parameters were analyzed using the Receiver operating characteristic (ROC) based on the Logistic regression method. A cut-off value of LASr was also found using ROC analysis. All data was analyzed using JMP version 14.0 (SAS Institute Inc., Cary, North Carolina)

Inter-observer and intra-observer variability. Images from 10 patients were randomly selected, and a second independent blinded observer measured the images to assess the inter-observer variability. The first observer who measured all patients' views remeasured the same randomly selected 10 patients' views at least 6 weeks apart from the first measurement. Inter-observer and intra-observer variability were assessed using the Intra Class Correlation Coefficient (ICC) method.

Results

Baseline characteristics. A total of 71 patients (mean age 63.2 ± 9.75 , 70.4% male) underwent left heart catheterization comprised the study population. All patients were divided into two groups by their invasive LV pre-A pressure value. >12 mmHg group (41 patients; 57.8%) was defined as elevated LAP group and, ≤ 12 mmHg group (30 patients, 42.2%) was defined as normal LAP group. Demographic, clinical characteristics, laboratory results, medication use, and TTE results were compared between groups (Table 1). There were no differences in age, gender, medication use, and co-morbidities. Laboratory results (obtained within 24 hrs. prior LV catheterization) including Hemoglobin, Platelet, ALT, and AST were also similar between groups. In addition, baseline SBP and SBP during catheterization were not different between groups.

Echocardiographic Measurements. Even though $E(E; 0.72 \pm 0.19$ vs. 0.62 ± 0.11 , $p=0.0055$), $E/e'(13.2 \pm 5.44$ vs. 8.65 ± 2.51 , $p<0.0001$) and E/A ratio ($E/A; 0.96 \pm 0.32$ vs. 0.73 ± 0.16 , $p=0.0002$) were significantly higher in patients with elevated LAP group, there were no differences in A value between groups. We were able to measure TR jet velocity in 50 patients among the study population, and it was significantly higher in the elevated LAP group (TR velocity; 2.74 ± 0.50 vs. 2.28 ± 0.57 , $p=0.0054$). However, LAVi was similar between groups.

LA global longitudinal strain: LA longitudinal strain was performed in 71 patients whose image quality were suitable to measure. LASr (20.44 ± 6.52 vs. 33.1 ± 9.22 , $p<0.0001$), LAcD (-9.13 ± 5.57 vs. -13.6 ± 7.05 , $p=0.0055$) and LASct (-12.0 ± 7.06 vs. -16.2 ± 10.6 , $p=0.032$) were found significantly impaired in patients with elevated LAP. Intra-observer (ICC 0.97, CI 95%: 0.91-0.99) and inter-observer (ICC 0.94, CI 95%: 0.78-0.98) agreement of strain measurements was excellent.

ROC Analysis

Estimated LAP was determined by using the algorithm recommended by the 2016 ASE/EACVI guideline. 9(12.7%) of 71 patients were defined as indeterminate based on the algorithm. Of those, 6 patients had elevated pre-A pressure, and 3 patients had normal Pre-A pressure. 27(38%) patients were defined as elevated LAP, and 35(49.3%) patients were defined as normal LAP according to the 2016 ASE/EACVI algorithm. The individual effect of parameters used in algorithm was analyzed and LAVi was found to be lower in accuracy (AUC: 0.61, specificity 73%, sensitivity 63%) than TR velocity (AUC: 0.76, specificity 81%, sensitivity 74%) and E/e' (AUC: 0.75, specificity 87%, sensitivity 63%) (Table 2, figure 1)) to estimate LAP. Although LAScd (AUC=0.70, specificity 67%, sensitivity 80%) and LASct (AUC=0.69, specificity 80%, sensitivity 59%) had lower accuracy to estimate LAP, LASr (AUC: 0.86, specificity 77%, sensitivity 85%) had higher accuracy and sensitivity to evaluate the LAP (Table 2, figure 2). The cut-off value for LASr was found as 25.5%, and based on the cut-off value, the LASr below 25.5% was defined as elevated LAP. LASr 25.5% had higher sensitivity (AUC=0.79, specificity 77%, sensitivity 80%) to estimate LV filling pressure compared to the 2016 ESC/ ASE algorithm (AUC=0.75, specificity 77%, sensitivity 70%) (Table 3, figure 3)

Correlation Analysis

Pearson correlation method was used to assess the correlation between pre-A pressure and echo parameters. There was no correlation between pre-A and LAVi($r=0.18$). There was also a weak correlation between invasive Pre-A pressure, E/e' ($r=0.34$), and TR velocity($r=0.35$). However, there were a moderate correlation between LASr ($r= -0.56$) and invasive pre-A pressure (Table4). However, there was not a good correlation between LASr and diastolic echo parameters. E/e' ($r= -0.31$, $p=0.0066$) LAVi($r= -.009$, $p=0.40$) and TR velocity($r= -0.25$, $p=0.043$)(figure4).

Discussion

This study confirmed that the LA global longitudinal strain is practical and reproducible in patients with preserved EF. Our population also demonstrated that LASr has higher accuracy with higher sensitivity and specificity compared to LAVi to assess LV filling pressure. We also observed that LASr estimates the LAP with higher sensitivity compared to the 2016 ASE/EACVI algorithm.

As it is known, increased myocardial stiffness and prolongation of active myocardial relaxation are the main reasons for HFpEF, which leads to elevated LV filling pressure. Thus, invasive evaluation of elevated LV filling pressure is the gold standard method to define diastolic dysfunction in patients with HF symptoms. However, invasive assessment is not practical and reproducible for all patients with HF symptoms. For this reason, the 2009 American Society of Echocardiography (ASE) and European Association of Echocardiography (now European Association of Cardiovascular Imaging [EACVI]) guideline was simplified and a practical algorithm was developed in 2016 guideline to estimate LV filling pressure. The studies designed to validate the algorithm with invasive LV filling pressure presented conflicting results. Some of them demonstrated good agreement with invasive LV pressure. (Balaney, et al. 2018; Andersen, et al. 2017)(12, 13). For instance, the Euro-Filling study demonstrated a substantial sensitivity to diagnose elevated LV filling pressures with the 2016 recommendations in patients undergoing invasive LV end-diastolic pressure measurement. However, they concluded that the algorithm was suboptimal in patients with preserved ejection fraction (14). Obokata et al. reported that the new algorithm was specific but poorly sensitive, being able to identify only 34% of individuals with HFpEF diagnosis (15). Our study also presented that the new algorithm had good specificity but lower sensitivity to predict LV filling pressure.

Even though transthoracic echocardiography is practical and reproducible to determine the diastolic dysfunction, it is not feasible in some instances, including atrial fibrillation and mitral annular calcification, as an indeterminate group defined in the guideline. Almedia et al. showed an increase in indeterminate cases in the 2016 algorithm in comparison with the 2009 guideline. (16) The inclusion of TR velocity to the new algorithm might be an important reason for increased indeterminate cases. TR velocity generally reflects severe HFpEF; therefore, the early stage of disease may not be evaluated. Moreover, 30% of patients show normal resting diastolic function by standard echocardiographic assessment. (17, 18) Although the cumulative effect of the parameters using the algorithm gives substantial information about LV filling pressure individually, parameters have some limitations. Especially E/e' is load-dependent and might be affected from angle intonation and has poor predictivity

with 37% estimation to detect elevated LV filling pressures. (3) Nevertheless, LAVI is an adequate parameter to estimate the cumulative effect of increased LV filling pressures (4, 5, 19). It might be inadequate to detect early LV diastolic dysfunction since this volumetric parameter reflects essentially the chronic effect of elevated LV filling pressure. Our study observed a weak correlation between TR jet velocity, E/e' , and invasive pre-A pressure and no correlation between LAVI and invasive pre-A pressure. Additionally, LAVI had lower specificity and sensitivity (specificity 73%, sensitivity 63%) compared to E/e' TR jet velocity and LASr

Although LA enlargement is the major finding in patients with HFpEF and predicts a poor prognosis, the significance of LA function in HFpEF is not well understood. Chronic elevation of LA pressure is the essential reason for LA enlargement in patients with diastolic dysfunction. It is strictly associated with LV pressure, which is exposed to the atrium during the diastolic period (20, 21). LA enlargement is an independent predictor for morbidity and mortality in diastolic dysfunction. Furthermore, LA volume was found to be highly associated with severity of diastolic dysfunction and disease burden..(17, 22, 23).

Nevertheless, one-third of patients still have normal LA size with HFpEF(22, 24). As it is known, LA enlargement occurs in the chronic phase of diastolic dysfunction and increases with the severity of the disease. However, in the early phase of diastolic dysfunction, LA size is still normal despite the impairment of its functions consisting in the reservoir, conduit, and contraction. (21). The PARAMOUNT trial showed worse reservoir, conduit, and contraction in HFpEF patients regardless of LA size(25). Besides, Chronic dilatation of LA results in deteriorated LA function due to atrial myopathy, which leads to atrial fibrosis(26, 27) and, hence, incomplete recovery of LA after treatment (21).

Previous studies researched a new method for the early detection of LA dysfunction in diastolic dysfunction. Due to the nonuniform dilatation and unequal geometry of LA anteroposterior dimension it is not recommended to assess the LA function(28). LAVi is the most accurate technique to evaluate the LA volume compared to computed tomography(CT), and it is over the area length method(21, 29, 30), Although LAVi was found highly correlated with the severity of diastolic dysfunction(DD) and cardiovascular risk in patients without AF or valvular heart disease(22), it is not recommended as a parameter to assess LAP in patients with AF, mitral valve disease, bradycardia and high output states(5). Although LAVi is recognized as a method to evaluate the estimated LAP, LA enlargement is the chronic result of diastolic dysfunction and its individual sensitivity is poor to identify elevated LV filling pressure as we confirmed in our study

Recently, Speckle tracking 2D LA strain has become a common tool to evaluate LA function due to its higher sensitivity and specificity, as shown in several studies. Morris, D. A., et al. observed the LA strain as a greater sensibility than LAVI for estimating LV filling pressure as recommended by 2016 guidelines. They also found a cut-off value of peak atrial longitudinal strain (PALS) as 23%, and $PALS < 23\%$ showed 73% sensitivity and 76% specificity in the determination of DD(19). Cameli M., et al. also showed the global PALS as a determinant of the LVEDP, and the cutoff value 18.0% of PALS was found as greater predictor of LVDP above 12 mmHg compared with E/e' (31).

Additionally, PALS is highly correlated with pulmonary capillary wedge pressure compared to other conventional echo parameters, including E/A, E/e', and LAVI, in patients with symptomatic HFpEF (32). Likewise, Brecht, A., et al. observed specific alterations in different stages of DD. In particular, reservoir and conduit functions of LA were significantly reduced before symptoms and LA enlargement occur. Our study also confirmed that LASr has higher accuracy and better sensitivity (AUC:0.86, specificity 77%, sensitivity 85%) for non-invasive estimation of the LV filling pressure than LAVI (AUC:0.61, specificity 77%, sensitivity 63%). We believe that left atrial strain might be more determinant compared to LAVI to give early and accurate information about early-stage of diastolic dysfunction, as shown in recent studies(19, 33) .

Study Limitation

Our study has several limitations with a single center and small patient group. We only included patients with preserved EF; therefore, we could not compromise all patient groups with diastolic dysfunction.

Because of our small number of patients, the study had only 9 indeterminate patients, so we could not demonstrate whether LA strain is adequate to define diastolic dysfunction in those patients' group. Prospective studies will be essential to demonstrate the additional effect of LA strain on the 2016 ASE/EACVI algorithm.

Conclusion

LA enlargement caused by chronic elevation of LV filling pressure is an independent predictor of hospitalization and mortality in HFpEF patients. Particularly, LA enlargement might be irreversible due to LA fibrosis; therefore, early detection of LA dysfunction might be crucial to improve survival in HFpEF. Our findings suggest that LASr may provide an impressive contribution to the conventional algorithm and may be a more effective parameter to use instead of LAVI on early diagnosis of HFpEF.

Abbreviations

HF, Heart failure

LV, Left ventricle

LA, Left atrium

LVEF, Left ventricular ejection fraction

HFpEF, Heart failure with preserved ejection fraction

DD, Diastolic dysfunction

TTE, Transthoracic echocardiogram

TR, Tricuspid regurgitation

AUC, Area Under the curve

Declarations

Author Declaration

The authors have no relevant relationships with industry to disclose. No funding was received for this work. We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We confirm that the manuscript has been read and approved by all named authors.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355(3):251-9.
2. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, et al. Trends in Hospitalizations and Survival of Acute Decompensated Heart Failure in Four US Communities (2005-2014): ARIC Study Community Surveillance. *Circulation*. 2018;138(1):12-24.
3. Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H. Diagnostic Accuracy of Tissue Doppler Index E/e' for Evaluating Left Ventricular Filling Pressure and Diastolic Dysfunction/Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2016;5(1).
4. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. *Journal of the American Society of Echocardiography*. 2009;22(2):107-33.
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*. 2016;29(4):277-314.
6. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA Strain for Categorization of LV Diastolic Dysfunction. *JACC Cardiovasc Imaging*. 2017;10(7):735-43.
7. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. *J Am Coll Cardiol*. 2008;51(7):679-89.
8. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(15):1961-77.

9. Singh A, Medvedofsky D, Mediratta A, Balaney B, Kruse E, Ciszek B, et al. Peak left atrial strain as a single measure for the non-invasive assessment of left ventricular filling pressures. *Int J Cardiovasc Imaging*. 2019;35(1):23-32.
10. Badano LP, Koliass TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19(6):591-600.
11. Voigt JU, Mălăescu GG, Haugaa K, Badano L. How to do LA strain. *Eur Heart J Cardiovasc Imaging*. 2020;21(7):715-7.
12. Balaney B, Medvedofsky D, Mediratta A, Singh A, Ciszek B, Kruse E, et al. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines: Head-to-Head Comparison with the 2009 Guidelines. *J Am Soc Echocardiogr*. 2018;31(1):79-88.
13. Andersen OS, Smiseth OA, Dokainish H, Abudiyab MM, Schutt RC, Kumar A, et al. Estimating Left Ventricular Filling Pressure by Echocardiography. *Journal of the American College of Cardiology*. 2017;69(15):1937-48.
14. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging*. 2017;18(9):961-8.
15. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. *Circulation*. 2017;135(9):825-38.
16. Almeida JG, Fontes-Carvalho R, Sampaio F, Ribeiro J, Bettencourt P, Flachskampf FA, et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. *European Heart Journal Cardiovascular Imaging*. 2018;19(4):380-6.
17. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124(23):2491-501.
18. Obokata M, Reddy YNV, Borlaug BA. The Role of Echocardiography in Heart Failure with Preserved Ejection Fraction: What Do We Want from Imaging? *Heart Fail Clin*. 2019;15(2):241-56.
19. Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, et al. Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. *JACC Cardiovasc Imaging*. 2018;11(10):1405-15.
20. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. *J Am Coll Cardiol*. 1993;22(7):1972-82.

21. Mandoli GE, Sisti N, Mondillo S, Cameli M. Left atrial strain in left ventricular diastolic dysfunction: have we finally found the missing piece of the puzzle? *Heart Fail Rev.* 2020;25(3):409-17.
22. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol.* 2002;90(12):1284-9.
23. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol.* 2005;45(1):87-92.
24. Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol.* 2007;49(6):687-94.
25. Santos AB, Kraigher-Krainer E, Gupta DK, Claggett B, Zile MR, Pieske B, et al. Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2014;16(10):1096-103.
26. Kebed KY, Addetia K, Lang RM. Importance of the Left Atrium: More Than a Bystander? *Heart Fail Clin.* 2019;15(2):191-204.
27. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac Fibrosis in Patients With Atrial Fibrillation: Mechanisms and Clinical Implications. *J Am Coll Cardiol.* 2015;66(8):943-59.
28. Wade MR, Chandraratna PA, Reid CL, Lin SL, Rahimtoola SH. Accuracy of nondirected and directed M-mode echocardiography as an estimate of left atrial size. *Am J Cardiol.* 1987;60(14):1208-11.
29. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. *Am J Cardiol.* 1999;84(7):829-32.
30. Khankirawatana B, Khankirawatana S, Porter T. How should left atrial size be reported? Comparative assessment with use of multiple echocardiographic methods. *Am Heart J.* 2004;147(2):369-74.
31. Cameli M, Sparla S, Losito M, Righini FM, Menci D, Lisi M, et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. *Echocardiography.* 2016;33(3):398-405.
32. Hummel YM, Liu LCY, Lam CSP, Fonseca-Munoz DF, Damman K, Rienstra M, et al. Echocardiographic estimation of left ventricular and pulmonary pressures in patients with heart failure and preserved ejection fraction: a study utilizing simultaneous echocardiography and invasive measurements. *Eur J Heart Fail.* 2017;19(12):1651-60.
33. Mandoli GE, Sisti N, Mondillo S, Cameli M. Left atrial strain in left ventricular diastolic dysfunction: have we finally found the missing piece of the puzzle? *Heart Fail Rev.* 2019.

Tables

Table1: Baseline Characteristics divided by invasive Left Atrial Pressure			
Characteristics	Elevated LAP Group (n=41)	Normal LAP Group (n=30)	P value
Age	63.34±9.11	63.0±9.11	0.89
Gender			
Male	65.85%	76.67%	0.32
Female	34.15%	23.33%	0.32
BSA m ²	1.89±0.16	1.89±0.15	0.99
SBP mmHg	120.5±10.5	120.1±11.8	0.85
SBP-Catheter mmHg	129.2±10.5	128.06±10.07	0.63
HT%	80.49	76.67	0.69
DM%	34.15	43.33	0.43
HL%	34.15	36.67	0.82
Medication			
ACE inhibitors%	39.02	36.67	0.83
ARB%	41.46	40	0.90
Beta Blocker%	43.90	46.67	0.82
Aldosterone inhibitors%	9.76	6.67	0.64
Diuretic%*	39.02	33.33	0.62
Statin%	21.95	30	0.44
Laboratory Result			
Hemoglobin g/dl	13.6±1.57	14.4±2.49	0.11
Platelet	249±75.05	246.7±64.2	0.88
Creatinine (mg/dl)	0.82±0.12	0.84±0.14	0.64
ALT U/L	21.4±3.58	21.2±3.96	0.88
AST U/L	21.3±2.33	21.4±2.96	0.84
Catheter Result			
Invasive Pre-A pressure	17.1±2.96	7.4±2.14	<0.0001

Echocardiography			
LVEDD mm	48.3±4.55	48.9±5.38	0.61
LVESD mm	27.02±2.97	28.6±4.84	0.15
EF%	58.8±4.26	57.5±3.46	0.16
E m/sec	0.72±0.19	0.62±0.11	0.0055
A m/sec	0.81±0.13	0.78±0.19	0.39
E/A ratio	0.96±0.32	0.73±0.16	0.0002
E/e' ratio	13.2±5.44	8.65±2.51	<0.0001
TR velocity	2.74±0.50	2.28±0.57	0.0054
LAVI ml/m ² #	33.2±6.64	31.08±4.78	0.11
LA Global Longitudinal Strain			
LASr %	20.44±6.52	33.1±9.22	<0.0001
LAScd %	-9.13±5.57	-13.6±7.05	0.0055
LASct %	-12.0±7.06	-16.2±10.6	0.032
Data are expressed as mean± SD or as (%). * Including furosemide and torsemide. # Calculation of left atrial volume ratio body surface area. BSA; body surface area; SBP: systolic blood pressure ; ACE: angiotensin converting enzyme; ARB=Aldosterone receptor antagonist; ALT: alanine amino transferase; AST: aspartate amino transferase LVEDD: left ventricular end diastolic diameter: LVESD: left ventricular end systolic diameter: EF: ejection fraction; TR: tricuspid regurgitation; LAVI: left atrial volume index; LV: left ventricular; LASr: left atrial strain during reservoir phase; LAScd: left atrial strain during conduit phase; LASct: Left atrial strain during contraction phase; p=probability.			

Table2 Receiver operating characteristic of echo parameters						
Variable	Specificity %	Sensitivity %	PPV	NPV	AUC (95%CI)	P
E/e' ratio	87%	63%	87%	64%	0.75(0.61-0.84)	<0.0001
TR jet velocity	81%	74%	83%	71%	0.76(0.59-0.87)	0.0034
LAVI ml/m ²	73%	63%	76%	60%	0.61(0.49-0.73)	0.12
LASr %	77%	85%	83%	79%	0.86(0.74-0.92)	<0.0001
LAScd%	67%	80%	77%	72%	0.70(0.56-0.82)	0.036
LASct%	80%	59%	79%	60%	0.69(0.45-0.80)	0.04
PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; GLS: global longitudinal strain; Other abbreviations as in Table 1.						

Table3 Receiver operating characteristic of echo parameters						
Variable	Specificity %	Sensitivity %	PPV	NPV	AUC (95%CI)	P
Estimated LAP	77%	70%	80%	66%	0.75(0.64-0.84)	0.0002
25.5% cut point of LASr	77%	80%	83%	74%	0.79(0.68-0.86)	<0.0001
PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; GLS: global longitudinal strain; Other abbreviations as in Table 1.						

Table4 Correlation of invasive LAP and echo parameters		
Variable	r	P value
E/e' ratio	0.34	0.0028
LAVi	0.18	0.12
TR velocity	0.35	0.0041
LASr	-0.56	<0.0001
LAScd	0.41	0.0003
LASct	0.29	0.016
r: correlation coefficient; Other abbreviations as in Table 1.		

Figures

Figure 1

An example of a study patients' LA strain result. LASr= 38.2%. LAScd= -27.64% and LASct= -10.56%

Figure 2

Receiver-operating curves of estimated LV filling pressure. E/e' AUC=0.75(95%CI:0.61-0.84), LAVi AUC=0.61(95%CI:0.49-0.73), LASr AUC= 0.86(95%CI:0.74-0.92) and TR jet velocity AUC=0.76(95%CI:0.59-0.87)

Figure 3

Receiver-operating curves of estimated LV filling pressure. Cut point 25.5% of LASr AUC = 0.79(CI95%:0.68-0.86, $p < 0.0001$) and Estimated LAP (the 2016 ASE/EACVI algorithm) AUC=0.75(CI 95%:0.64-0.84, $p = 0.0002$) alone.

Figure 4

Correlation of LASr with LAV_i , E/e' , and TR velocity. No correlation between LA reservoir strain and LAV_i ($r = -0.09$, $p = 0.40$) (A) Weak correlation between LA reservoir strain and E/e' ($r = 0.31$, $p = 0.0066$) (B). No correlation between LA reservoir strain and TR velocity ($r = -0.25$, $p = 0.043$) (C).