Cardiovascular Ultrasound

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# Left atrial dysfunction relates to symptom onset in patients affected by severe degenerative mitral regurgitation

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## Abstract

**Background** Left atrium (LA) is far from simply being a passive connection chamber between left ventricle and the pulmonary circulation. In patients affected by mitral regurgitation (MR) an impairment in LA compliance and reservoir function, which can be evaluated using Speckle Tracking echocardiography, lead to elevated atrial pressure, resulting in increased pulmonary capillary pressures and the onset of dyspnea. Our study aims to evaluate the correlation between left atrial dysfunction and symptoms onset in patients with severe degenerative MR. Identifying left atrial dysfunction as a predictor of symptoms could be helpful to guide management strategy of asymptomatic patients with severe degenerative MR.

**Methods** In a retrospective analysis, we examined all patients diagnosed with severe degenerative MR who underwent evaluation for potential cardiac surgery using transthoracic and transesophageal echocardiogram between May 2019 and July 2022 at IRCCS San Raffaele Hospital. The cohort was stratified into two groups: symptomatic patients (NYHA > I) and asymptomatic (NYHA = I) patients. A comprehensive assessment of LA function and compliance was performed including: LA fractional atrial change, LA reservoir strain (LASr), LASr/E/e', and LA reservoir work.

**Results** The final study cohort comprised 401 patients. There were no significant differences observed in terms of left ventricle size, function, and mitral regurgitation volume between the two groups.

Atrial dysfunction and dilatation were significantly associated with symptoms. Among the atrial functional indexes LASr, a marker of LA compliance, showed the strongest association with symptoms (AUC: 0.85, OR: 7.45, $p < 0.001$). A LASr value below 22% emerged as an effective threshold, identifying symptomatic patients with 86% specificity and 68% sensitivity.

**Conclusions** The onset of symptoms in severe degenerative mitral regurgitation (MR) is closely associated with left atrial dysfunction. LASr < 22% identified symptomatic patients with 86% specificity and 68% sensitivity.

**Keywords** Atrial cardiomyopathy, Atrial function, Atrial strain, Degenerative mitral regurgitation, Predictor of symptoms, Symptoms onset

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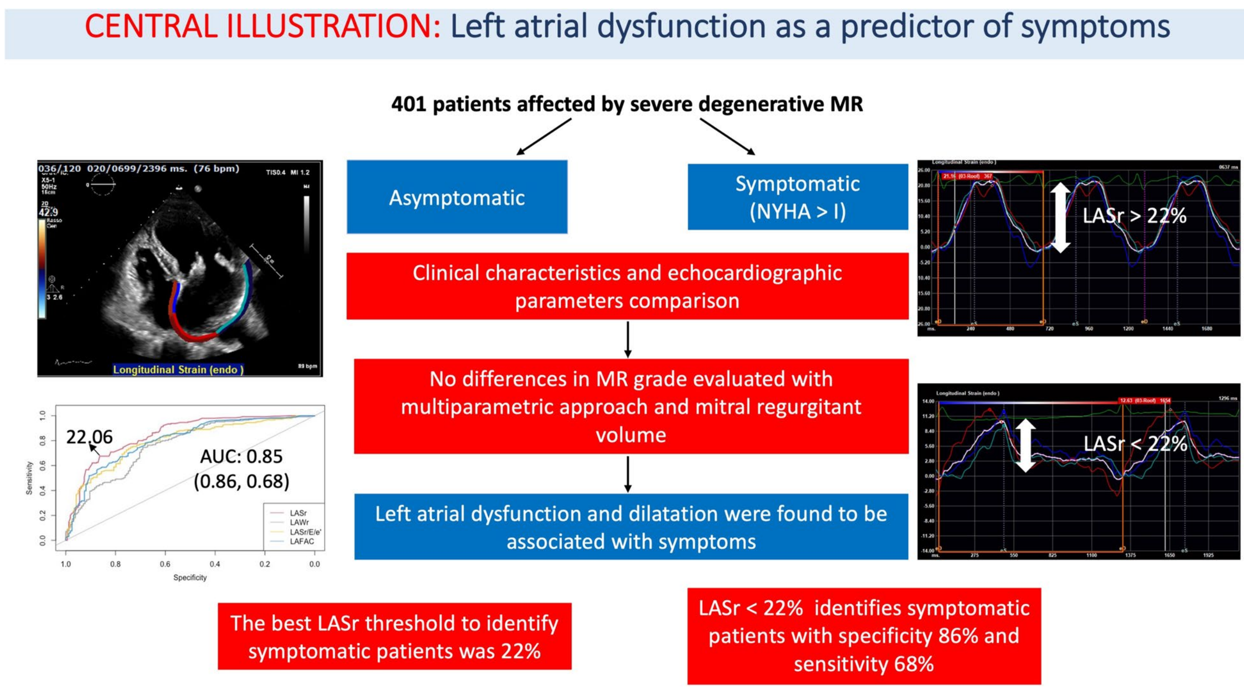
**Graphical Abstract**




## Background

Degenerative etiology is the most frequent cause of mitral regurgitation (MR) in Western countries [1]. Current guidelines recommend intervention in case of symptoms onset or maladaptive cardiac remodelling [2–4].

In asymptomatic patients with severe MR who are likely to undergo durable repair and show no signs of maladaptive cardiac remodeling, identifying predictors of symptom development could guide the management strategy, balancing between early mitral valve repair and watchful waiting.

Dyspnoea due to elevated pressure in the pulmonary circulation is one of the first symptoms in MR. Since the left atrium (LA) is a thin-walled structure, it is extremely sensitive to the high-pressure regurgitant volume. In patients affected by MR, evidence of atrial cardiomyopathy with cardiomyocyte morphological changes and replacement fibrosis has already been demonstrated [5]. Atrial cardiomyopathy reduces LA compliance and impairs its reservoir function, resulting in elevated atrial pressure. This elevation leads to increased resistance to pulmonary venous inflow and contributes to augmented pulmonary capillary pressures. The appearance of atrial cardiomyopathy could explain why among patients with the same degree of regurgitation some are symptomatic, and others are not. However, the impact of atrial dysfunction on the onset of symptoms among patients affected by severe degenerative MR have not yet been fully evaluated.

LA longitudinal strain enables the measurement of atrial wall lengthening and LA reservoir strain (LASr) serves as an echocardiographic performance index to assess the LA compliance. Recently, two new parameters based on LASr have been developed to expand the assessment of left atrial compliance and left atrial reservoir function (LASr/E/e' and left atrial reservoir work (LAWr)) [6, 7].

The study aimed to assess the correlation between symptoms onset and left atrial dysfunction, assessed using LASr and these new parameters, in patients with severe degenerative MR.

## Methods

### Study population

This single-center retrospective cohort study enrolled all consecutive patients with severe degenerative MR evaluated at IRCCS San Raffaele Hospital for a potential cardiac surgery intervention between May 2019 and July 2022. The collected data included medical history, clinical and laboratory assessments, as well as 2D and 3D transthoracic echocardiograms (TTE) and transesophageal echocardiograms (TEE).

Exclusion criteria were:

- Atrial fibrillation during examination
- Cardiomyopathies
- COPD (GOLD Stage ≥ 2)
- more than mild left heart valvulopathies associated with MR
- lack of complete and adequate echocardiographic imaging both at TTE and at TEE

If the patient's New York Heart Association (NYHA) class was I, they were defined as asymptomatic. This indicates that the patient has the capacity to complete activities requiring up to a maximum of 7 METs. If the patient's NYHA class was > I, they were defined as symptomatic.

The study population was divided in 2 groups:

- Group A: asymptomatic patients (NYHA = I)
- Group B: symptomatic patients (NYHA > I)

The study protocol was approved by the internal review board (NERVAM VESPRO 2022) and all patients provided written informed consent for anonymous collection of their clinical data.

The study was conducted according to institutional guidelines and legal requirements.

### Echocardiographic assessment

Comprehensive TTE and TEE were performed with commercially available ultrasound system (Vivid E9 and Vivid E95 GE (General Electric Healthcare, Milwaukee, WI, USA) with MS5-D and 6VT-D probes; Philips EPIQ7 (Philips Electronics, Amsterdam, The Netherlands) with X5, X8-2t and X7-2t probes). Data acquisition was made in accordance with the most recent guidelines [8, 9]. Two blinded operators (D. M. and G. P.) evaluated the echocardiographic images off-line on dedicated workstations, using Suitestensa CVIS (Ebit, Esaote) and TomTec Arena (TOMTEC Imaging Systems GmbH Software).

Severity of MR was evaluated using a multiparametric approach in accordance with the most recent recommendations including the 3D-Vena Contracta Area (VCA) [10].

The assessment of left ventricle (LV) systolic function involved the utilization of both the biplane Simpson's method and global longitudinal strain (GLS).

Pickelhaube sign was described as an increased systolic contraction velocity of left ventricular basal segments (s' TDI > 16 cm/s) [9]. Due to the narrow connection between mitral anulus and atrial wall, we compared strain value among patients with and without Pickelhaube sign to assess its potential effects on left atrial strain values.

### Left atrial size and function

LA volume (LAV) was obtained by the biplane area-length method from apical 4- and 2-chamber views. A comprehensive assessment of left atrial function including bilateral pulmonary venous blood flow by TEE, left atrial ejection fraction (LAEF), left atrial fractional atrial change (LAFAC) (difference in end-diastolic area and end-systolic area divided by the end-diastolic area from apical 4-chamber) and longitudinal atrial strain was performed [11, 12]. According to pulmonary venous flow (PVF) pattern with at least one side of the pulmonary veins with normal vein flow were considered to have normal left atrial pressure (LAP), otherwise they were regarded as patients with high LAP.

LA reservoir strain was measured using specific software (2D Cardiac Performance Analysis; Tomtec Arena 2.4) with end diastole as the nadir reference point [13]. This parameter was assessed from an apical 4-chamber view with non-foreshortened LA to obtain a reliable delineation of LA endocardial border and a minimum frame rate of 55 frames per second.

LA reservoir function was further estimated using the product of LASr (as a surrogate for LA pressure change) and LA reservoir volume (increase of LA volume from minimum to maximum), providing a simplified index of left atrial reservoir work (LAWr) [6].

Since it has proven to be a promising parameter to predict LA compliance, we have also analysed the ratio between LASr and E/e' mean (LASr/E/e') [7, 14].

### Statistical analysis

Continuous variables were expressed as mean ± standard deviation or medians with interquartile ranges [IQRs] as appropriate; categorical variables were expressed as absolute numbers and percentages. Normality of distributions across different groups were tested using Shapiro-Wilk test. Between-group differences were assessed by unpaired T-tests, Mann-Whitney test, $\chi^2$ test, or Fisher exact test as appropriate.

For the identification of the predictors of symptoms the different variables between symptomatic and asymptomatic groups were evaluated. Variance Inflation Factor was used to detect multicollinearity between variables. Candidate variables were assessed in univariable logistic regression models. A receiver operating characteristic curve (ROC curve) was used to find the capability of LAFAC, LASr, LAWr, LASr/E/e' to detect symptomatic patients and to identify the best threshold value.

To validate symptom predictors, four distinct multivariate regression models incorporating respectively LAFAC, LASr, LAWr, and LASr/E/e' were conducted using the optimal threshold values obtained from ROC curve analysis. Results of logistic regression were reported as adjusted odds ratio (OR) and 95% confidence interval (95% CI). The Hosmer-Lemeshow (H-L) goodness of-fit test and C-statistic were used to confirm good calibration and discrimination of the multivariable model.

A linear regression analysis was adopted to correlate LASr with LAV, systolic pulmonary arterial pressure (sPAP), and LV GLS. Moreover, univariable and multivariate logistic regression models were performed to identify the predictors of LASr reduction.

A $p$ value $< 0.05$ was considered statistically significant. The R version 3.6.2 software (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

## Results

Out of 533 patients evaluated, 132 met the exclusion criteria and 401 were included in the analysis. Median age was 59 years (IQR 51-70), 45% were female.

One hundred and sixty-one patients were asymptomatic (group A) and 240 symptomatic (group B).

The baseline characteristics of the study population are shown in Table 1. Patients in the group B were older and they presented a higher prevalence of hypertension, dyslipidemia, coronary artery disease and paroxysmal atrial fibrillation compared with those in group A.

Echocardiographic parameters are summarized in Table 2 supplementary appendix. Overall, the LV exhibited mild dilation with normal function, and there were no significant differences between the groups. In the individual parameters of MR quantification and the MR volume/LAVi ratio, no significant differences were found between the two groups. However, there were significant differences between the two groups in terms of LA size and function parameters. The group of symptomatic patients exhibited larger LAVi, along with lower LASr, LAWr, and LASr/E/e'. Furthermore, symptomatic patients demonstrate a higher prevalence of elevated atrial pressure and pulmonary artery pressures (sPAP).

There was no significant difference in prevalence of Pickelhaube sign between symptomatic and asymptomatic patients, as well as no significant difference in LASr values between patients with and without Pickelhaube sign ($p = 0.30$).

### Echocardiographic characteristics of symptomatic patients

The results of the univariate and multivariate regression analyses are shown in Tables 3 and 4. In the univariate regression analysis, significant associations were observed between symptoms and atrial dilatation, atrial dysfunction, as well as elevated sPAP. Among all the atrial functional indexes, LASr presented the strongest association with symptoms (Fig. 1). The ROC curve analysis showed that the best LASr threshold to identify symptomatic patients was 22%, with an area under the curve (AUC) of 0.85 (specificity 0.86, sensitivity 0.68).

After adjusting for confounders in multivariable models LASr, LAFAC, LASr/E/e' and LAWr were confirmed to be associated with symptoms with an OR of 7.4, 4.4, 5.2, and 7.5 respectively. The multivariable model incorporating LASr demonstrated a C-statistic of 0.877 and a Hosmer-Lemeshow $p$-value of 0.889.

**Table 1** Baseline clinical characteristics of population according to groups: NYHA = I patients (n 161) and NYHA > I patients (n 240)

| | **Asymptomatic patients ($N = 161$)** | **Symptomatic patients ($N = 240$)** | **Total (N.401)** | ***p*-value** |
|---|---|---|---|---|
| Age, y | 55.0 (45.0- 61.0) | 64.0 (55.0- 74.0) | 59.0 (51.0- 70.0) | **< 0.001** |
| Female Sex | 65 (40.4%) | 118 (49.2%) | 183 (45.6%) | 0.083 |
| BMI | 24.0 (21.4- 25.9) | 23.9 (21.5- 26.4) | 24.0 (21.5- 26.0) | 0.611 |
| Hypertension | 44 (27.3%) | 116 (48.3%) | 160 (39.9%) | **< 0.001** |
| Dyslipidemia | 14 (8.7%) | 49 (20.4%) | 63 (15.7%) | **0.002** |
| Diabetes | 4 (2.5%) | 11 (4.6%) | 15 (3.7%) | 0.278 |
| Current smoker | 12 (7.5%) | 24 (10%) | 36 (9%) | 0.383 |
| CAD | 5 (3.1%) | 20 (8.3%) | 25 (6.2%) | **0.034** |
| Prior PCI | 6 (3.7%) | 11 (4.6%) | 17 (4.2%) | 0.676 |
| Paroxysmal atrial fibrillation | 9 (5.6%) | 41 (17.1%) | 50 (12.5%) | **< 0.001** |

Values are mean ± SD, n (%), or median (Q1-Q3)

*BMI* body-mass index, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention

**Table 2** Baseline echocardiographic characteristics of population according to groups: NYHA = I patients (n 161) and NYHA > I patients (n 240)

| Variable | Asymptomatic patients (n 161) | Symptomatic patiens (n 240) | Total (N.401) | *p*-value |
|---|---|---|---|---|
| EDVi, ml | 68.9 (60.0-80.0) | 73.1 (61.5-86.6) | 71.2 (60.5-83.7) | 0.120 |
| EDD, mm | 52 (48- 56) | 52 (48- 57) | 52 (48- 56) | 0.926 |
| ESD, mm | 32 (29-35) | 32 (28-34) | 32 (28-34) | 0.870 |
| LVEF, % | 64 (60.0- 66.0) | 62 (59.0- 66.0) | 63 (60.0 66.0) | 0.065 |
| LV GLS, % | 21.1 (3.4) | 20.5 (2.9) | 20.8 (3.2) | 0.206 |
| Barlow disease | 66 (41.0%) | 92 (38.3%) | 153 (39.4%) | 0.829 |
| EROA-PISA, cmq | 0.5 (0.4- 0.6) | 0.5 (0.4- 0.6) | 0.45 (0.4- 0.6) | 0.310 |
| Reg Vol-PISA, ml | 42 (32.7- 51.5) | 41.4 (34.2- 54.2) | 41.5 (33.5- 53.0) | 0.676 |
| 3D-VCA, cmq | 0.6 (0.5- 0.8) | 0.6 (0.5- 0.8) | 0.6 (0.5- 0.8) | 0.930 |
| Reg Fraction % | 52 (46.2- 60) | 55 (48- 60) | 53 (48- 60) | 0.073 |
| AP diameter, mm | 36 (32- 40) | 36 (32- 41)) | 36 (32- 40 | 0.370 |
| IC diameter, mm | 39.0 (33.0- 43.0) | 38.0 (32.0- 43.0) | 38.0 (33.0- 43.0) | 0.497 |
| E/e'mean | 9 (6- 11) | 9.7 (7- 12.2) | 9 (7- 12) | **0.006** |
| LAVi, ml/mq | 40 (32- 49) | 48 (38- 62) | 45 (35- 57) | **< 0.001** |
| Reg Vol/LAVi, % | 58 (50- 67) | 52 (43- 69) | 55 (45- 69) | 0.837 |
| LAEF, % | 52 (45.4- 61) | 38 (29- 47) | 45 (33.2- 55) | **< 0.001** |
| LAFAC, % | 40.0 ± 10.5 | 28.3 ± 9.8 | 33.0 ± 11.6 | **< 0.001** |
| Pickelhaube sign | 26 (21.5%) | 25 (16.4%) | 51 (18.7%) | 0.289 |
| LASr (%) | 35 (25- 45) | 19.8 (16- 25) | 23.8 (18- 33) | **< 0.001** |
| LAWr % x ml | 1530.0 (896.0-2441.6) | 830.4 (501.1-1152.5) | 1009.6 (621.1-1620.0) | **< 0.001** |
| LASr/E/e' | 4.0 (2.9-5.7) | 2.0 (1.4-2.9) | 2.7 (1.7-4.1) | **< 0.001** |
| High LAP estimated through PVF | 99 (61.5%) | 171 (71.2%) | 270 (67.3%) | **0.041** |
| TAPSE, mm | 25.0 (22.0- 28.0) | 24.0 (21.0- 27.0) | 24.0 (22.0- 27.0) | **0.043** |
| sPAP, mmHg | 30.0 (25.0- 30.0) | 30.0 (25.0- 40.0) | 30.0 (25.0- 35.0) | **< 0.001** |
| TR severity > 1 | 27 (16.8%) | 57 (23.8%) | 84 (20.9%) | 0.092 |

Values are mean ± SD, n (%), or median(Q1-Q3)

*EDVi* index end diastolic volume, *EDD* end diastolic diameter, *LVEF* left ventricular ejection fraction, *LV GLS* left ventricle Global Longitudinal Strain, *EROA-PISA* effective regurgitation orifice area assessed by PISA method, *Reg Vol-PISA* regurgitant volume assessed by PISA method, *3D-VCA* three dimensional vena contracta area, *Reg Fraction* regurgitant fraction, *AP diameter* annular anteroposterior diameter, *IC diameter* annular intercommissural diameter, *LAVi* Left atrial volume indexed, *Reg vol/LAVi* regurgitant volume/left atrial volume ratio, *LAEF* left atrial ejection fraction, *LAFAC* atrial fractional area change, *LASr* Left atrial reservoir strain, *LAWr* left atrial reservoir work, *LAP* left atrial pressure, *PVF* pulmonary vein flow, *TAPSE* tricuspid annular pulmonary systolic excursion, *sPAP* systolic pulmonary artery pressure, *TR* tricuspid regurgitation

We did not find a significant difference in LASr values between patients with high and low LAP estimated by pulmonary vein pattern (Fig. 2 Supplementary Appendix).

### Echocardiographic determinants of left atrial reservoir strain

There were no significant correlations between LASr and LAVi (adjusted R-squared of 0.07), as well as between LASr and sPAP (adjusted R-squared of 0.15), and between LASr and LV GLS (adjusted R-squared of 0.001) by linear regression (Fig. 3a, 3b and 3c Supplementary Appendix).

At univariate and multivariate logistic regression LAVi and LAFAC were independent predictor of LASr < 22%, while sPAP and LV GLS did not (Table 5).

## Discussion

The main findings of the present study are: 1) atrial dysfunction and dilatation were associated with symptoms in severe degenerative MR; 2) among the atrial functional indexes LASr, a marker of LA compliance, showed the strongest association with symptoms and a threshold value of LASr < 22% identified symptomatic patients with 86% specificity and 68% sensitivity and 3) reduced LASr values were associated, as expected, with LA dilatation (Graphical Abstract).

**Table 3** Univariate and multivariate regression logistic analysis

| | Univariate Regression Model of Predictors of NYHA > I | | Multivariable regression model of predictors of of NYHA > I<br>Model 1: LASr < 22% | | Multivariable regression model of predictors of NYHA > I<br>Model 2: LAFAC < 36% | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| Age | 1.05 (1.03-1.07) | < 0.001 | 1.01 (0.98-1.04) | 0.9 | 1.01 (0.98-1.03) | 0.5 |
| Hypertension | 2.49 (1.57-3.69) | < 0.001 | 1.57 (0.81-3.10) | 0.2 | 1.34 (0.70-2.57) | 0.4 |
| CAD | 2.84 (1.12-8.67) | 0.041 | 1.70 (0.41-9.14) | 0.5 | 1.74 (0.45-8.85) | 0.5 |
| E/e' | 1.09 (1.03-1.16) | 0.005 | | | 1.00 (0.93-1.09) | 0.9 |
| LAVi | 1.04 (1.02-1.05) | < 0.001 | 1.02 (1.00-1.04) | **0.041** | 1.03 (1.01-1.05) | **0.008** |
| LAEF | 0.92 (0.90-0.94) | < 0.001 | | | | |
| LAFAC | 0.89 (0.87-0.91) | < 0.001 | | | | |
| LAFAC < 36% | 7.60 (4.87-12-20) | < 0.001 | | | 4.39 (2.46-7.98) | **< 0.001** |
| LASr | 0.86 (0.83-0.89) | < 0.001 | | | | |
| LASr < 22% | 10.7 (6.48-18.4) | < 0.001 | 7.45 (3.91-14.9) | **< 0.001** | | |
| LAWr | 1.00 (1.00-1.00) | < 0.001 | | | | |
| LAWr < 1135% x mL | 6.53 (4.18-10.40) | < 0.001 | | | | |
| LASr/E/e' | 0.58 (0.49-0.68) | < 0.001 | | | | |
| LASr/E/e' < 2.9 | 8.39 (5.00-14.40) | < 0.001 | | | | |
| LV GLS | 0.94 (0.86-1.03) | 0.200 | | | | |
| TAPSE | 0.95 (0.90-0.99) | 0.041 | 0.96 (0.89-1.03) | 0.3 | 0.97(0.91-1.03) | 0.4 |
| sPAP | 1.10 (1.06-1.13) | < 0.001 | 1.04 (1.00-1.09) | **0.039** | 1.05 (1.01-1.10) | **0.012** |
| High LAP PVF | 1.55 (1.02-2.37) | 0.042 | 1.04 (0.56-1.93) | 0.9 | 1.15 (0.62-2.13) | 0.7 |

LAEF was excluded from multivariable regression analysis because, as expected, it is characterized by high collinearity with LAFAC (VIF > 10) and LAEF is less used in clinical practice

*CAD* coronary artery disease, *LAVi* Left atrial volume indexed, *LAEF* left atrial ejection fraction, *LAFAC* left atrial fractional area change, *LASr* Left atrial reservoir strain, *LAWr* left atrial reservoir work, *LV GLS* left ventricle global longitudinal strain TAPSE: tricuspid annular pulmonary systolic excursion, *sPAP* systolic pulmonary artery pressure, *TR* tricuspid regurgitation, *PVF* pulmonary vein flow

LA is far from merely serving as a passive conduit between left ventricle and pulmonary circulation. The dynamic shortening and lengthening of LA preserves the pulmonary vasculature from the pressure increase caused by MR and LV filling pressure.

Indeed, preserving low atrial pressure values throughout the cardiac cycle allows to drain blood from the pulmonary circulation without raising pulmonary capillary pressures. Three recent studies have confirmed the role of atrial function revealing the significant prognostic impact of a parameter that combine atrial dilatation with atrial function in heart failure and the correlation between atrial dysfunction and pulmonary hypertension in MR [9, 10, 15]. In early phases of significant MR LA compliance allows LA/pulmonary vein pressure dissociation through significant dilatation to accommodate blood returning from the ventricle while maintaining low pressure in the pulmonary circulation.

However, over time, MR leads to maladaptive remodelling with the onset of atrial cardiomyopathy [5]. This remodelling results in cardiomyocyte hypertrophy and fibrosis, impairing LA function [11]. The reduction of LA compliance with dilatation is supported by the observation that dilatation is predictor of pulmonary hypertension, independent of left ventricular systolic function and degree of MR [16].

MR pressure and volume overloads associated with reduced LA compliance induce augmented pressure in LA and upstream in the pulmonary circulation. Elevation of pulmonary capillary pressure is the trigger of dyspnoea onset. As observed in heart failure with impaired and preserved ejection fraction, LA compliance assessed using speckle tracking analysis appears to be a critical pathophysiological component, similar to atrial size, in symptom development and prognostic stratification [12, 17, 18].

In our study, LASr reduction was found to be associated with the presence of symptoms more strongly than combined parameters (LASr/E/e' and LAWr (product of LASr and LA reservoir volume)) and LAFAC.

LASr is an indirect marker of LA compliance and correlates with the amount of atrial fibrosis as demonstrated

**Table 4** Univariate and multivariate regression logistic analysis

| | Univariate regression model of predictors of NYHA > I | | Multivariable regression model of predictors of of NYHA > I | | Multivariable regression model of predictors of NYHA > I | |
|---|---|---|---|---|---|---|
| | | | Model 3: LASr/E/e' < 2.9 | | Model 4: LAWr < 1135% x mL | |
| | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| Age | 1.05 (1.03-01.07) | < 0.001 | 1.00 (0.98-1.02) | 0.7 | 1.01 (0.98-1.03) | 0.8 |
| Hypertension | 2.49 (1.57-3.69) | < 0.001 | 1.67 (0.88-3.22) | 0.12 | 1.45 (0.73-2.87) | 0.3 |
| CAD | 2.84 (1.12-8.67) | 0.041 | 1.63 (0.42-8.44) | 0.5 | 1.95 (0.45-10.7) | 0.4 |
| E/e' | 1.09 (1.03-1.16) | 0.005 | | | 1.05 (0.97-1.14) | 0.3 |
| LAVi | 1.04 (1.02-1.05) | < 0.001 | 1.02 (1.00-1.04) | **0.037** | 1.04 (1.02-1.07) | **< 0.001** |
| LAEF | 0.92 (0.90-0.94) | < 0.001 | | | | |
| LAFAC | 0.89 (0.87-0.91) | < 0.001 | | | | |
| LAFAC < 36% | 7.60 (4.8712-20) | < 0.001 | | | | |
| LASr | 0.86 (0.83-0.89) | < 0.001 | | | | |
| LASr < 22% | 10.7 (6.48-18.4) | < 0.001 | | | | |
| LAWr | 1.00 (1.00-1.00) | < 0.001 | | | | |
| LAWr < 1135% x mL | 6.53 (4.18-10.40) | < 0.001 | | | 7.56 (3.92-15.3) | **< 0.001** |
| LASr/E/e' | 0.58 (0.49-0.68) | < 0.001 | | | | |
| LASr/E/e' < 2.9 | 8.39 (5.00-14.40) | < 0.001 | 5.26 (2.84-9.99) | **< 0.001** | | |
| LV GLS | 0.94 (0.86-1.03) | 0.200 | | | | |
| TAPSE | 0.95 (0.90-0.99) | 0.041 | 0.94 (0.88-1.01) | 0.1 | 1.00 (0.93-1.08) | 0.9 |
| sPAP | 1.10 (1.06-1.13) | < 0.001 | 1.06(1.02-1.09) | **0.010** | 1.06 (1.01-1.11) | **0.005** |
| High LAP PVF | 1.55 (1.02-2.37) | 0.042 | 1.02 (0.55-1.87) | 0.9 | 1.09 (0.62-2.13) | 0.8 |

LAEF was excluded from multivariable regression analysis because, as expected, it is characterized by high collinearity with LAFAC (VIF > 10) and LAEF is less used in clinical practice

*CAD* coronary artery disease, *LAVi* Left atrial volume indexed, *LAEF* left atrial ejection fraction, *LAFAC* left atrial fractional area change, *LASr* Left atrial reservoir strain, *LAWr* left atrial reservoir work, *LV GLS* left ventricle global longitudinal strain, *TAPSE* tricuspid annular pulmonary systolic excursion, *sPAP* systolic pulmonary artery pressure, *TR* tricuspid regurgitation, *PVF* pulmonary vein flow

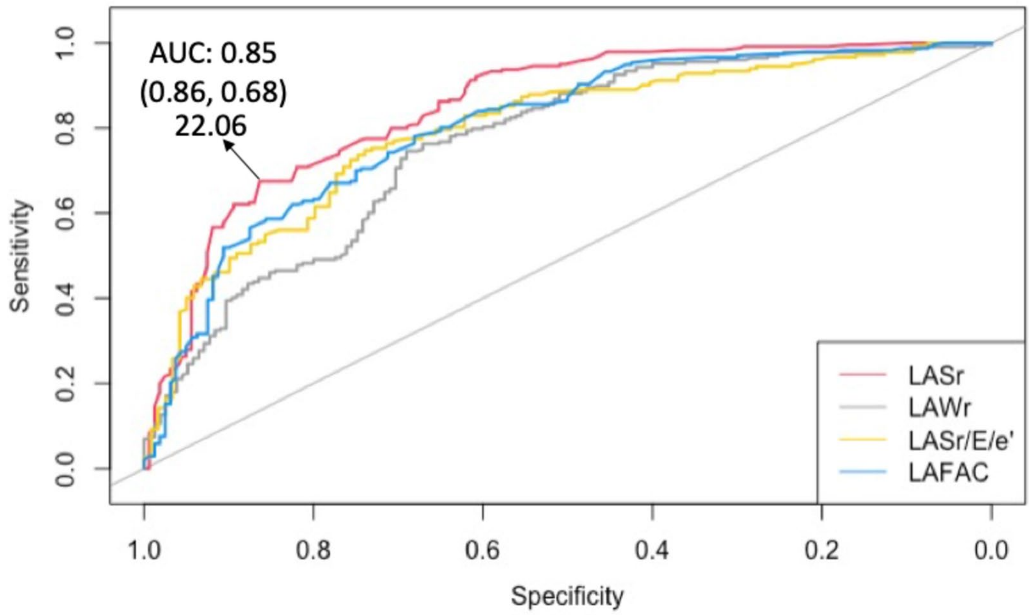
by a cardiac magnetic resonance imaging study [19]. The inverse correlation between LASr and LAP was demonstrated through indirect estimators such as E/e' values in MR [20], NT-proBNP [21], and right heart catheterization in advanced heart failure [22]. Moreover, although the interaction between atrial and ventricular function influences LV filling, no significant correlation was found between LV GLS and LASr value. This result is likely due to the prevalence of LA dilatation in this study, as it has been demonstrated that LAVi has a more significant impact on LASr than LV GLS in patients with LA enlargement [23]. Given the notable prevalence of the Pickelhaube sign in degenerative MR and the anatomical and functional relationship between mitral anulus and atrial wall, we investigated its possible role as a confounding factor on atrial strain. Our findings showed that the presence of Pickelhaube sign with the rapid systolic lateral annular motion had no significant influence on LASr values.

In the setting of primary mitral LASr seems to be a marker of LA compliance rather than a marker of LV filling pressure: concordantly, Pourznazary et al. provided direct evidence of a direct relation between LA compliance and LASr both before and after TEER [24].

In the setting of degenerative MR, the best outcomes are provided by surgical repair, which is feasible for nearly all patients in experienced high-volume centres [2, 3]. In asymptomatic patients with primary MR and preserved LV, surgery should be considered if at least one among atrial fibrillation, pulmonary hypertension or severe LA dilatation is present. Therefore, LA dilatation, the only other parameter independent associated with symptoms emerged in this study along with atrial function, is a parameter already integrated in current management.

The most appropriate strategy among asymptomatic patients with primary severe MR who do not fulfil the recommended criteria for surgery remains controversial, and the watchful waiting approach remains still an option.

In our analyses, atrial dysfunction was found to be associated with symptoms, and among the parameters of LA reservoir function, LASr emerged as the strongest predictor of symptoms. In this context, LASr could be helpful to stratify asymptomatic patients with




| | Area under the curve (AUC) | 95% Confidence Interval |
|---|---|---|
| LASr | 0.85 | 0.81-0.89 |
| LAWr | 0.76 | 0.71-0.81 |
| LASr/E/e’ | 0.79 | 0.74-0.84 |
| LAFAC | 0.80 | 0.75-0.85 |

**Fig. 1** Diagnostic accuracy of atrial function indexes for detecting the onset of symptoms

**Table 5** Echocardiographic determinants of LASr at Univariate and Multivariate Regression Logistic Analysis

| | Univariate regression model of predictors of LASr < 22% | | Multivariable regression model of predictors of LASr < 22% | |
|---|---|---|---|---|
| | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| E/e’ | 1.09 (1.04-1.16) | **0.002** | 1.05 (0.97-1.14) | 0.2 |
| LAVi | 1.04 (1.03-1.06) | **< 0.001** | 1.03 (1.00-1.06) | **0.005** |
| Reg Vol/ LAVi % | 0.41 (0.06-2.77) | 0.4 | 5.06 (0.02-1.22) | 0.6 |
| sPAP | 1.08 (1.05-1.11) | **< 0.001** | 1.03 (1.00-1.07) | 0.086 |
| LAFAC | 0.82 (0.78-0.85) | **< 0.001** | 0.82 (0.78-0.86) | **< 0.001** |
| LAEF | 0.88 (0.86-0.90) | **< 0.001** | | |
| LV GLS | 0.92 (0.83-1.00) | **0.06** | | |

LAEF was excluded from multivariable regression analysis because, as expected, it is characterized by high collinearity with LAFAC (VIF > 10) and LAEF is less used in clinical practice

*LAVi* left atrial volume indexed, *Reg vol/LAVi* regurgitant volume/atrial volume ratio, *LAFAC* atrial fractional area change, *sPAP* systolic pulmonary artery pressure, *LAEF* left atrial ejection fraction, *LV GLS* left ventricle Global Longitudinal Strain

degenerative MR. Two recent studies have elucidated the prognostic value of LASr in patients with severe MR [25, 26]. The proposed cut off (LASr < 22%) for the latter study, that analysed outcomes in patients with primary MR undergoing mitral valve repair, was equal to the best cut-off value that discriminates symptomatic from asymptomatic patients in our cohort.

As expected, in our cohort the reduction of LA strain (LASr value < 22%) was associated with LAVi dilatation and dysfunction. However, no significant linear correlation between atrial strain values and LA enlargement was found. These results could be related to the limitations of longitudinal strain in assessing atrial compliance: reduced atrial wall thickness, structures interrupting the wall like pulmonary vein ostia, and the orientation of the atrial fibres with respect to longitudinal shortening.

In this perspective it is valuable to use a threshold, like LASr value < 22%, to discriminate patients with reduced compliance rather than analysing the LA strain as a continuous variable.

## Limitations

Symptom assessment was based on anamnestic evaluation of functional capacity measured in METs. No examination such as 6 Minutes Walking Test or Cardiopulmonary Exercise Test were available to validate the functional capacity.

Furthermore, the biomarkers such as NT-proBNP were available in a too small percentage of patients to be used in the analysis.

## Conclusions

Our findings show the role of LA function as a determinant of symptoms in severe degenerative MR. The decrease of LASr appears to be associated with symptoms onset and a value of LASr < 22% identifies symptomatic patients with 86% specificity and 68% sensitivity.

From this perspective, LASr could serve as a valuable parameter in therapeutic decision-making by identifying patients at an early stage who are likely to develop symptoms. However, prospective studies are needed to confirm its role in helping to identify the optimal timing for mitral surgery.

### Abbreviations

GLS Global longitudinal strain
LA Left atrium
LAEF Left atrial ejection fraction
LAFAC Left atrial fractional atrial change
LAP Left atrial pressure
LASr Left atrial reservoir strain
LAV Left atrial volume
LAWr Left atrial reservoir work
LV Left ventricle
MR Mitral regurgitation
PVF Pulmonary venous flow
sPAP Systolic pulmonary arterial pressure
TEE Transesophageal echocardiogram
TTE Transthoracic echocardiogram

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12947-024-00333-z.

Supplementary Material 1: Fig 2. Supplementary Appendix High/normal LAP estimated through PVFP and LASR value. Figure 3a. Supplementary Appendix Linear correlation between LASr and Indexed Atrial Volume. Figure 3b. Supplementary Appendix Linear correlation between LASr and sPAP. Figure 3c Supplementary Appendix Linear correlation between LASr and LV GLS.

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### Authors' contributions

G.I, G.P, D.M., L.I, and A.E were involved in the conception and design of the study, and in the drafting of the manuscript.F.A, S.S, F.B, A.T, M.B, M.S, M.B, M.M, J.W, A.C., M.D.B, M.F, A.E were involved in the analysis and interpretation of data. A.C, F.M, and A.E revised critically the manuscript improving it with important intellectual content. The also performed the final approval of the manuscript submitted.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by the internal review board of San Raffaele Hospital (NERVAM VESPRO 2022, CE:115/INT/2022)) and all patients provided written informed consent for anonymous collection of their clinical data. The study was conducted according to institutional guidelines and legal requirements.

### Consent for publication

Not applicable.

### Competing interests

Professor Eustachio Agricola is one of the editors of this journal.

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### References

1. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet. 2009;373(9672):1382–94.
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):e35-e71. https://doi.org/10.1161/CIR.0000000000000932.
3. Vahanian A, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-thoracic surgery (EACTS). Rev Esp Cardiol (Engl Ed). 2022;75(6):524. https://doi.org/10.1016/j.rec.2022.05.006.
4. van Wijngaarden AL. Prognostic impact of extra–mitral valve cardiac involvement in patients with primary mitral regurgitation. JACC Cardiovasc Imaging. 2022;15(6):961–70. https://doi.org/10.1016/J.JCMG.2021.11.009.
5. Goette RA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace. 2016;18(10):1455–90. https://doi.org/10.1093/europace/euw161.
6. Cramariuc D, et al. Atrial dysfunction in significant atrial functional mitral regurgitation: phenotypes and prognostic implications. Circulation Cardiovasc Imaging. 2023;16(5):e015089.
7. Lin J, 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(1):11.
8. Lang M, 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):1–39. https://doi.org/10.1016/j.echo.2014.10.003.
9. Galderisi M, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imag. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301–10. https://doi.org/10.1093/ehjci/jex244.
10. Lancellotti P, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position

paper. Eur Heart J Cardiovasc Imaging. 2022;23(5):E171-232. https://doi.org/10.1093/ehjci/jeab253.
11. Cameli M, et al. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. Am J Cardiol. 2013;111(4):595–601. https://doi.org/10.1016/j.amjcard.2012.10.049.
12. Maffeis C, et al. Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction. ESC Hear Fail. 2021;8(1):116–28. https://doi.org/10.1002/ehf2.13143.
13. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, D'Hooge J, Donal E, Fraser AG, Marwick T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a con-sensus document of the EACVI/ASE/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018;19:591–600.
14. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;7:891–900.
15. Gomes DA, et al. Peak left atrial longitudinal strain is associated with all-cause mortality in patients with ventricular functional mitral regurgitation. Cardiovascular ultrasound. 2023;21(1):9. https://doi.org/10.1186/s12947-023-00307-7.
16. Rossi A, et al. Left atrial dilatation in systolic heart failure: a marker of poor prognosis, not just a buffer between the left ventricle and pulmonary circulation. J Echocardiogr. 2018;16(4):155–61. https://doi.org/10.1007/s12574-018-0373-9.
17. Maffeis C, et al. Left atrial strain predicts exercise capacity in heart failure independently of left ventricular ejection fraction. ESC Hear Fail. 2022;9(2):842–52. https://doi.org/10.1002/ehf2.13788.
18. Cameli M, et al. Prognostic value of left atrial strain in patients with moderate asymptomatic mitral regurgitation. Int J Cardiovasc Imaging. 2019;35(9):1597–604.
19. Kuppahally SS, et al. Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablation delayed enhancement of left atrium by magnetic resonance imaging. Am Heart J. 2010;160(5):877–84. https://doi.org/10.1016/j.ahj.2010.07.003.
20. Cameli M, et al. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography. Echocardiography. 2011;28(3):327–34. https://doi.org/10.1111/j.1540-8175.2010.01329.x.
21. Liu L, et al. Reduced left atrial contractile strain with speckle tracking analysis predicts abnormal plasma NTproBNP in an asymptomatic community population. Cardiovascular ultrasound. 2022;20(1):27. https://doi.org/10.1186/s12947-022-00297-y.
22. Cameli M, 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(1):1–9. https://doi.org/10.1186/1476-7120-8-14.
23. Gan GCH, et al. Determinants of LA reservoir strain: independent effects of LA volume and LV global longitudinal strain. Echocardiography (Mount Kisco N Y). 2020;37(12):2018–28.
24. Pournazari P, et al. Hemodynamic determinants of left atrial strain in symptomatic patients with significant primary mitral regurgitation. Circulation Cardiovasc Imaging. 2022;15(3):e013836.
25. Stassen, et al. Left atrial Reservoir function and outcomes in secondary mitral regurgitation. J Am Soc Echocardiogr. 2022;35(5):477–85. https://doi.org/10.1016/j.echo.2022.01.007.
26. Stassen, et al. Prognostic value of left atrial reservoir function in patients with severe primary mitral regurgitation undergoing mitral valve repair. Eur Hear J Cardiovasc Imaging. 2022. https://doi.org/10.1093/ehjci/jeac058.

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