



EDITORIAL COMMENT

Left atrial function and left ventricular diastolic dysfunction – Just the marionette and its master?



Função auricular esquerda e disfunção diastólica ventricular – apenas a marionete e o seu mestre?

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Left ventricular diastolic dysfunction (LVDD) usually precedes systolic dysfunction in the early phase after acute myocardial infarction (MI).^{1,2} Previous studies have shown that in MI patients, LVDD may promote progression of heart failure (HF) from stage B to stage C, even in HF with preserved left ventricular (LV) ejection fraction (HFpEF).^{3,4}

In about one fifth of patients after MI, the left atrium undergoes significant remodeling, defined as increase in left atrial (LA) volume of ≥ 8 ml/m² over a 12-month period (although it may be evident after one month).^{3,5}

It has been reported that after MI, increased LV end-diastolic pressure (LVEDP) induces higher LA afterload and hence mechanical stress on the atrium that leads to higher LA volumes, mechanical dysfunction and increased stiffness, which in turn, by a tandem effect, reduce LA emptying, LV filling and cardiac output during exertion. The backward effects of LA enlargement and dysfunction are pulmonary venous congestion and vascular pulmonary vasoconstriction that may eventually trigger right ventricular overload and dysfunction. Accordingly, the evolving stages of HFpEF are associated with right ventricle-to-pulmonary circulation

uncoupling, impaired gas exchange, and exercise ventilation inefficiency.^{6–8}

LA dilatation has emerged as a robust marker of the presence, severity and duration of increased LVEDP and as an independent predictor of adverse events in HFpEF, including after MI.⁹

Recent studies in HF after MI have reported that LA phasic function has better diagnostic accuracy and prognostic performance than the well-established parameter of LA maximum volume.^{4,10}

LA phasic function consists of three main mechanical components, the reservoir, conduit, and booster functions, which can be derived from conventional volumetric indices or measured with high accuracy and feasibility by strain and strain rate using two-dimensional speckle-tracking echocardiography (2DSTE).¹¹

LA reservoir function takes place during LV systole with the filling of the left atrium from the pulmonary veins; its major determinants are LV longitudinal function (since it depends on the descent of the LV base during systole) and LA stiffness (or its inverse, distensibility).^{6,7} Reservoir function can be estimated by analysis of LA deformation to yield peak atrial longitudinal strain (PALS) and strain rate.⁹

PALS and strain rate are surrogates of atrial can indicate the presence of atrial fibrosis and structural remodeling, since they can be used to measure LA stiffness, which correlates logarithmically with filling pressures

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and is more accurate in predicting LVEDP >15 mmHg than the E/e ratio.¹² LA stiffness is assessed by the ratio of invasively measured pulmonary capillary wedge pressure (PCWP) to global PALS (PCWP/PALS) or by non-invasive estimates in which PCWP is replaced by transmitral E/e' (E/e'/PALS).^{12,13}

LA conduit function occurs during early LV diastole, contributing to early LV filling, and coincides with early mitral inflow (E wave). Because the mitral valve is open in diastole, conduit function is also dependent on LV relaxation and preload. Conduit function can be assessed by PALS minus peak atrial contraction strain (PACS).¹¹

LA booster function, during late diastole, reflects LA contractile function and coincides with late mitral inflow (A wave). It is affected by atrial preload, intrinsic contractility, LVEDP (atrial afterload), and electromechanical coupling. The echocardiographic strain parameter used to assess booster function is PACS.⁹

LA function is complex and there is a critical interplay between LA mechanics and LV diastolic and systolic performance.

In this issue of the *Journal*, Fontes-Carvalho et al.¹⁴ report the diagnostic value of LA volumes and functional indices (volumetric and strain measures) extracted from time-volume curves analyzed by Velocity Vector Imaging (VVI) software and correlated with data from cardiopulmonary exercise testing (CPET), in 94 patients in sinus rhythm and LVpEF, one month after MI. The above mentioned indexes were also compared with Doppler diastolic parameters and LVEF.

The study population configures of asymptomatic patients at risk of developing HFpEF (stages A and B HF). This represents a relatively early HFpEF phenotype, which can be challenging in terms of identification and risk stratification, although an earlier diagnosis could be made by exercise testing to determine diastolic function or by LA functional analysis.

Obokata et al. analyzed patients with HFpEF with prospective simultaneous echocardiographic and catheterization studies at rest and during exercise with expired gas analysis. They found that although exercise E/e' >14 improved sensitivity (to 90%) compared to the resting criteria, it decreased specificity (71%) and was not sufficiently discriminative to identify individuals at high risk for developing progressive HFpEF, given that the prevalence of abnormal diastolic exercise response in HFpEF cohorts may be up to 70%.¹⁵

In the study presented, 2DSTE strain imaging was performed according to standard methods, but with less commonly used strain analysis software, VVI, which is vendor-independent.^{14,16} This software automatically provides time-volume and strain curves from the displacement of LA endocardial pixels from which indices of phasic LA function can be derived by volumes or by strain and strain rate measures.

For the purposes of their analysis, the authors,¹⁴ like others,^{10,17,18} obtained LA longitudinal strain and strain rate using the most common processing methodology, in which the strain analysis begins at QRS onset, i.e. ventricular cycle or systolic gating. Volume and strain curves generated for each of six atrial segments were obtained from

biplane apical views at different phases of the cardiac cycle, depicting specific LA phasic strain patterns, corresponding to systolic reservoir function (PALS), diastolic conduit function (PALS-PACS) and diastolic booster pump function (PACS).¹⁴⁻¹⁸

When the authors analyzed data from LA phasic volume and strain functional parameters and their correlation with the three main CPET parameters (exercise duration, peak VO₂ and VO₂ at anaerobic threshold), Doppler diastolic parameters (E' and E/e' ratio) and LVEF, the key findings were:

- 1) reduced LA conduit function, defined by volume or by strain/strain rate, showed the best correlation with all CPET parameters and with diastolic function (E' and E/e');
- 2) reduced strain reservoir function measured by PALS, but not by volumes, showed a significant correlation with exercise duration, peak VO₂ and VO₂ at anaerobic threshold ($r=0.30$, $p<0.01$; $r=0.35$, $p<0.01$; $r=0.24$, $p=0.02$), with E' and E/e', and with LVEF;
- 3) by contrast, LA booster function, assessed by volumes or by PACS and strain rate during atrial contraction, did not correlate with any exercise performance parameter.

These results are in line with previous reports showing that LA reservoir and conduit function are the best predictors of exercise tolerance and progression to overt HF and are also strong prognostic markers.^{10,17}

In a study combining echocardiography, cardiac magnetic resonance imaging, CPET, and catheterization, von Roeder et al.¹⁸ found that in the early stages of HFpEF, LA conduit strain was the strongest predictor of exercise intolerance. The group with lower peak VO₂ (≤ 16 ml/kg/min) showed worse LA conduit strain ($6\pm 2\%$ vs. $12\pm 4\%$; $p<0.001$), lower LV stroke volume (41 ± 6 vs. 50 ± 5 ml/m²; $p=0.002$), and earlier abnormal diastolic filling.

Others have reported that LA reservoir dysfunction as assessed by PALS is a better predictor of LVDD.

In fact, Morris et al.¹⁰ reported that LA strain could identify preclinical patients (stages A and B HFpEF). PALS and LA volume index (LAVI) were compared against the guidelines for the evaluation of LVDD¹⁹ in 517 patients at risk for HFpEF. The authors showed that in patients with LVDD and elevated LV filling pressures, in the subgroup of normal LAVI (<34 ml/m²) the abnormal PALS group had a greater frequency of HF symptoms (New York Heart Association class III/IV), PCWP >15 mmHg, and HF hospitalization at two years. In the normal LAVI subgroup, abnormal PALS was the only independent risk marker for developing HF after adjusting for age and gender (adjusted odds ratio 9.5; 95% confidence interval 1.9-46.4; $p<0.01$). The authors proposed that LA strain (PALS cutoff 23%) should be incorporated in an updated algorithm including earlier stages of HFpEF, since adding it to LAVI increased the rate of detection of LVDD from 13.5% to 23.4% ($p<0.01$).¹⁰

LA reservoir function is mechanically governed by LV longitudinal shortening, although it is also modulated by LA chamber stiffness.^{6,13} In a prospective study of 843 patients with MI, Ersbøll et al.²⁰ showed that, not surprisingly, there was a highly significant correlation between global longitudinal strain (GLS) and PALS within 48 hours of admission

($p < 0.001$; $r = -0.71$). In this early assessment after MI, PALS, not surprisingly, did not add further information on adverse outcome over GLS and LA dilatation.²⁰

Complementary information came from a study by Kurt et al. analyzing the late follow-up of MI patients. LA stiffness index (E/E' over PALS), obtained by simultaneous right heart catheterization and echocardiographic imaging, was the most accurate index to differentiate patients with HFpEF from those with LVDD and no HF.⁶

So it appears that in the course of HFpEF progression, starting with elevation of LVEDP in mild diastolic dysfunction, LA conduit function is the first to be impaired.¹⁸ When LA stiffness increases, LA reservoir function as assessed by PALS becomes the best diagnostic and prognostic marker, even before LA enlargement occurs,¹⁰ although LA dilatation retains its diagnostic capability.^{14,21}

Booster function is apparently increased in the early and intermediate stages of HFpEF, to compensate for the double impairment of LA conduit and reservoir function, as stated by Guan et al.²²

Fontes-Carvalho et al. are to be commended for expanding the existing literature on the assessment of LA mechanics by 2DSTE-based volumetric and deformation measures, and for highlighting the importance of atrioventricular coupling, which can directly influence global cardiac function, cardiac output and exercise capacity.

They also chose an exercise protocol which determined the ventilatory anaerobic threshold, using the V-slope method, which has the advantage of being relatively effort-independent.

Finally, the VVI software used in the study enables the routine assessment of atrial function, since it can be applied to two-dimensional images from all vendors, with a low exclusion rate (only 2% of eligible subjects, in contrast to the 15% reported by Freed et al.¹⁷) and acceptable intra- and interobserver reproducibility.¹⁴

The study has some limitations. No information was provided on LV structural abnormalities, including diastolic dysfunction previous to the study, which are common among MI patients; and these results can only be extrapolated for the software used in this article, since VVI software is little used in the literature, and there is significant intervendor variability in strain measurements.

Conclusions and potential applications

It is clear that LA function is not merely a marker of disease severity but also an active participant in the interplay between heart and lungs that carries significant clinical and prognostic implications. It is in fact more the left ventricle's master than its marionette.

LA strain and strain rate parameters are more sensitive than conventional parameters of atrial function, since they can depict alterations prior to alterations in LA volumes, with the potential for early diagnosis of HFpEF.^{10,22}

A routine combined approach to both LA volume and strain could be a future option for more accurate assessment of diastolic function because of the established prognostic value of LA volumes and its potential reverse remodeling.^{10,17,21}

Provocative testing combining LA strain analysis with stress tests may be of value and could represent a novel additional target for intervention.¹⁸

LA strain parameters may also be useful in understanding responsiveness to LA unload therapies.

Assessment of LA strain as analyzed by the new 2DSTE software is simple, accurate and reproducible, although it has limitations that are crucial to routine clinical application. There are no validated strain algorithms developed exclusively for assessment of LA function; most studies use software that was developed for the left ventricle, with adjustments to the width of the region of interest for the left atrium. There is no standardized method for LA strain acquisition and analysis, especially concerning the timing of the reference point (QRS vs. P-wave gating), and its use has been somewhat heterogeneous between studies.²³

Three-dimensional assessment of LA volume and strain should be more readily available and more robust.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Moller JE, Pellikka PA, Hillis GS, et al. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. *Circulation*. 2006;114:438–44.
2. Shanks M, Ng AC, vandeVeire NR, et al. Incremental prognostic value of novel left ventricular diastolic indexes for prediction of clinical outcome in patients with ST-elevation myocardial infarction. *Am J Cardiol*. 2010;105:592–7.
3. Popovic AD, Neskovic AN, Marinkovic J, et al. Serial assessment of left ventricular chamber stiffness after acute myocardial infarction. *Am J Cardiol*. 1996;77:361–4.
4. Antoni ML, ten Brinke EA, Atary JZ, et al. Left atrial strain is related to adverse events in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2011;97:1332–7.
5. Anwar AM, Geleijnse ML, Soliman OII, et al. Left atrial Frank-Starling law assessed by real-time, three dimensional echocardiographic left atrial volume changes. *Heart*. 2007;93:1393–7.
6. Kurt M, Wang J, Torre-Amione G, et al. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging*. 2009;2:10–5.
7. Morris DA, Gailani M, Vaz Pérez A, et al. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr*. 2011;24:651–62.
8. Borlaug BA, Kane GC, Melenovsky V, et al. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37:3293–302.
9. Kuppahally SS, Akoum N, Burgon NS, 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;3:231–9.
10. Morris DA, Belyavskiy E, Radhakrishnan A-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. *J Am Coll Cardiol*. 2017.
11. Vieira MJ, Teixeira R, Goncalves L, et al. Left atrial mechanics: echocardiographic assessment and clinical implications. *J Am Soc Echocardiogr*. 2014;27:463–78.

12. Guazzi M, Villani S, Generati G, et al. Right ventricular contractile reserve and pulmonary circulation uncoupling during exercise challenge in heart failure: pathophysiology and clinical phenotypes. *J Am Coll Cardiol HF*. 2016;4:625–35.
13. Barbier P, Solomon SB, Schiller NB, et al. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation*. 1999;100:427–36.
14. Fontes-Carvalho R, Sampaio F, Teixeira M, et al. Left atrial deformation analysis by speckle tracking echocardiography to predict exercise capacity after myocardial infarction. *Rev Port Cardiol*. 2018;10:37.
15. Obokata M, Kane G, Reddy I. The role of diastolic stress testing in the evaluation for HFpEF: a simultaneous invasive-echocardiographic study. *Circulation*. 2017;135:825–38.
16. Valocik G, Druzbacká L, Valocikova I, et al. Velocity vector imaging to quantify left atrial function. *Int J Cardiovasc Imaging*. 2010;26:641–9.
17. Freed BH, Daruwalla V, Cheng JY, 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:e003754.
18. von Roeder M, Rommel K-P, Kowallick JT, et al. Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging*. 2017;10:e005467.
19. Nagueh SF, Smiseth OA, Appleton CP, 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;29:277–314.
20. Ersbøll M, Andersen M, Valeur N, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging*. 2013;6:26–33.
21. Russo C, Jin Z, Homma S, Rundek T, et al. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. *Heart*. 2012;98:813–20.
22. Guan Z, Zhang D, Huang R, et al. Association of left atrial myocardial function with left ventricular diastolic dysfunction in subjects with preserved systolic function: a strain rate imaging study. *Clin Cardiol*. 2010;33:643–9.
23. Pathan F, D'Elia N, Nolan MT, et al. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. *J Am Soc Echocardiogr*. 2017;30:59–70, e8.