Left Atrial Strain in the Analysis of LV Diastolic Function: Ready to Use?

Antonio Amador Calvilho Júnior,[1,2] *Jorge Eduardo Assef,*[1] *João Moron Saes Braga,*[3] *Andrea de Andrade Vilela,*[1,4] *Antonio Tito Paladino Filho,*[1,5] *Gustavo Nishida*[1]

Instituto Dante Pazzanese de Cardiologia,[1] *São Paulo, SP – Brazil*
Conjunto Hospitalar de Sorocaba,[2] *Sorocaba, SP – Brazil*
Faculdade de Medicina de Marília,[3] *Marília, SP – Brazil*
Grupo Fleury,[4] *São Paulo, SP – Brazil*
Vila Nova Star,[5] *São Paulo, SP – Brazil*

Abstract

Left atrial (LA) dilation is a common indicator of diastolic dysfunction, and its analysis through a volume calculation reflects the cumulative effects of the left ventricular (LV) filling pressures. However, an increase in LA volume is not exclusive to diastolic dysfunction, which has also been observed in other clinical conditions. Thus, the evaluation of the LA strain enables a functional study of this chamber, adding to the morphological analysis through the volume calculation.

The LA strain, measured using the speckle tracking technique, brings information on the reservoir, conduction, and contractile functions of the LA, and is related to the LV function. Moreover, the changes in the LA strain precede the volumetric changes by nearly a decade, and correlate inversely with the degree of LA fibrosis – this has an important relationship with the diastolic dysfunction and its grading system. Albeit insufficient to explain its totality, LA fibrosis can partially justify the functional changes of this heart chamber and can favor the use of this variable as a complement to the current protocols for the analysis of the diastolic function.

Although further study is still warranted to establish other clinical applications, the LA strain stands out in the analysis of diastolic dysfunction and can be considered ready to use, offering a great potential to improve the evaluation of the overall cardiac function.

Introduction

The study of myocardial deformation can be considered definitely implemented in the current echocardiographic routine. Although some people believe this topic is recent, or in the research and pre-implementation stage, it is not true. The first studies of myocardial deformation are as old as the use of two-dimensional images in echocardiography, and the vast majority of these studies address left ventricular myocardial deformation. From the first experimental studies with sonomicrometry crystals directly inserted into the myocardium of dogs through the use of Doppler echocardiography, maturity was reached with the development of speckle tracking, a widely validated method for use in echocardiography and magnetic resonance imaging.[1–3]

Keywords

Echocardiography; Myocardium; Left Ventricular Dysfunction.

Mailing Address: Antonio Amador Calvilho Júnior •
Av. Dr. Dante Pazzanese, 500. Postal code: 04012-909. Vila Mariana São Paulo, SP – Brazil
E-mail: dr.calvilho@gmail.com
Manuscript received October 15, 2022; revised October 21, 2022; accepted November 2, 2022;
Editor responsible for the review: Daniela do Carmo Rassi

DOI: https://doi.org/10.36660/abcimg.2022357i

Multiplicity of speckle tracking variables in the assessment of different cardiac structures

Speckle tracking is the standard tool to study myocardial deformation by echocardiography and, when applied to the left ventricle (LV), provides a great amount of information that goes beyond the mere quantification of absolute deformation. Therefore, it is essential to standardize these measures.

The expression strain is used as a synonym for myocardial deformation, which reduced the applicability of the method to this measure, which is certainly incomplete, because speckle tracking also allows for the measurement of rotational variables, even enabling to estimate myocardial work. Although terminology is internationally standardized, misunderstandings are still frequent. In Brazil, for example, the expression "two-dimensional strain" is used to refer to speckle tracking, which is in disagreement with international standards.[4]

LV longitudinal strain is the most renowned measure for use in speckle tracking echocardiography (STE). Examples of its applicability include: determination of subclinical myocardial disease in apparently normal ventricles, early diagnosis of chemotherapy cardiotoxicity, differentiation between the main causes of increased myocardial thickness, risk segmentation in different heart diseases, and in a myriad of other clinical conditions affecting the myocardium.[5–8]

LV circumferential and radial deformations can also be measured by the same method; moreover, the velocity at which these deformations occur, the so-called strain rate, can also be obtained. Rotational variables measured at the basal, medial, and apical segments may also complement the assessment, as well as LV twist, which is the difference between LV basal and apical rotations.[4] These assessment methods have a complementary role to that of LV longitudinal strain and do not imply its replacement.

The right ventricle can also be assessed with regard to deformation; in this case, longitudinal strain of its free wall is the most validated and recommended measure.[9–12] The same applies to left atrial (LA) longitudinal strain, a promising approach for functional studies and the focus of this review, which will subsequently describe the peculiarities of this measure, focusing on the study of LV diastolic function (DF).

Quantification of cardiac mechanics and its studies in diastology

There is a significant number of publications on the complementation of DF analysis by techniques to quantify cardiac muscle mechanics, and the vast majority of these publications is related to the study of the LV with a focus on determining its filling pressure.[13–16] Despite the favorable results of these techniques, their effective implementation to this end did not occur, which may be explained, among other reasons, by the complexity of these analyses compared to the traditional measures of LV DF by Doppler echocardiography.[17]

However, although the assessment of LV filling pressure by STE is not part of 2016 recommendations for the assessment of DF, STE is indeed recommended to determine myocardial disease, especially LV global longitudinal strain, which may be used to determine myocardial disease and thus help in the initial analysis of DF.[18]

What is the role of LA in the assessment of LV DF?

Differently from other techniques to assess DF, which reveal cardiac hemodynamic status at the time of examination, the assessment of LA by calculating its volume reflects the cumulative effects of LV filling pressures.

The use of LA dimensions in clinical practice precedes even the first guidelines for the assessment of DF diastole by the American Society of Echocardiography (ASE), published in 2009.[19] Many studies showed that increased LA volume is closely related not only to diagnosis, but also to the prognosis of patients with diastolic dysfunction (DD).[20–28] However, it is important to emphasize that LA enlargement is not exclusive to DD and can also be observed in mitral valve disease, long-lasting arrhythmia, anemia, and intense and prolonged practice of physical activity. However, LA enlargement in patients with arterial hypertension is considered, by some authors, as a diagnostic feature of DD, even when not associated with other echocardiographic features of DD.[29]

From another perspective, the identification of normal-sized LA does not rule out the presence of DD, because recent or intermittent increases in LV filling pressure may not be sufficient to cause LA enlargement, which certainly makes it possible for this cavity to be assessed not only morphologically, but also functionally, more specifically by measuring its strain.

Functional analysis of the LA by speckle tracking and its potential applicability in diastology

Morphofunctional knowledge

Relationship between LA function and LV function

LA strain as measured by STE provides information on the reservoir, conduit, and contractile functions of this chamber (Figure 1). The usefulness of these measures is based on the close relationship between LA and LV functions. For example, the performance of reservoir and conduit functions is determined by, in addition to atrial compliance, ventricle relaxation and by transmitral pressure gradient.[30] The conditions that impair any aspect of atrial function, especially mechanical alterations that lead to abnormalities in pressure-volume relationships, may affect overall cardiac performance, leading to unfavorable symptoms and outcomes.[31]

Causes of LA dysfunction

The hemodynamic effects of ventricle diseases seem insufficient to explain all the changes leading to LA dysfunction, because, in some patients, this dysfunction occurs even in the absence of significant morphological and/or functional changes in the LV.[32] This is corroborated by studies with previously healthy populations, in which LA function and its remodeling were independently associated and preceded the clinical manifestation of heart failure.[33] Another aspect that favors functional studies of LA results from the fact that, although

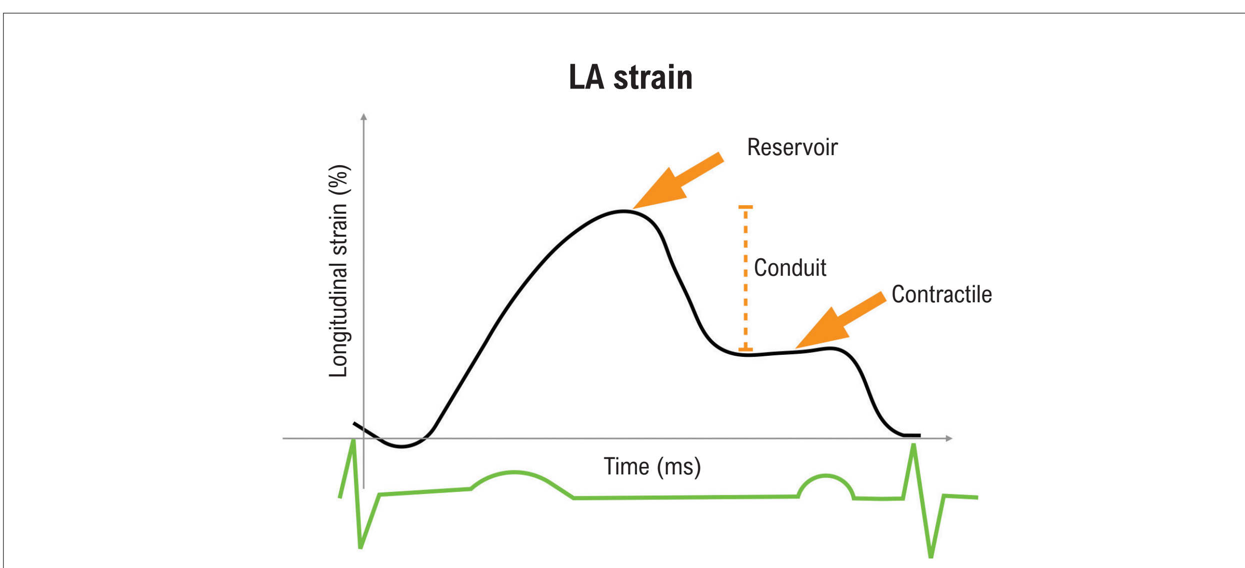

Figure 1 – *Phases of left atrial function evidenced by the study of longitudinal deformation. LA: left atrial.*

LA strain is not totally independent from load, myocardial deformation tends to be less affected by load than LA volume would be.[34] Furthermore, changes in LA strain precede volume changes in almost a decade.[35]

LA dysfunction is believed to result, at least in part, from LA myocardial fibrosis. This process has been associated with several biological factors, practically the same one that impact ventricular myocardium.[33] LA strain is inversely correlated with the degree of LA fibrosis (Figure 2).[36, 37] This association alone would not be sufficient to favor the use of this variable as a complementary tool in current protocols of DF analysis. However, LA function was shown to be a determinant factor of the time of decompensation of heart failure with preserved ejection fraction (HFpEF), one of the reasons for the discussion on the potential use of LA strain as a marker of elevated LV filling pressures.[38] However, although functional changes may be partially justified by LA fibrosis, it is insufficient to fully explain the phenomenon, which is one of the topics that justify studies on the applicability of LA strain in diastology.

Applicability of functional analysis of LA aimed at the study of LVDD

To apply the study of LA deformation in LV diastology, it is important to first consider the intended purpose, which may be:

1. To optimize the diagnosis of DD in general;

2. To determine the presence or absence of increased filling pressure.

A significant number of studies confirm the usefulness of measuring LA strain to diagnose DD by demonstrating a decrease in LA reservoir strain in critical situations such as hypertension, diabetes, and chronic kidney disease, even when LA volume and/or emptying pressure is still normal.[39–41] Similar findings were observed in a study of patients with hypertension, diabetes, or coronary disease, all of them with preserved LVEF, which revealed an increase close to 10% in the diagnosis of diastolic dysfunction when adding LA strain to the algorithm for DD detection used in the 2016 guidelines of ASE with the European Association of Cardiovascular Image (EACVI) (Figure 3).[42]

In addition to diagnosis, LA strain may also be applied to categorize DD, because both reservoir and conduit functions decrease as the grade of DD increases.[43] Analyses of ROC curve show that reservoir strain has high accuracy to grade DD compared to LV volume index.[44]

Despite this gradual and progressive reduction of reservoir and conduit functions, it should be observed that, a different behavior was observed in the first phases with regard to contractile function, which increases in DD grade 1 before decreasing, after grade 2.[44] Another interesting observation is that, in cases of changes in LV relaxation, there is an increase in the relative contribution of LA contractile function to its filling, while the conduit function decreases. When LV filling pressures increase significantly, the limits of LA preload are reached, and the LA will behave predominantly as a conduit.[45] Such characteristics would not necessarily be useful to make the use of LA strain effective in diastology, but its knowledge may help avoid mistaken interpretations by simplifying the effects of LV diastolic function on LA.

Standardization and atrial strain measures by speckle tracking

Despite measuring LA two-dimensional strain by STE is relatively simple and direct, methodological differences initially contributed to a certain variation in normal values. This was improved with the recent systematization and standardization proposed by several international societies and by the industry, which defined the longitudinal strain, which is the strain the direction tangential to the endocardial atrial border in an apical view, as the only one recommended. The same document advise against a segmental study; therefore, only the overall value obtained in the analyzed view.[46]

It is possible to combine measures obtained by the 4- and 2- chamber views to calculate global longitudinal LA strain, and it was even recommended in a previous consensus (Figure 4).[47] However, studies using a single view are acceptable, specifically the 4-chamber view in this case, due to its practicality. Results from a recent meta-analysis including 30 studies, totaling 2038 healthy individuals, provided the normal reference values currently accepted for LA strain during the reservoir, conduit, and contraction phases.[48]

Therefore, recommendation allows for the analysis to be conduct in an apical 4-chamber view, avoiding cavity shortening, and with the region of interest measuring nearly 3 mm in width.[46]

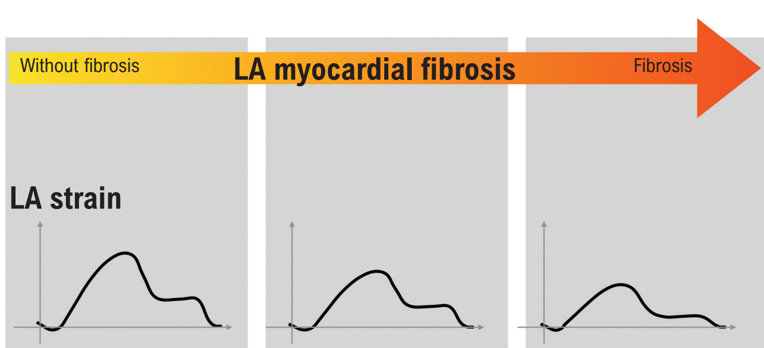

Figure 2 – *LA strain and myocardial atrial fibrosis. LA: left atrial*

Patients with preserved LVEF with risk for DD

1. Average E/e' > 14
2. Septal e' velocity < 7 or lateral e' velocity < 10 cm/s
3. TR velocity > 2.8 m/s
4. LA volume index > 34 mL/m^2 or LA strain < 23%

> 50% of positive (altered) variables

Increase of approximately 10% in the rate of diagnosis of DD

Figure 3 – *Increase in the diagnosis of DD by including LA strain to the algorithm. Adapted from Morris et al. (reference 42). E: E wave velocity of the transmitral flow in pulse Doppler; e': mitral annulus protodiastolic velocity in tissue Doppler; LA: left atrial; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation; DD: diastolic dysfunction.*

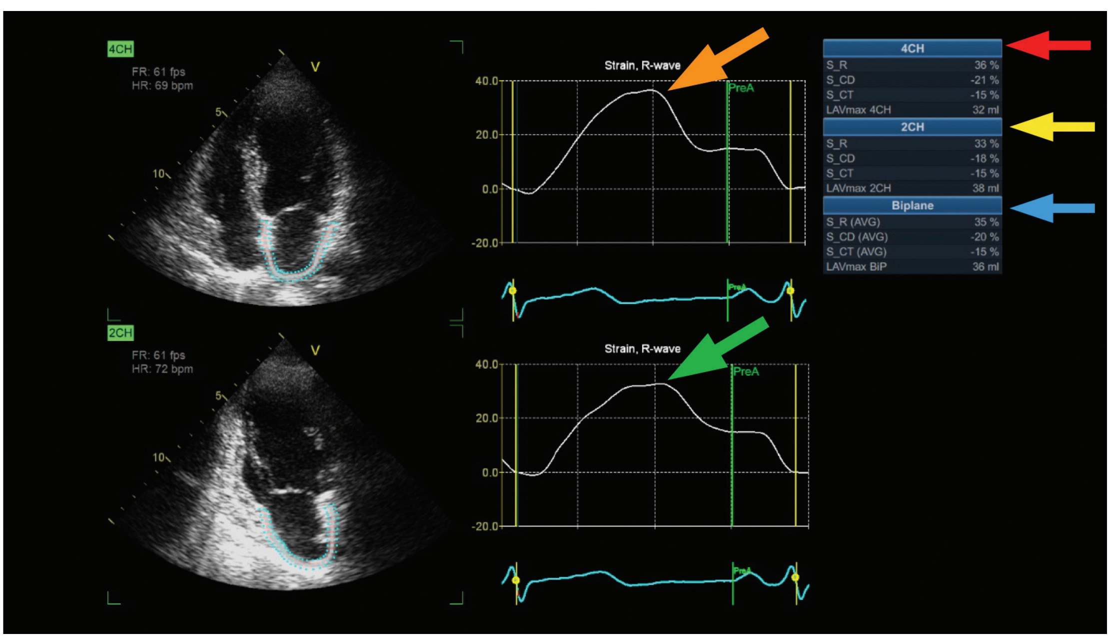

Figure 4 – *Measures of left atrial strain by speckle tracking. Orange and green arrows point to peak reservoir strains for the 4- and 2-chamber echocardiographic views, respectively. Red and yellow arrows indicate the automatic results for the reservoir, conduit, and contraction measures in the 4- and 2-chamber views, respectively, and the blue arrow highlights overall results (mean values) for the 2 views.*

Normal values of left atrial strain

As observed in Figure 1, LA deformation may be assessed by means of 2 peaks: maximum deformation (also known as reservoir strain) and atrial contraction deformation (also known as contractile strain), and the difference between these peaks, which is the third measure known as conduit strain. Normal values currently accepted derive from the aforementioned 2017 meta-analysis and are the following:[48]

- Reservoir strain 39% (95% confidence interval: 38% to 41%)
- Conduit strain 23% (95% confidence interval: 21% to 25%)
- Contractile strain 17% (95% confidence interval: 16% to 19%)

How to use altered LA strain values in diastology?

It would be convenient, with regard to diagnosis and classification of DD, that abnormal LA strain succeed elevated LV filling pressures, being a direct consequence of the latter. However, as previously shown, what actually occurs is the progressive reduction of LA strain as DD grade increases; therefore interpretation of the abnormality should be performed with caution and contextualized in the interest of the investigation.

Applicability of LA strain to determine cardiovascular prognosis

Abnormalities resulting from LA deformation may be studied in order to determine cardiovascular risks. In these cases, these abnormalities show an independent correlation with cardiovascular events.[49,50] Cutoff values found in these situations would not necessarily be useful to determine and categorize DD.

Applicability of LA strain to classify DD

Measures of LA deformation can also be used to help grade DD, which will also imply in determining prognosis, because, as already well established, the risk of cardiovascular events is directly correlated with grade of DD.[51,52]

Many studies were conducted to correlate reduction in LA myocardial deformation with increased LV filling pressures, especially pulmonary artery systolic pressure (PASP) and mean pulmonary capillary wedge pressure. One of these studies, conducted in 2009 by Kurt *et al.*, assessed the so-called LA stiffness, calculated as the ratio of E/e´ (average) to LA strain during systole (currently more often referred to as LA reservoir strain). These researchers showed that LA stiffness presented a good correlation with the invasive measure of PASP.[53] Subsequent studies started to focus on reservoir strain alone.

In 2019, Singh *et al.* showed that peak LA strain lower than 20% was able to accurately identify pre-A wave LV diastolic pressure higher than 15 mmHg, significantly improving the classification of DD made by current guidelines (2016), especially in individuals with preserved LVEF.[54] Similar results were published in 2021 by Inoue *et al.*, in whose study LA reservoir strain < 18% and LA contractile strain < 8% determined increased LV filling pressure better than LA volume and other conventional Doppler parameters.[55]

In 2020, an editorial published in *Journal of American College of Cardiology - Cardiovascular Imaging* by Jae Oh proposed a new diagnostic approach of DD. Of the proposals, the use of LA reservoir strain to differentiate undetermined cases.[56] In 2021, following exactly the same line, LA strain was included in an European consensus, in the case concerning the use of multimodality imaging in patients with HFpEF.[57] This incorporation took into account the 2016 algorithm for the analysis of DF and the results from the study by Inoue *et al.* (Figure 5).[55]

When not using LA strain to classify DD

In some situations, the measure of LA strain should not be considered, such as in limitations of echocardiographic images and in detriments to the analysis of two or more LA wall segments.

Similarly, patients with AF should not have their LA reservoir strain analyzed for the purpose of estimating LV filling pressure.[55] This also applies to patients who presented with episodes of AF for more than 48 hours in the 90 days before the test. Such fact results from the possible presence of LA myocardial stunning, a situation characterized by very low reservoir strain low values. Therefore, this measure should not be used to diagnose HFpEF when there is possibility of atrial stunning.

Final considerations

The importance of assessing LA function is unquestionable in several clinical situations and in specific patient populations. Considering the presented studies and the current technologies involved, the authors believe that LA strain is indeed ready to use, because it was shown that LA strain, especially its reservoir component, progressively decreases as LVDD worsens and may be useful in the reclassification of “undetermined” cases. Obviously, many questions remain to be answered regarding changes in LA function, especially in the context of diastology. However, this tool has potential for immediate use as a complementary diagnostic parameter.

The EACVI made a right decision when recommending the use of LA reservoir strain as an additional measure in cases when filling pressures would be classified as undetermined by the algorithm of the 2016 guidelines to assess DF.[57]

It is important to emphasize that the use of LA strain is not limited to diastology, as previously described. Changes in LA deformation are associated with prognostic implications in several scenarios, such as in the prediction of a cardioembolic event.[58] Furthermore, LA has been the focus of discussions and investigations that reinforce its role in a myriad of cardiovascular situations, including new concepts, such as the definition of atrial failure.[59]

Hence, there is a great potential in the use of LA myocardial deformation in the context of analysis of LV DF to improve the accuracy of algorithms employed in clinical practice.

Author Contributions

Writing of the manuscript: Calvilho Júnior AA, Assef JE and Braga JMS; conception and design of the research, acquisition of data and critical revision of the manuscript for intellectual content: Vilela AA, Paladino Filho AT and Nishida G.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

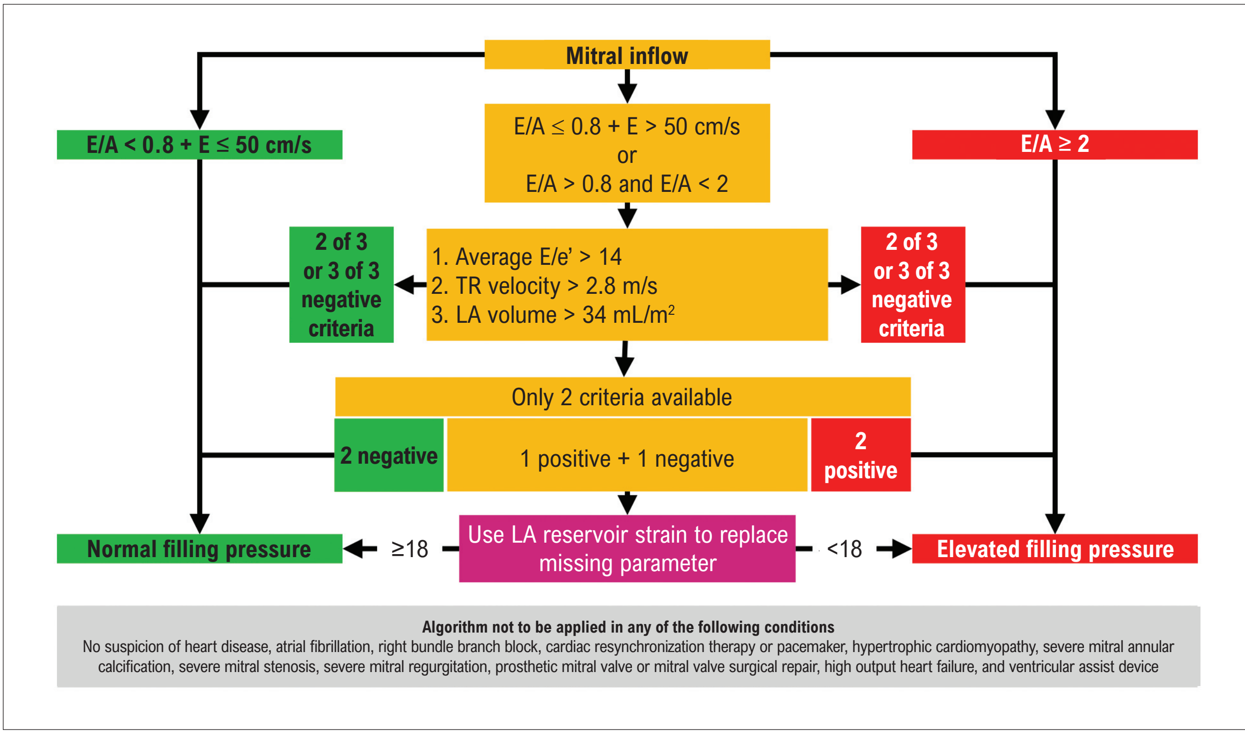

Figure 5 – *Algorithm proposed to grade DD using left atrial reservoir strain. Adapted from Smiseth et al. (reference 57). A: transmitral flow A wave velocity in pulse Doppler; E: E wave velocity of the transmitral flow in pulse Doppler, e': mitral annulus protodiastolic velocity in tissue Doppler; LA: left atrial; TR: tricuspid regurgitation.*

References

1. Mirsky I, Parmley WW. Assessment of Passive Elastic Stiffness for Isolated Heart Muscle and the Intact Heart. Circ Res. 1973;33(2):233-43. doi: 10.1161/01.res.33.2.233.

2. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial Strain by Doppler Echocardiography. Validation of a New Method To Quantify Regional Myocardial Function. Circulation. 2000;102(10):1158-64. doi: 10.1161/01.cir.102.10.1158.

3. Stendahl JC, Parajuli N, Lu A, Boutagy NE, Guerrera N, Alkhalil I, et al. Regional Myocardial Strain Analysis Via 2D Speckle Tracking Echocardiography: Validation With Sonomicrometry and Correlation with Regional Blood Flow in the Presence of Graded Coronary Stenoses and Dobutamine Stress. Cardiovasc Ultrasound. 2020;18(1):2. doi: 10.1186/s12947-019-0183-x.

4. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current And Evolving Echocardiographic Techniques for the Quantitative Evaluation of Cardiac Mechanics: ASE/EAE Consensus Statement on Methodology and Indications Endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr. 2011;24(3):277-313. doi: 10.1016/j.echo.2011.01.015.

5. Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. J Am Coll Cardiol. 2017;69(8):1043-56. doi: 10.1016/j.jacc.2016.12.012.

6. Halliday BP, Senior R, Pennell DJ. Assessing Left Ventricular Systolic Function: From Ejection Fraction to Strain Analysis. Eur Heart J. 2021;42(7):789-97. doi: 10.1093/eurheartj/ehaa587.

7. Almeida ALC, Gjesdal O, Mewton N, Choi EY, Teixido-Tura G, Yoneyama K et al. Speckle-Tracking pela Ecocardiografia Bidimensional – Aplicações Clínicas. Rev Bras Ecocardiogr Imagem Cardiovasc. 2013;26(1):38-49.

8. Oliveira AAA, Oliveira TA, Oliveira LA, Meneses GC, Bezerra GF, Martins AMC, et al. Association Between Angiopoietin-2 and Functional Cardiac Remodeling in Hemodialysis Patients with Normal Left Ventricular Ejection. J Clin Hypertens (Greenwich). 2022;24(4):502-12. doi: 10.1111/jch.14465.

9. Motoki H, Borowski AG, Shrestha K, Hu B, Kusunose K, Troughton RW, et al. Right Ventricular Global Longitudinal Strain Provides Prognostic Value Incremental to Left Ventricular Ejection Fraction in Patients With Heart Failure. J Am Soc Echocardiogr. 2014;27(7):726-32. doi: 10.1016/j.echo.2014.02.007.

10. Morris DA, Krisper M, Nakatani S, Köhncke C, Otsuji Y, Belyavskiy E, et al. Normal Range and Usefulness of Right Ventricular Systolic Strain to Detect Subtle Right Ventricular Systolic Abnormalities in Patients With Heart Failure: A Multicentre Study. Eur Heart J Cardiovasc Imaging. 2017;18(2):212-23. doi: 10.1093/ehjci/jew011.

11. D'Andrea A, Stanziola A, D'Alto M, Di Palma E, Martino M, Scarafile R, et al. Right Ventricular Strain: An Independent Predictor of Survival in Idiopathic Pulmonary Fibrosis. Int J Cardiol. 2016;222:908-910. doi: 10.1016/j.ijcard.2016.07.288.

12. Platz E, Hassanein AH, Shah A, Goldhaber SZ, Solomon SD. Regional Right Ventricular Strain Pattern in Patients With Acute Pulmonary Embolism. Echocardiography. 2012;29(4):464-70. doi: 10.1111/j.1540-8175.2011.01617.x.

13. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global Diastolic Strain Rate For the Assessment of Left Ventricular Relaxation and Filling Pressures. Circulation. 2007;115(11):1376-83. doi: 10.1161/CIRCULATIONAHA.106.662882.

14. Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N. Usefulness of New Diastolic Strain and Strain Rate Indexes For the Estimation of Left Ventricular Filling Pressure. Am J Cardiol. 2008;101(10):1504-9. doi: 10.1016/j.amjcard.2008.01.037. Epub 2008 Mar 21.

15. Nguyen JS, Lakkis NM, Bobek J, Goswami R, Dokainish H. Systolic and Diastolic Myocardial Mechanics In Patients With Cardiac Disease and Preserved Ejection Fraction: Impact of Left Ventricular Filling Pressure. J Am Soc Echocardiogr. 2010;23(12):1273-80. doi: 10.1016/j.echo.2010.09.008.

16. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved Left Ventricular Twist and Circumferential Deformation, but Depressed Longitudinal and Radial Deformation in Patients with Diastolic Heart Failure. Eur Heart J. 2008;29(10):1283-9. doi: 10.1093/eurheartj/ehn141.

17. Calvilho AA Jr, Assef JE, Le Bihan D, Barretto RBM, Paladino ATF, Abizaid AAC, et al. E/E` Ratio Is Superior to Speckle Tracking For Detecting Elevated Left Ventricular End-Diastolic Pressure in Patients with Coronary Artery Disease and Preserved Ejection Fraction. Echocardiography. 2019;36(7):1263-72. doi: 10.1111/echo.14407.

18. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, 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. J Am Soc Echocardiogr. 2016;29(4):277-314. doi: 10.1016/j.echo.2016.01.011.

19. 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. J Am Soc Echocardiogr. 2009;22(2):107-33. doi: 10.1016/j.echo.2008.11.023.

20. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of Cardiovascular Outcomes with Left Atrial Size: Is Volume Superior To Area Or Diameter? J Am Coll Cardiol. 2006;47(5):1018-23. doi: 10.1016/j.jacc.2005.08.077.

21. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left Atrial Volume as an Index of Left Atrial Size: A Population-Based Study. J Am Coll Cardiol. 2003;41(6):1036-43. doi: 10.1016/s0735-1097(02)02981-9.

22. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, et al. Left Atrial Volume: Important Risk Marker of Incident Atrial Fibrillation in 1655 Older Men and Women. Mayo Clin Proc. 2001;76(5):467-75. doi: 10.4065/76.5.467.

23. Fatema K, Barnes ME, Bailey KR, Abhayaratna WP, Cha S, Seward JB, et al. Minimum Vs. Maximum Left Atrial Volume for Prediction of First Atrial Fibrillation or Flutter in an Elderly Cohort: A Prospective Study. Eur J Echocardiogr. 2009;10(2):282-6. doi: 10.1093/ejechocard/jen235.

24. Abhayaratna WP, Fatema K, Barnes ME, Seward JB, Gersh BJ, Bailey KR, et al. Left Atrial Reservoir Function As A Potent Marker for First Atrial Fibrillation or Flutter in Persons > Or = 65 Years Of Age. Am J Cardiol. 2008;101(11):1626-9. doi: 10.1016/j.amjcard.2008.01.051.

25. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left Atrial Volume: A Powerful Predictor of Survival after Acute Myocardial Infarction. Circulation. 2003;107(17):2207-12. doi: 10.1161/01.CIR.0000066318.21784.43.

26. Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, et al. Long-Term Prognostic Significance of Left Atrial Volume in Acute Myocardial Infarction. J Am Coll Cardiol. 2004;44(2):327-34. doi: 10.1016/j.jacc.2004.03.062.

27. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left Atrial Size and The Risk of Stroke and Death. The Framingham Heart Study. Circulation. 1995;92(4):835-41. doi: 10.1161/01.cir.92.4.835.

28. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, Gersh BJ, et al. Usefulness of Left Atrial Volume in Predicting First Congestive Heart Failure in Patients > Or = 65 Years Of Age with Well-Preserved Left Ventricular Systolic Function. Am J Cardiol. 2005;96(6):832-6. doi: 10.1016/j.amjcard.2005.05.031.

29. Nagueh SF. Left Ventricular Diastolic Function: Understanding Pathophysiology, Diagnosis, and Prognosis With Echocardiography. JACC Cardiovasc Imaging. 2020;13(1 Pt 2):228-44. doi: 10.1016/j.jcmg.2018.10.038.

30. Bowman AW, Kovács SJ. Left Atrial Conduit Volume is Generated by Deviation from the Constant-Volume State of the Left Heart: A Combined MRI-Echocardiographic Study. Am J Physiol Heart Circ Physiol. 2004;286(6):H2416-24. doi: 10.1152/ajpheart.00969.2003.

31. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left Atrial Remodeling and Function in Advanced Heart Failure with Preserved Or Reduced Ejection Fraction. Circ Heart Fail. 2015;8(2):295-303. doi: 10.1161/CIRCHEARTFAILURE.114.001667.

32. Habibi M, Chahal H, Opdahl A, Gjesdal O, Helle-Valle TM, Heckbert SR, et al. Association of CMR-Measured LA Function with Heart Failure Development: Results From the MESA Study. JACC Cardiovasc Imaging. 2014;7(6):570-9. doi: 10.1016/j.jcmg.2014.01.016.

33. Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and Clinical Significance. JACC Cardiovasc Imaging. 2017;10(1):65-77. doi: 10.1016/j.jcmg.2016.11.003.

34. Genovese D, Singh A, Volpato V, Kruse E, Weinert L, Yamat M, et al. Load Dependency of Left Atrial Strain in Normal Subjects. J Am Soc Echocardiogr. 2018;31(11):1221-8. doi: 10.1016/j.echo.2018.07.016.

35. Boyd AC, Richards DA, Marwick T, Thomas L. Atrial Strain Rate is A Sensitive Measure of Alterations in Atrial Phasic Function in Healthy Ageing. Heart. 2011;97(18):1513-9. doi: 10.1136/heartjnl-2011-300134.

36. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left Atrial Strain And Strain Rate in Patients with Paroxysmal and Persistent Atrial Fibrillation: Relationship to Left Atrial Structural Remodeling Detected By Delayed-Enhancement MRI. Circ Cardiovasc Imaging. 2010;3(3):231-9. doi: 10.1161/CIRCIMAGING.109.865683.

37. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. JAMA. 2014;311(5):498-506. doi: 10.1001/jama.2014.3.

38. Sanchis L, Gabrielli L, Andrea R, Falces C, Duchateau N, Perez-Villa F, et al. Left Atrial Dysfunction Relates To Symptom Onset in Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction. Eur Heart J Cardiovasc Imaging. 2015;16(1):62-7. doi: 10.1093/ehjci/jeu165.

39. Morris DA, Takeuchi M, Krisper M, Köhncke C, Bekfani T, Carstensen T, et al. Normal Values and Clinical Relevance of Left Atrial Myocardial Function Analysed by Speckle-Tracking Echocardiography: Multicentre Study. Eur Heart J Cardiovasc Imaging. 2015;16(4):364-72. doi: 10.1093/ehjci/jeu219.

40. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, et al. Early Detection of Left Atrial Strain Abnormalities by Speckle-Tracking in Hypertensive and Diabetic Patients with Normal Left Atrial Size. J Am Soc Echocardiogr. 2011;24(8):898-908. doi: 10.1016/j.echo.2011.04.014.

41. Kadappu KK, Abhayaratna K, Boyd A, French JK, Xuan W, Abhayaratna W, et al. Independent Echocardiographic Markers of Cardiovascular Involvement in Chronic Kidney Disease: The Value of Left Atrial Function and Volume. J Am Soc Echocardiogr. 2016;29(4):359-67. doi: 10.1016/j.echo.2015.11.019.

42. 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. doi: 10.1016/j.jcmg.2017.07.029.

43. 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. doi: 10.1016/j.jcmg.2016.08.014.

44. Brecht A, Oertelt-Prigione S, Seeland U, Rücke M, Hättasch R, Wagelöhner T, et al. Left Atrial Function in Preclinical Diastolic Dysfunction: Two-Dimensional Speckle-Tracking Echocardiography-Derived Results from the BEFRI Trial. J Am Soc Echocardiogr. 2016;29(8):750-8. doi: 10.1016/j.echo.2016.03.013.

45. 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. doi: 10.1016/j.jacc.2019.01.059.

46. Badano LP, Kolias 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. doi: 10.1093/ehjci/jey042.

47. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update From the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70. doi: 10.1093/ehjci/jev014.

48. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal Ranges of Left Atrial Strain by Speckle-Tracking Echocardiography: A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr. 2017;30(1):59-70.e8. doi: 10.1016/j.echo.2016.09.007.

49. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, et al. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure with Preserved Ejection Fraction: Importance of Left Atrial Strain. Circ Cardiovasc Imaging. 2016;9(3):10.1161/CIRCIMAGING.115.003754e003754. doi: 10.1161/CIRCIMAGING.115.003754.

50. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, et al. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2016;9(4):e002763. doi: 10.1161/CIRCHEARTFAILURE.115.002763.

51. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality Rate in Patients with Diastolic Dysfunction and Normal Systolic Function. Arch Intern Med. 2011;171(12):1082-7. doi: 10.1001/archinternmed.2011.244.

52. Kitzman DW, Little WC. Left Ventricle Diastolic Dysfunction and Prognosis. Circulation. 2012;125(6):743-5. doi: 10.1161/CIRCULATIONAHA.111.086843.

53. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left Atrial Function in Diastolic Heart Failure. Circ Cardiovasc Imaging. 2009;2(1):10-5. doi: 10.1161/CIRCIMAGING.108.813071.

54. 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. doi: 10.1007/s10554-018-1425-y.

55. Inoue K, Khan FH, Remme EW, Ohte N, García-Izquierdo E, Chetrit M, et al. Determinants of Left Atrial Reservoir and Pump Strain and Use of Atrial Strain For Evaluation of Left Ventricular Filling Pressure. Eur Heart J Cardiovasc Imaging. 2021;23(1):61-70. doi: 10.1093/ehjci/jeaa415.

56. Oh JK, Miranda WR, Bird JG, Kane GC, Nagueh SF. The 2016 Diastolic Function Guideline: Is it Already Time to Revisit or Revise Them? JACC Cardiovasc Imaging. 2020;13(1 Pt 2):327-335. doi: 10.1016/j.jcmg.2019.12.004.

57. Smiseth OA, Morris DA, Cardim N, Cikes M, Delgado V, Donal E, et al. Multimodality Imaging in Patients with Heart Failure and Preserved Ejection Fraction: An Expert Consensus Document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2022;23(2):e34-e61. doi: 10.1093/ehjci/jeab154.

58. Bhat A, Chen HHL, Khanna S, Mahajan V, Gupta A, Burdusel C, et al. Diagnostic and Prognostic Value of Left Atrial Function in Identification of Cardioembolism and Prediction of Outcomes in Patients with Cryptogenic Stroke. J Am Soc Echocardiogr. 2022;35(10):1064-76. doi: 10.1016/j.echo.2022.05.018.

59. Bisbal F, Baranchuk A, Braunwald E, Luna AB, Bayés-Genís A. Atrial Failure as a Clinical Entity: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;75(2):222-232. doi: 10.1016/j.jacc.2019.11.013.