Relationship between the strain measures of left atrial function and heart failure worsening

Massimo Iacoviello[1], Davide Diomede[1], Erica Terazzi[1], Nicolangelo Diomede[1], Gianmarco Alcidi[1], Rosanna Pugliese[1], Sara Ioannoni[1], Matteo Romano[1], Michele Granatiero[2], Vito Di Terlizzi[2], Michele Correale[1], Matteo Di Biase[1], and Natale Daniele Brunetti[1]

[1]Universita degli Studi di Foggia Dipartimento di Scienze Mediche e Chirurgiche
[2]Azienda Ospedaliera Universitaria Foggia

April 12, 2023

Abstract

Background. Two-dimensional speckle tracking evaluation (2D-STE) is a useful tool to evaluate the complexity of atrial function by the analysis of the different phases of atrial deformation and by the combination with Doppler measurements of diastolic function. **Aim of the study.** To evaluate the role of the left atrial (LA) strain parameters to predict worsening chronic heart failure (CHF). **Methods.** We enrolled outpatients affected by CHF referred to our heart failure unit. Each patient underwent a medical visit, an electrocardiogram (ECG), and an echocardiographic examination. LA function was assessed by 2D-STE. The three phases of LA strain – i.e. the reservoir (LAr), the conduit (LAcd), and the contraction (LAct) – were evaluated. Moreover, the ratio between LAr and that of septal (LAr/Ees), lateral (LAr/Eel), and septal-lateral (LAr/Eem) E/e' were evaluated. During follow-up, the worsening of heart failure was evaluated. **Results.** Two hundred twenty-eight patients were enrolled. During a mean follow-up of 14±7 months, 47 patients showed at least one event related to heart failure worsening (40 hospitalisations, 5 heart transplantations, and 19 cardiovascular deaths). During univariate Cox regression analysis, LAr, LAcd, LAct, LAr/Ees, LAr/Eel, and LAr/Eem were all associated with events related to heart failure worsening, but during multivariate regression analysis, only LAr (HR: 0.94; 95% CI: 0.91–0.98; p: 0.007), LAr/Ees (HR: 0.49; 95% CI: 0.30–0.78; p: 0.002), and LAr/Eem (HR: 0.65; 95% CI: 0.47–0.89; p: 0.008) remained significantly associated with the events. Finally, LASr/Ee's showed accuracy in predicting outcomes greater than LASr (C-index 0.78 vs. 0.72, respectively). **Conclusions.** In CHF patients, the measure of the LA reservoir by 2D-STE is independently associated with heart failure worsening, but the accuracy in predicting the events is even greater when the reservoir is combined with the Doppler measures of diastolic function.

Introduction

While left atrial (LA) function could play a significant role in patients affected by cardiovascular diseases, it is poorly studied in several pathological conditions and is frequently considered a passive bystander of these pathophysiologic alterations [1]. However, the LA is a complex and active chamber which modulates left ventricle filling during ventricular systole through its reservoir function and during ventricular diastole as a conduit and booster pump functions [1–3]. Moreover, the interplay between LA and left ventricular (LV) functions throughout the cardiac cycle is crucial in several pathophysiological conditions [3, 4].

Recently, using two-dimensional spackle tracking evaluation (2D-STE), the significance of LA function impairment in heart failure has been demonstrated [5, 6]. However, the predictive value of the different phases of atrial function – i.e. reservoir, conduit, and contraction – still needs to be clarified. Moreover, the combination between the LA reservoir and Doppler measures of diastolic function has been demonstrated to be more accurate in detecting the presence of high LV filling pressure [7], but its association with heart failure outcome has not been investigated.

The aim of this study was to evaluate the role of the LA strain parameters reflecting the reservoir, conduit, and contraction as well as the combination with Doppler measurements of atrial function in predicting worsening chronic heart failure (CHF).

Methods

We enrolled patients affected by CHF who were referred to the Heart Failure Outpatients Clinic of the Cardiology Unit of the Polyclinic University Hospital Riuniti of Foggia, Italy, between October 2020 and January 2023. All the patients were enrolled in the Daunia registry, which was approved by the Institutional Ethics Committee of the Polyclinic University Hospital of Foggia, Italy (Protocol Code 68/CE/20, approved on 26 May 2020), and all provided written informed consent to participate.

The following inclusion criteria were considered: history of heart failure of any origin with recommended medical therapy at the time of the enrolment and in clinically stable condition for at least 30 days (e.g. no significant changes in hemodynamic status or medical therapy). Patients diagnosed with atrial fibrillation were enrolled if a regular ventricular paced rhythm was present, whereas they were excluded if an irregular rhythm was observed.

At the time of enrolment, each participant underwent a medical evaluation, including an electrocardiogram (ECG) and two-dimensional echocardiography.

Medical examination and electrocardiogram. Each participant's full medical history was collected. A physical examination and a 12-lead ECG were performed. Any evidence of ischemic cardiomyopathy, arterial hypertension, atrial fibrillation, diabetes mellitus, and/or dyslipidaemia was documented together with any history of chronic kidney disease and dialysis. New York Heart Association (NYHA) classes, anthropometric data, systolic and diastolic arterial pressures, and heart rhythms were also recorded. If available, the most recent routine blood chemistries were also documented. In particular, by serum creatinine, the glomerular filtration rate was calculated using the abbreviated CKD-EPI formula (GFR-EPI, ml/min/1.73 m^2) [8].

Echocardiographic evaluation. Two-dimensional echocardiographic imaging and Doppler acquisition were performed using an EPIQ CVx system (Philips, Amsterdam, the Netherlands) with an S5-1 transducer. At the baseline, five cycles of ECG-guided standard parasternal long- and short-axis, apical two-, three-, and four-chamber, and subcostal views were acquired. The LV end-diastolic diameter (LVEDD) and interventricular septum and LV posterior wall thicknesses were measured; the LV mass indexed for body surface area was calculated based on current recommendations [9]. Additionally, to analyse the tricuspid annular plane systolic excursion, an RV-focused four-chamber view was obtained. The LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) were calculated using Simpson's rule. The LA volume was also calculated using Simpson's rule and indexed for body surface area (LAVI). Using colour Doppler, mitral (MR) and tricuspid (TR) regurgitation were evaluated semi-quantitatively and assigned arbitrary units ranging from 0 to 4. The maximum trans-tricuspid valve pressure gradient was assessed using continuous-wave Doppler. Pulmonary systolic arterial pressure (PASP) was estimated based on the vena cava diameter. Peaks of early wave velocity at the mitral valve (E) were measured using pulsed Doppler. Furthermore, the early diastolic velocity peaks (e') at the level of the septal (e's) and lateral (e'l) mitral annulus were measured using pulsed and tissue Doppler imaging (TDI) [9]. Then the means of e's and e'l (e'm) as well as the ratios between E and e's (Ee's) and E and e'm (Ee'm) were calculated.

The AutoStrain application of the Philips EPIQ CVx ultrasound systems was used for the 'off-cart' analysis of strain from stored examinations. Values for LV global longitudinal strain (LV-GLS) were obtained from the analysis of two-, three-, and four-chamber views. The software automatically generated curves representing longitudinal strain; LV-GLS was calculated by averaging values obtained in all the segments. In this study, reduced systolic strain is indicated by values that are less negative than those determined at the baseline. The global longitudinal strain of the right ventricle (RVGLS) and that of the free wall (RVfwLS) were also calculated automatically from the values obtained in an RV-focused four-chamber view. In this study, reduced ventricular systolic strain is indicated by values that are less negative than those determined at the baseline.

By the standard four-chamber view, the AutoStrain application of the Philips EPIQ CVx ultrasound systems was also used for the 'off-cart' analysis of LA strain from stored examinations. As shown in Figure 1, the LA strain of *reservoir* (LAr), including those of*conduit* (LAcd) and *contraction* (LAct), were calculated (D.D., E.T.). Finally, the ratios between LAr and E/e's (LAr/Ees) and LAr and E/e'l (LAR/Eel) and that between LAr and E/e'm (LAr/Eem) were evaluated [7].

Follow-up

The patients were followed up as outpatients in the heart failure unit. The primary endpoint was heart failure progression defined as heart failure hospitalisation, heart transplantation, and/or cardiovascular death caused by heart failure worsening. The cause of death was verified by means of hospital records or the testimony of relatives and defined as being cardiovascular (death caused by heart failure worsening, acute coronary syndrome, and sudden death) or non-cardiovascular. Sudden death was defined as death within one hour after the onset of symptoms in a previously medically stable patient, death during sleep, or unwitnessed death.

Statistical analysis

The continuous variables are expressed as mean values ± SD. The intra- and inter-observer reproducibility of the LA strain measures were evaluated in 20 patients by two operators (M.I., N.D.) by means of the intraclass correlation coefficient (ICC), which measures the strength of the association between the two baseline recordings. The data were considered reproducible if the ICC was >0.60, and the reproducibility was considered almost perfect if the ICC was between 0.81 and 1.00 [10].

Pearson's linear correlations were used to assess the relationship between atrial strain measures and the other variables studied. Cox's proportional hazard model was used to verify the associations between the variables and the endpoints. Hazard ratios (HRs) are given with their 95% confidence intervals (CIs) and refer to a unit increase in the variable. The variables used in the forward stepwise multivariable models were selected based on their statistical significance during univariate analysis and the most relevant risk parameters for HF patients. Discrimination of the univariate and multivariate models was determined using a modified concordance statistic (C-index) for censored data.

Receiver operating characteristic (ROC) curves and the area under the curve (AUC) of the ROC were calculated to determine the associations between the studied variables and 1-year events. The best cut-off values for the analysed events were defined based on the highest sum of sensitivity and specificity. The event-free curves were based on Kaplan–Meier analysis stratified by the best cut-offs of LASr and LASr/Ees and were compared using a log-rank test. The proportional hazards assumption was formally assessed. Statistical analyses were performed using STATA, version 12 (StataCorp, College Station, Texas, USA), or Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA).P -values <0.05 were considered statistically significant.

Results

Out of the 274 patients, LA strain analysis was not evaluable in 39 because of the presence of atrial fibrillation with irregular rhythm and in 7 because of poor quality of imaging. The clinical and echocardiographic characteristics of the remaining 228 are shown in Table 1. Among the patients enrolled, 17 presented atrial fibrillation with regular ventricular paced rhythm; 31 (13.6%) were in KDOQI Class 1, 111 (48.7%) in Class 2, 43 (18.9%) in Class 3a, 34 (14.9%) in Class 3b, 8 (3.5%) in Class 4, and 1 in Class 5.

Left atrial strain measures' reproducibility. A high degree of intra-observer and intra-observer reproducibility was observed for LAr (average ICC = 0.93; 95% CI: 0.84–0.97 and ICC: 0.87; 95% CI: 0.71–0.95, respectively) as well as for LAcd (ICC: 0.93; 95% CI: 0.84–0.97 and ICC: 0.86; 95% CI: 0.68–0.94, respectively) and LAct (ICC: 0.89; 95% CI: 0.76–0.96 and ICC: 0.80; 95% CI: 0.56–0.91, respectively).

Clinical and echocardiographic correlates of left atrial strain measures. As shown in Supplementary Table 1, LAr was significantly and positively correlated with GFR-EPI, LVEF, TAPSE, e's, e'l, and e'm and significantly and negatively correlated with age, NYHA class, heart rate, LVEDV, LVESV, LAVi, MR, TR, E/e’s, E/e’m, LV-GLS, RV-GLS, and RVfwLS. LAcd was significantly and positively correlated with age, NYHA class, heart rate, LVEDV, LVESV, LAVi, TR, E/e’s, E/e’m, LV-GLS, RV-GLS, and RVfwLS and significantly and negatively correlated with GFR-EPI, LVEF, TAPSE, e’s, e’l, and e’m. LAct was significantly and positively correlated with NYHA class, heart rate, LVEDV, LVESV, LAVi, MR, TR, E/e’s, E/e’m, LV-GLS, RV-GLS, and RVfwLS and significantly and negatively correlated with GFR-EPI, LVEF, and TAPSE. LAr/Eel, LAr/Ees, and LAr/Eem were significantly and positively correlated with SAP, GFR-EPI, LVEF, TAPSE, e’s, e’l, and e’m and significantly and negatively correlated with age, NYHA class, heart rate, LVESV, LAVi, MR, TR, E/e’s, E/e’m, LV-GLS, RV-GLS, and RVfwLS.

Left atrial strain measures and heart failure worsening. During a mean follow-up of 14±7 months, at least one event related to heart failure worsening (40 hospitalisations caused by acute decompensated heart failure, 5 heart transplantations, and 19 cardiovascular deaths) occurred in 47 patients. As shown in Table 2, during univariate Cox regression analysis, LAr, LAcd, and LAct were all associated with events related to heart failure worsening. In forward stepwise Cox regression analysis, LAr (HR: 0.94; 95% CI: 0.91–0.98; p: 0.006) and LAct (HR: 1.05; 95% CI: 1.00–1.10; p: 0.043) but not LAcd remained associated with events after correction for NYHA class, heart rate, age, MR, TR, LVEF, GFR-EPI, and TAPSE.

Analogously, LAr/Eel, LAr/Rrs, and LAr/Eem were associated with events during univariate analysis, but only LAr/Ees and LAr/Eem remained significantly associated with them during multivariate analysis (HR: 0.49; 95% CI: 0.30–0.78; p: 0.002 and HR: 0.65; 95% CI: 0.47–0.89; p: 0.008, respectively) after correction for NYHA class, heart rate, age, MR, TR, LVEF, GFR-EPI, and TAPSE. As shown in Figure 2, the presence of a reduced or mildly reduced/preserved LVEF did not influence the prognostic value of all the LA strain measures as well as of those derived by the combination with Doppler measures.

ROC curves. As shown in Supplementary Figure 1, among the LA measures derived by strain analysis, LASr/Ees (AUC 0.76; 95% CI: 0.67–0.85) showed the greater ROC AUC, followed by LASr/Eem (AUC 0.75; 95% CI: 0.65–0.84), LASr (AUC 0.71; 95% CI: 0.63–0.80), LASct (AUC 0.70; 95% CI: 0.61–0.78), and LAScd (AUC 0.60; 95% CI: 0.52–0.69). For LASr, the best cut-off was 17% (sensitivity of 72% and specificity of 60%), for LASr/Ees 1.28 (sensitivity of 80% and specificity of 64%), and for LASr/Eem 1.60 (sensitivity of 77% and specificity of 59%). Figure 3 shows the Kaplan–Meier curves of the patients dichotomised according to the best cut-off of LASr (Panel A) and LASr/Ees (Panel B).

Discussion

The main result of this study is that in CHF outpatients, the LA reservoir, a 2D-STE measure of atrial function, is independently associated with worsening heart failure. Moreover, the integration of the LA reservoir with the ratio between mitral early diastolic peak velocity at pulsed Doppler and TDI provides a measure reflecting the interaction between atrial and ventricular function which is even more accurate to stratifying prognosis.

LA function is often considered only a passive bystander of LV dysfunction. However, several studies have shown that LA contractile function is determined by intrinsic LA contractility, LV compliance, LV filling pressures (LA afterload), and pulmonary vascular capacitance [1]. Atrial function improves ventricular filling by storing blood during ventricular systole while the atrioventricular valves are closed (reservoir function), as a passive conduit and emptying during early ventricular filling (conduit function), and providing additional ventricular filling with active contraction before atrioventricular valve closure (booster pump function). The interplay between LA and LV functions throughout the cardiac cycle (LA–LV coupling) is crucial in several pathophysiological conditions [3]. In this pathophysiological setting 2D-STE could represent a useful tool not only to evaluate the LV and RV functions [11-13] but also to provide measures reflecting the atrial function [14]. In particular, it allows the study of the complexity of the atrial deformation by analysing three sequential phases, i.e. the reservoir, the conduit, and the contraction.

The reservoir phase begins at the closure of the atrio-ventricular valves and ends with their opening at the end of isovolumic ventricular relaxation. In this phase, the atrial pressure quickly rises while receiving blood from the veins, and the atria stretch to their maximum capacity. The greater the atrial stretch, the greater the value of the reservoir. The other two phases of atrial function are reciprocal to the reservoir. The first is the conduit phase, which is related to the first half of ventricular diastole, after the opening of the atrioventricular valves. During this phase, the atria quickly unload in the ventricles the blood accumulated in the reservoir phase (passive atrial emptying), and the strain analysis will register a negative deflection of the curve, followed by a plateau which corresponds to the diastasis, when the blood directly flows from the veins to the ventricles. This phase is influenced by the compliance of the ventricles and the diastolic function [14]. The last phase is the contraction phase, corresponding to the atrial systole. This phase reflects the contractile capacity of the atria, along with the ventricular stiffness and the ventricular end diastole filling pressures [14].

Previous studies have demonstrated the role of peak atrial strain in predicting heart failure prognosis [5, 6]. However, different from these studies, we attempted to evaluate the prognostic role of all the phases of the atrial function. Interestingly, all the measures were associated with heart failure worsening, but only LASr remained independently associated with the occurrence of events during multivariate regression analyses. This evidence could be related to the ability of the reservoir to reflect a global atrial dysfunction. Consequently, although the conduit and contraction phases could help to define more clearly the mechanisms responsible for atrial dysfunction, the reservoir, being the expression of both the other phases, is associated with more important prognostic information.

This hypothesis is supported by the studies demonstrating the close relationship between a reduced LASr and the pathophysiological mechanisms underlying atrial dysfunction [14–16], i.e. the increased LV filling pressure, the LA remodelling, and the loss of contractile capacity. For this reason, the impairment of LASr could precede anatomical alterations [15], thus allowing a more accurate identification of diastolic dysfunction than conventional echo variables, such as LA volume index or E/e' [17-20]. Moreover, the therapeutic strategies able to improve LV function can be associated with the improvement of atrial function [21].

The relevance of our study is also related to the demonstration that the combination of the strain measure of LA function, LASr, and that of LV filling pressure based on pulsed Doppler and TDI, E/e', is characterised by even greater prognostic accuracy in predicting heart failure worsening. In previous studies, the ratio between LASr and E/e' showed greater accuracy in detecting high filling pressure [7, 22], but this measure should also be considered as a parameter that can better reflect the relationship between LA and LV functions. In fact, LV function worsening could cause an increase in LV end-diastolic pressures, which can then cause LA wall stiffening, thereby resulting in decreased LA relaxation and decreased LA strain peak during LV systole. Conversely, the decreased LA function could further favour the increase in LV filling pressure, thus leading to a vicious circle responsible for heart failure progression. Consequently, lower ratio between LASr and E/e' corresponds to worse interaction between LA and LV functions, i.e. greater LV filling pressure and worse LA function, thus allowing to provide a significant parameter of prognostic stratification.

In conclusion, 2D-STE is an echocardiographic technique able to provide measures of atrial function independently associated with heart failure worsening. Among these measures, the reservoir shows greater accuracy in predicting the events. Moreover, this accuracy is even greater when the strain measure of the reservoir is combined with the Doppler measures related to LV filling pressure. These data further strengthen the possible usefulness of 2D-STE in providing information about both ventricular and atrial functions.

References

1. Appleton CP, Kovács SJ. The role of left atrial function in diastolic heart failure. Circ Cardiovasc Imaging. 2009;2:6-9.
2. Bowman AW, Kovacs SJ. The 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: H2416–H2424.
3. Margulescu AD, Rees E, Coulson R-M, Rees AD, Vinereanu D, Fraser AG. Do left atrial strain and strain rate reflect intrinsic atrial function, or are they determined by left ventricular function? Kardiol Pol 2015; 73:539 – 548.

4. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J. 2001;22:22-36.
5. Cameli M, Lisi M, Focardi M et al. Left atrial deformation analysis by speckle tracking echocardiography for prediction of cardiovascular outcomes. Am J Cardiol 2012; 110:264– 269.
6. Cameli M, Lisi M, Mondillo S, et al. Left atrial longitudinal strain by speckle tracking echocardiography correlates well with left ventricular filling pressures in patients with heart failure. Cardiovasc Ultrasound. 2010;8:14.
7. Lin J, Ma H, Gao L et al. Left atrial reservoir strain combined with E/E' as a better single measure to predict elevated LV filling pressures in patients with coronary artery disease. Cardiovasc Ultrasound. 2020;18:11.
8. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
9. Lang RM, Badano LP, Mor-Avi V 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. J Am Soc Echocardiogr 2015;28:1–39.
10. Fleiss JL. Reliability of measurements. In: The Design and Analysis of Clinical Experiments. New York: Wyley. 1986: 1-32.
11. Iacoviello M, Puzzovivo A, Guida P et al. Independent role of left ventricular global longitudinal strain in predicting prognosis of chronic heart failure patients. Echocardiography. 2013;30:803-11. doi: 10.1111/echo.12142.
12. Iacoviello M, Citarelli G, Antoncecchi V et al. Right Ventricular Longitudinal Strain Measures Independently Predict Chronic Heart Failure Mortality. Echocardiography. 2016;33:992-1000. doi: 10.1111/echo.13199.
13. Iacoviello M, Monitillo F, Citarelli G et al. Right ventriculo-arterial coupling assessed by two-dimensional strain: A new parameter of right ventricular function independently associated with prognosis in chronic heart failure patients. Int J Cardiol. 2017;241:318-321. doi: 10.1016/j.ijcard.2017.04.051.
14. Todaro MC, Choudhuri I, Belohlavek M, et al. New echocardiographic techniques for evaluation of left atrial mechanics. Eur Heart J Cardiovasc Imaging. 2012;13:973-984.
15. Dernellis JM, Stefanadis CI, Zacharoulis AA, Toutouzas PK. Left atrial mechanical adaptation to longstanding hemodynamic loads based on pressure-volume relations. Am J Cardiol. 1998;81:1138-43. doi: 10.1016/s0002-9149(98)00134-9.
16. Ancona R, Comenale Pinto S, Caso P et al.. Left atrium by echocardiography in clinical practice: from conventional methods to new echocardiographic techniques. ScientificWorldJournal. 2014;2014:451042. doi: 10.1155/2014/451042.
17. Miglioranza MH, Badano LP, Mihăilă S, Peluso D, Cucchini U, Soriani N, Iliceto S, Muraru D. Physiologic Determinants of Left Atrial Longitudinal Strain: A Two-Dimensional Speckle-Tracking and Three-Dimensional Echocardiographic Study in Healthy Volunteers. J Am Soc Echocardiogr. 2016;29:1023-1034.e3. doi: 10.1016/j.echo.2016.07.011.
18. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA Strain for Categorization of LV Diastolic Dysfunction. JACC Cardiovasc Imaging. 2017;10:735-743. doi: 10.1016/j.jcmg.2016.08.014.
19. Singh A, Medvedofsky D, Mediratta A 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;35:23-32. doi: 10.1007/s10554-018-1425-y.
20. Bytyçi I, Bajraktari G, Lindqvist P, Henein MY. Compromised left atrial function and increased size predict raised cavity pressure: a systematic review and meta-analysis. Clin Physiol Funct Imaging. 2019;39:297-307. doi: 10.1111/cpf.12587.
21. Andrea A, Caso P, Romano S, et al. Different effects of cardiac resynchronization therapy on left atrial function in patients with either idiopathic or ischaemic dilated cardiomyopathy: a two-dimensional speckle strain study. Eur Heart J. 2007;28:2738-2748.
22. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation

of heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;21:891-900.

Figure legends

Figure 1. Left atrial strain measures, Doppler measures of diastolic function, and combined atrial/Doppler measurements.

E: peaks of early wave velocity at the mitral valve by pulsed Doppler; e': early diastolic velocity peaks at tissue Doppler imaging; e's: septal e'; e'l: lateral e'; e'm: mean septal-lateral e'; LAr: left atriale reservoir; LAcd: left atrial conduit; LAct: left atrial contraction.

Figure 2. Cox univariate regression analyses for all the left atrial measures , according with the presence of a reduced or not left ventricular ejection fraction.

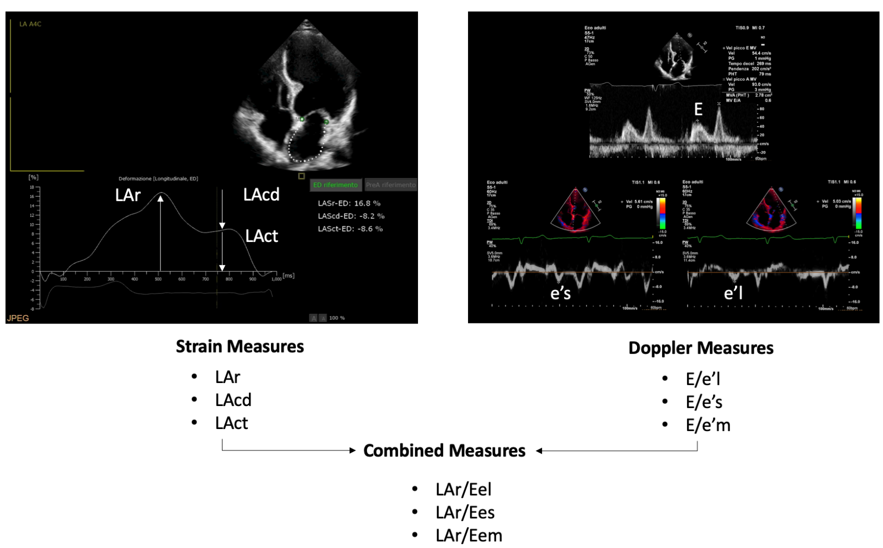
CI: confidence interval; HR: hazard ratio; LAcd: left atrial conduit; LAct: left atrial contraction; LAr: left atrial reservoir; LAr/Eel: ratio between LAr and the ratio between peak of E at pulsed Doppler and mitral lateral e' at lateral Tissue Doppler Imaging; LAr/Eem: ratio between LAr and the ratio between peak of E at pulsed Doppler and mean mitral septal and lateral e' at Tissue Doppler Imaging; LAs/Ees: ratio between LAr and the ratio between peak of E at pulsed Doppler and mitral septal e' at Tissue Doppler Imaging.

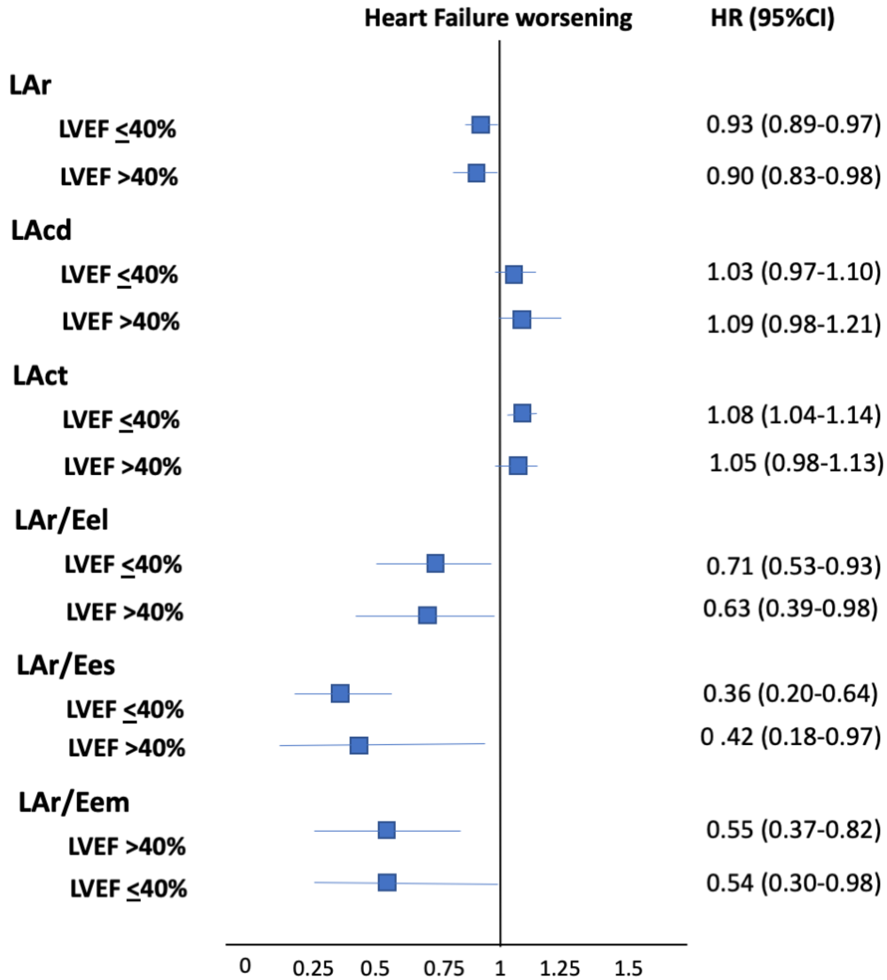
Figure 3. Kaplan Meier curves according to the best cut-offs of LASr and LASr/Ees.

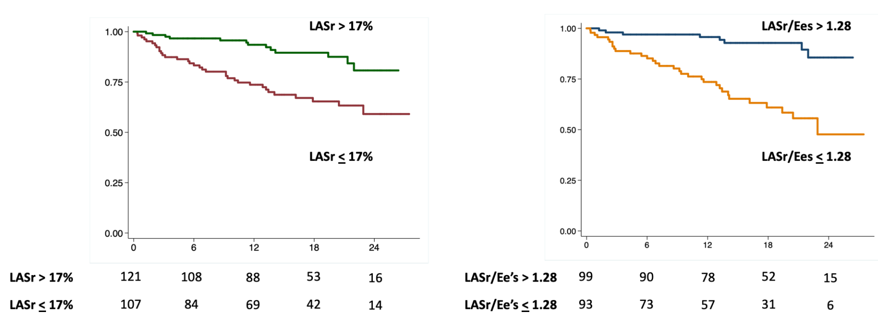
LAr: left atriale reservoir; LAr/Ees: ratio between LAr and the ratio between E (peaks of early wave velocity at the mitral valve by pulsed Doppler) and septal e' (early diastolic velocity peaks at septal mitral tissue Doppler imaging).

Supplementary Figure 1. ROC curves of left atrial strain derived measures for one year events related to heart failure worsening.

LAcd: left atrial conduit; LAct: left atrial contraction; LAr: left atrial reservoir; LAr/Eel: ratio between LAr and the ratio between peak of E at pulsed Doppler and mitral lateral e' at lateral Tissue Doppler Imaging; LAr/Eem: ratio between LAr and the ratio between peak of E at pulsed Doppler and mean mitral septal and lateral e' at Tissue Doppler Imaging; LAs/Ees: ratio between LAr and the ratio between peak of E at pulsed Doppler and mitral septal e' at Tissue Doppler Imaging.







Hosted file

Tables.docx available at https://authorea.com/users/605712/articles/635068-relationship-between-the-strain-measures-of-left-atrial-function-and-heart-failure-worsening