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ORIGINAL PAPER

Prognostic value of left atrial strain in patients with moderate asymptomatic mitral regurgitation

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Abstract

For patients with asymptomatic mitral regurgitation (MR), the criteria identifying the groups at higher-risk and their clinical outcome are still uncertain. Therefore, in these patients, optimal time of surgery remains controversial. The purpose of this study was to compare left atrial (LA) strain to other echocardiographic left ventricular (LV) and LA parameters for the prediction of cardiovascular outcomes in patients with moderate asymptomatic MR. We enrolled 395 patients with primary degenerative moderate asymptomatic MR. Exclusion criteria were: history of atrial fibrillation, myocardial infarction, heart failure, cardiac surgery or heart transplantation, severe MR, mitral valve surgery during follow-up. Patients were prospectively followed for 3.5 ± 1.6 years for the development of cardiovascular events i.e. atrial fibrillation, stroke/transient ischaemic attack, acute heart failure, cardiovascular death. Of 276 patients (mean age 66 ± 8 years) who met eligibility criteria, 108 patients had 141 new events. Patients who developed cardiovascular events presented reduced global peak atrial longitudinal strain (PALS), reduced LA emptying fraction, larger LA volume indexed and lower LV strain at baseline ($p < 0.0001$). With receiving operating characteristics (ROC) curve analysis, global PALS < 35% showed the greatest predictive performance (AUC global PALS: 0.87). Bland–Altman analysis demonstrated good intra- and interobserver agreement with small bias and Kaplan–Meier analysis showed a graded association between PALS and event-free-survival rates. Speckle tracking imaging could provide a useful index, global PALS, to estimate LA function in asymptomatic moderate MR in order to optimize timing of surgery before the development of irreversible myocardial dysfunction.

Keywords Mitral regurgitation · Prognosis · Speckle tracking · Left atrial dysfunction · Mitral surgery timing

Background

In patients with chronic mitral regurgitation (MR), the appearance of symptoms or early signs of left ventricular (LV) dysfunction is correlated with high morbidity and mortality rates, if managed with medical therapy alone, thus it is considered an indication for the surgical treatment of this valvular disease [1, 2].

Patients with symptomatic MR or reduced ejection fraction (EF) are at a higher risk of progressive LV dysfunction and have a worse outcome, based on prior outcome studies [3]. Yet, the criteria identifying the high-risk asymptomatic MR subgroups are uncertain and their clinical outcome is inadequately defined [4].

Therefore, in asymptomatic patients with preserved LV function, the optimal time of surgery remains controversial.

Left atrial (LA) dilatation is a pathological response to volume overload in primary MR, which takes place in order to compensate the increase in LA pressure [5]. An increased LA volume is considered to be a powerful predictor of cardiovascular morbidity and mortality [6, 7].

The improvements in LA contractile performance observed post-operatively suggest the presence of pre-existing different degrees of LA dysfunction before surgery, even in patients with preserved LV function. In addition to LA dimensional indexes, the evaluation of LA performance, including the reservoir, conduit, and booster pump phases,

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provides further information concerning the LA mechanical function [8].

Hence, the appraisal of LA size and function may offer supplementary information about cardiac performance, which could aid in recognizing the optimal timing for cardiac surgery [9].

Speckle tracking echocardiographic analysis allows an excellent assessment of the atrial deformation profile during an entire cardiac cycle, closely following the LA physiology. Particularly, the parameter evaluating LA longitudinal strain, peak atrial longitudinal strain (PALS), represents the first useful index that can represent LA functional analysis [10].

The purpose of this study was to compare LA strain to other conventional LV and LA parameters for the prediction of cardiovascular outcomes in patients with moderate asymptomatic MR.

Methods

Consecutive patients with primary degenerative moderate asymptomatic MR referred to our echocardiographic laboratory during 25 months for a cardiologic examination were included in the study.

The mitral disease was graded using the Doppler quantitative technique and, according to the American Society of Echocardiography (ASE) criteria [11], was defined as moderate if there was a mitral regurgitant fraction (RF) between 30 and 50%.

After a first evaluation, the patients underwent a further exercise echocardiography stress test, in order to confirm they were completely asymptomatic, both at rest and during physical exertion.

The exclusion criteria were any of the following: absence of sinus rhythm, previous myocardial infarction, previous heart failure (HF), previous cardiac surgery or heart transplantation or inadequate examination window. Patients with severe MR at the beginning of the study and those who underwent mitral valve surgery during follow-up were excluded from our analysis.

The history of every patient was collected during the first consult. All patients were prospectively followed for 3 years for the occurrence of cardiovascular events, which included new onset atrial fibrillation (AF), stroke or transient ischaemic attack (TIA), hospitalization for acute HF and cardiovascular death. They were screened every 6 months by performing a clinical and echocardiographic evaluation, much closer compared to the follow-up recommendations reported on the latest guidelines for the management of valvular heart diseases [12].

All subjects gave their written informed consent for their participation in the study. All work was in compliance with the declaration of Helsinki and was performed with the approval of the local ethics committee.

Echocardiographic studies were performed using a high-quality machine (Vivid 7, GE, USA), equipped with a 2.5 MHz transducer. The subjects were examined in the left lateral recumbent position. Measurements of LV and LA size, LV ejection fraction (LVEF), and diastolic LV filling velocities were made in accordance with the current ASE recommendations [13]. LVEF, measured using Simpson's method, was used as a standard index of global LV systolic function. The ratio between peak early (E) and late (A) diastolic LV filling velocities was used as standard indexes of LV diastolic function [14]. LA volumes were measured using the area-length method, from the apical four and two chamber views, and were subsequently indexed by body surface area (BSA), to produce the LA volume index (LAVI). LA emptying fraction (LAEF) was then calculated by the following formula: (LA volume max- LA volume min)/LA volume max $\times$ 100 (%). Care was taken to exclude pulmonary veins and the LA appendage from the LA tracing. The time interval between the onset of the QRS on the electrocardiogram and the aortic and mitral valve opening and closure were measured using pulsed-wave Doppler recordings from the LV outflow tract and inflow area, respectively.

LV longitudinal function was explored by pulsed Tissue Doppler imaging, placing the sample volume at the level of mitral lateral annulus from the apical four-chamber view [15]. Peak systolic (S′), early diastolic (E′), and late diastolic (A′) annular velocities were obtained. S′ was considered as a relatively load-independent index of LV longitudinal systolic function. E' and the derived E′/A′ ratio were used as load-independent markers of ventricular diastolic relaxation [16]. The E/E′ ratio was also calculated and used as a reliable index of LV filling pressures [17]. M-mode measurements of mitral annular plane systolic excursion (MAPSE) were performed by placing the cursor perpendicular to the lateral site of the annulus [18].

For speckle tracking analysis, apical four- and two-chamber views images were obtained using conventional two-dimensional grayscale echocardiography, during breath hold and with a stable electrocardiographic recording. Care was taken to obtain true apical images using standard anatomic landmarks in each view and to not foreshorten the LA, in order to obtain a reliable delineation of LA endocardial border. Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second. The first level echocardiographic data were recorded on-line by a single experienced echocardiographer who was not directly involved in the clinical management and follow up of patients, whereas, for the calculation of speckle tracking parameters, images recorded were analysed off-line by a single experienced and independent echocardiographer, using a

commercially available semi-automated two-dimensional strain software (EchoPac, GE, Milwaukee, USA). The examiner was not directly involved in the image acquisition and was blinded regarding the outcome of patients and other conventional echocardiographic parameters representing LV, LA and valvular structure or function.

As previously described [9], and as stated in the latest European Association of Cardiovascular Imaging (EACVI)/ASE consensus document [19], the LA endocardial border was manually traced in both the four- and two-chamber views, thus delineating a region of interest (ROI), composed of six segments. Next, after the segmental tracking quality analysis and the manual adjustment of the ROI were performed, the longitudinal strain curves were automatically generated by the software for each atrial segment. PALS, measured at the end of the reservoir phase, was calculated both as the average of values observed for all LA segments (global PALS), and separately averaging values observed in the 4- and 2-chamber views (4- and 2-chamber average PALS) (Fig. 1). The time to peak longitudinal strain (TTP-LS) was also measured as both the average of all 12 segments (global TTP-LS) and by separately averaging values observed in the two apical views (4- and 2-chamber average TTP-LS).

To calculate LV global strain, the endocardial border was manually traced in the apical views (four-, three- and two-chamber views), thus delineating a ROI composed of six segments for each view. Then, after the segmental tracking quality analysis and the eventual manual adjustment of the ROI, the longitudinal strain curves were generated by the software for each ventricular segment. Global longitudinal strain (GLS) was calculated by the software as the average strain of all 17 segments of the LV model.

In patients in whom some segments were excluded because of the impossibility of achieving adequate tracking, PALS and GLS were calculated by averaging values measured in the remaining segments.

In order to assess the reproducibility of global PALS and GLS, 20 patient recordings were randomly selected for additional examinations. A Bland–Altman plot [20] was performed to evaluate the intra- and interobserver agreement, by comparing a repeated analysis which was done 1 week later by the same observer and another one by a second independent observer.

In the statistical analysis, data are shown as mean ± standard deviation (SD). A p value < 0.05 was considered statistically significant. Pearson's correlation coefficients were calculated to assess the relationship between the continuous

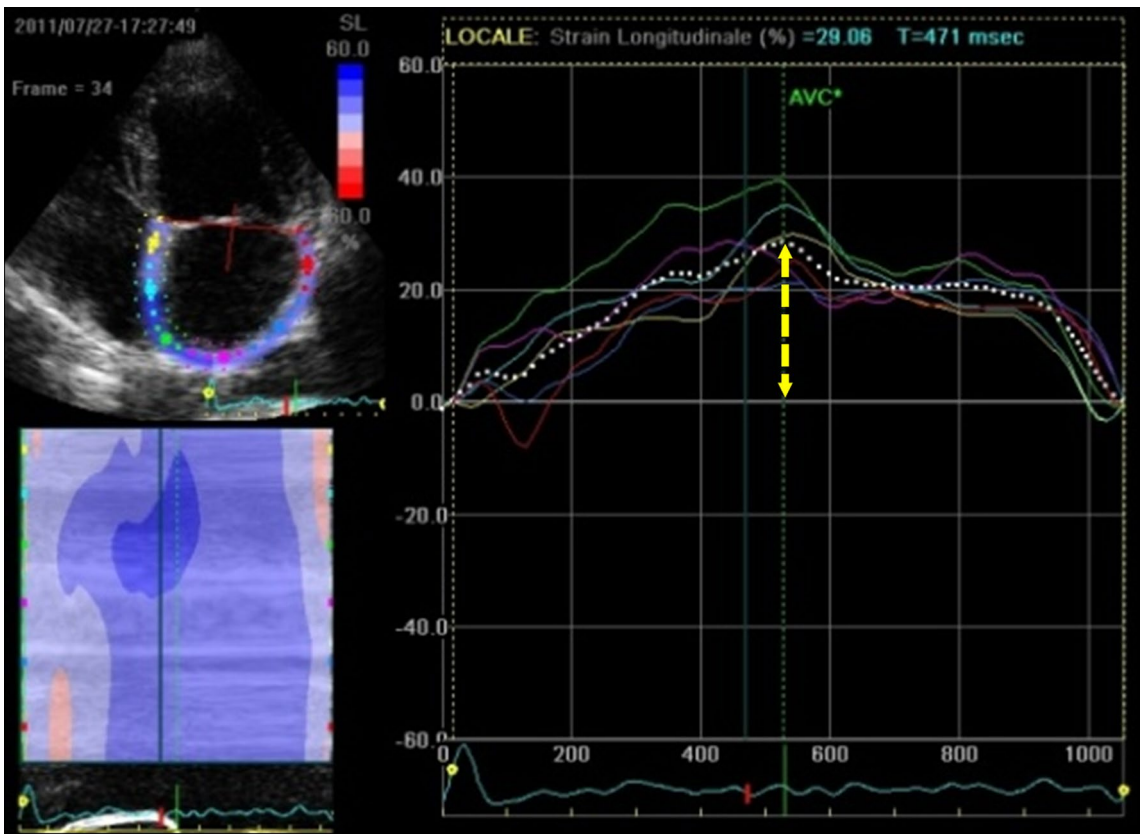

Fig. 1 Measurement of peak atrial longitudinal strain from a 4-chamber view

variables. Sensitivity and specificity were calculated using standard definitions, receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated for the prediction of cardiovascular events. A Cox proportional hazard model was used to determine the association between global PALS, LA volume, LAEF E/E′ ratio and GLS with future cardiovascular events, after adjusting for age, gender, the presence of arterial hypertension, diabetes mellitus or pulmonary hypertension and LVEF. Then a Kaplan–Meier analysis was used to determine the discriminative performance of PALS for event free survival rates in the study population. Analyses were performed using the SPSS (Statistical Package for the Social Sciences, IBM, Armonk, NY, USA) software Release 12.0.

Results

Of the 395 patients screened, 276 patients (mean age 66 ± 8 years) met the eligibility criteria during the study period and were enrolled, while 45 patients were excluded for non-sinus rhythm, 38 for severe mitral valve disease, 12 for previous myocardial infarction, 16 for previous HF and 8 for poor echocardiographic window. Table 1 shows the clinical and echocardiographic data of the study population.

During a mean follow-up period of 3.5 ± 1.6 years, out of the 276 subjects enrolled, 108 had 141 new events (52 new onsets of AF, 58 hospitalizations for acute HF, 23 stroke/TIA, 8 cardiovascular deaths).

While in the follow-up period, 41 patients underwent mitral valve surgery, because of the development of symptomatic severe MR, and were consequently excluded from the analysis.

Patients who developed cardiovascular events presented a reduced global PALS, reduced LAEF, larger LAVI and lower LV GLS at baseline ($p < 0.0001$ for all comparisons).

The ROC curve analysis was calculated and the greatest overall performance for the prediction of cardiovascular events was shown by global PALS, with a cut off value < 35% (AUC global PALS: 0.87; LAVI: 0.72; LAEF: 0.70; LV GLS: 0.65; LVEF: 0.58; E/E′ ratio: 0.53) (Fig. 2).

The Kaplan–Meier survival analysis showed a graded association between the severity of LA dysfunction estimated with global PALS and the risk of cardiovascular events: the cumulative 40 months free-of-events survival rates was 90% for those with global PALS > 35%, 78% with global PALS 25–35%, 62% with global PALS 15–25%, and 9% with global PALS 15% (Fig. 3).

Using Cox Proportional Hazard Model, in the multivariate regression analysis, after adjustment for age, gender, the presence of arterial hypertension, diabetes mellitus or pulmonary hypertension and LVEF, reduced global PALS values and higher LAVI were the only two most significant predictors of cardiovascular events (Table 2).

Regarding the LA strain reproducibility assessment, out of a total of 3312 segments analysed, the software was able to correctly track 3102 (93.6%) segments. The Bland–Altman plot demonstrated a good intra- and interobserver agreement,

Table 1 Clinical and echocardiographic data of the study population

Variable	Cardiovascular events	
	No	Yes
	n = 168	n = 108
Age (years)	66 ± 8	67 ± 9
Women (% of pts)	42%	43%
Body mass index (kg/m^2)	25.8 ± 4.6	25.7 ± 5.2
Heart rate (bpm)	74 ± 11	75 ± 10
Systolic blood pressure (mmHg)	121 ± 31	124 ± 32
Comorbidities		
Hypertension (% of pts)	60%	62%
Diabetes mellitus (% of pts)	34%	32%
COPD (% of pts)	31%	34%
Renal insufficiency (% of pts)	15%	16%
Peripheral arteriopathy (% of pts)	27%	29%
Malignancy (% of pts)	0%	0%
Medical therapy		
ACE-inhibitors (% of pts)	71%	69%
Beta-blockers (% of pts)	48%	47%
Loop diuretics (% of pts)	82%	84%
Platelet aggregation inhibitors (% of pts)	52%	54%
Echocardiographic data		
LV end-diastolic volume (ml)	95 ± 34	98 ± 34
LV ejection fraction (%)	59 ± 9	58 ± 10
LV mass index (g/m^2)	104 ± 25	109 ± 31
LV global longitudinal strain (%)	− 18.5 ± 3.4	− 17.6 ± 3.6*
LA A-P diameter (mm)	43 ± 6.5	44.9 ± 6.6
LA area (cm^2)	25.6 ± 5.8	28.2 ± 5.3*
LA indexed volume (ml/m^2)	32.5 ± 6.7	36.4 ± 7.1*
LA ejection fraction (%)	68 ± 13	62 ± 15*
E/A ratio	0.94 ± 0.14	0.95 ± 0.16
E/E′ ratio	11.2 ± 6.5	12.4 ± 7.1
Mitral regurgitant fraction (%)	38.9 ± 8.1	39.1 ± 9.4
EROA (cm^2)	0.34 ± 0.05	0.34 ± 0.06
PAPs (mmHg)	31 ± 7	32 ± 8
4-chamber PALS (%)	30.1 ± 7.9	17.8 ± 7.8*
2-chamber PALS (%)	34.0 ± 9.2	20.3 ± 8.9*
Global PALS (%)	32.5 ± 8.5	19.7 ± 8.1*
Global time-to-peak PALS (ms)	420 ± 51	412 ± 65

*Significative variation between the two groups

COPD chronic obstructive pulmonary disease, *EROA* end regurgitation orifice area, *LA* left Atrial, *LV* left ventricular, *PALS* peak atrial longitudinal strain, *sPAP* systolic pulmonary artery pressure

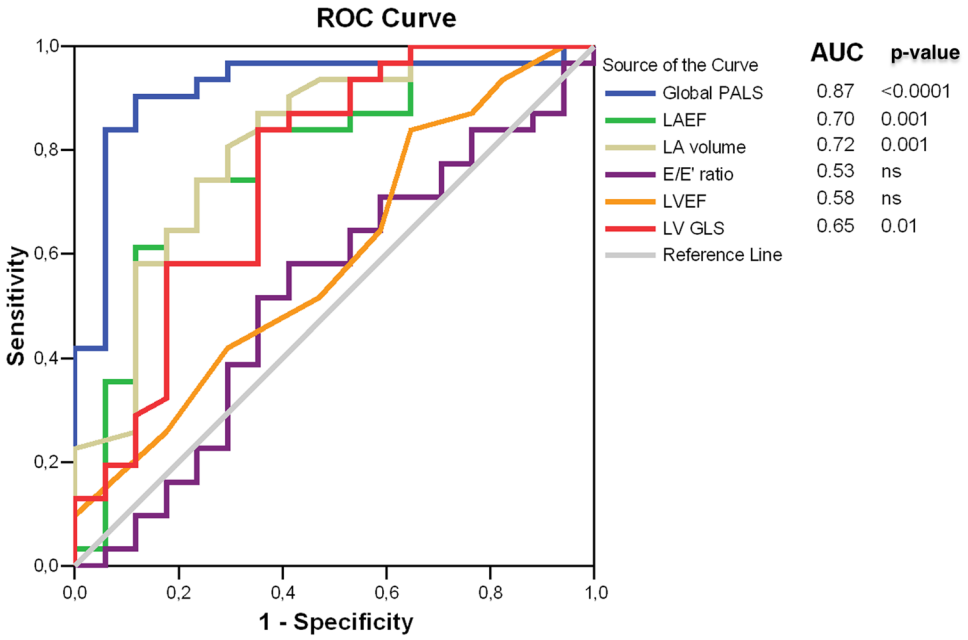

Fig. 2 ROC curves for the analysis of diagnostic accuracy in predicting cardiovascular events in the study population. (*AUC* area under the curve; GLS global longitudinal strain, *LA* left atrial, *LAEF* left atrial emptying fraction, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *PALS* peak atrial longitudinal strain, *ns* not significant)

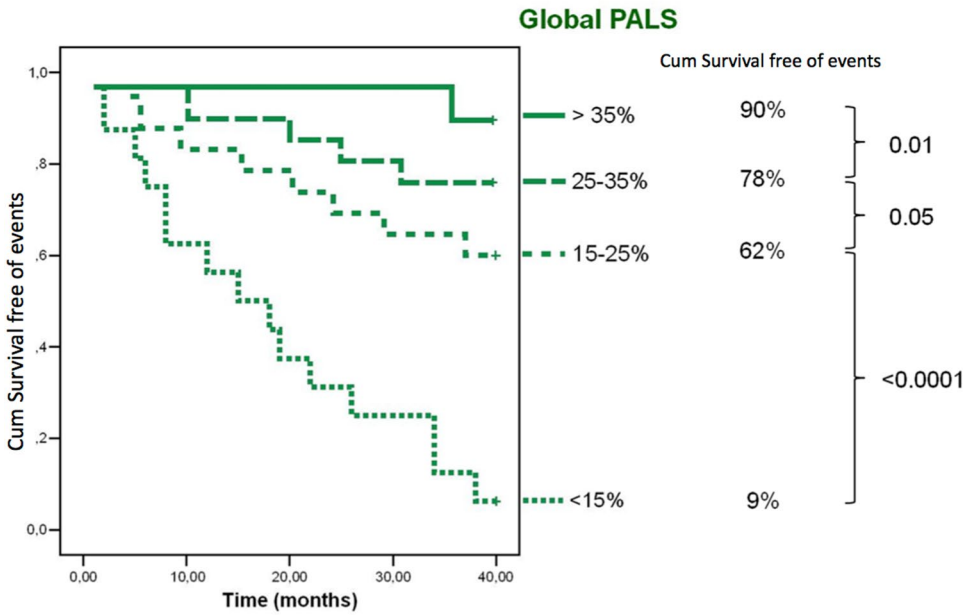

Fig. 3 Graded relationship between Kaplan–Meier cumulative event-free survival and categorical increment of global peak atrial longitudinal strain (PALS)

with a small bias not statistically significantly. Mean differences ± 2 SD were 0.2 ± 1.9% and 0.3 ± 2.2%, for intra- and interobserver agreement, respectively.

Discussion

This prospective study demonstrated a strong association between the decrease of LA function, assessed by myocardial deformation, and the new onset of cardiovascular events, even after adjustment for confounders such as age, gender, the presence of risk factors or pulmonary hypertension and LVEF. We have registered 141 new events out of 108 patients. The fact that some patient presented more than a single cardiovascular event could be explained by the fact that a single end-point could be caused or could be precipitated by another; often patients who developed AF presented also stroke or TIA and in a large part of patients new-onset AF caused frequent hospitalization for acute HF which in some patients end up in cardiovascular death.

LA reservoir function, measured by global PALS, is crucial for LV filling and is influenced by atrial compliance,

Table 2 Left Atrial parameters in Unadjusted and Multivariable models adjusting for gender, age and other covariates for the prediction of cardiovascular events in the study population (n = 276)

	%	Unadjusted		Adjusted*	
		Hazards ratio	p value	Hazards ratio	p value
Global PALS					
Mildly reduced	25	2.7	< 0.0001	2.5	< 0.0001
Moderately reduced	27	4.1		3.2	
Severely reduced	31	10.9		8.6	
LAEF					
Mildly reduced	29	2.1	0.001	1.8	0.01
Moderately reduced	24	4.0		2.4	
Severely reduced	27	4.3		2.8	
Indexed LA volume					
Mildly increased	31	2.0	< 0.0001	1.8	0.004
Moderately increased	25	4.0		3.7	
Severely increased	28	8.3		6.2	
E/E′ ratio					
Mildly increased	31	1.5	0.01	1.3	0.05
Moderately increased	20	3.5		2.1	
Severely increased	31	6.5		2.3	
GLS					
Mildly reduced	33	2.3	0.001	1.9	0.01
Moderately reduced	22	4.0		2.5	
Severely reduced	25	4.1		2.9	

GLS global longitudinal strain, *LA* left atrial, *LAEF* left atrial ejection fraction, *PALS* peak atrial longitudinal strain

*Multivariable model: adjusted for gender, age, presence of arterial hypertension, diabetes mellitus or pulmonary hypertension and left ventricular ejection fraction

atrial contraction, and LV mitral annulus systolic descent [21].

Chronic MR, which is a state of enhanced preload, induces progressive LA dilatation as a compensatory adaptation to volume overload [22]. In fact, in a report of patients with primary MR and sinus rhythm, severe LA dilatation ($LAVI \geq 60$ mL/m^2) was associated with a poor outcome, independently from known outcome predictors associated with MR, even in those without symptoms and with preserved LVEF [6]. However, MR provokes LA remodelling with ultrastructural changes, impairing LA elastic properties and compliance with subsequent elevation of LA pressure [23]. Hence, markers of LA reservoir function appear to be significantly compromised in patients with significant MR, probably due to poor atrial compliance [24].

In our previous studies, we demonstrated a progressive impairment of global PALS in patients with moderate and severe MR [25], with an additional reduction in those patients who experienced an episode of paroxysmal AF [26]. In a cohort of patients with MR undergoing mitral surgery, we were able to show a tight relationship between the extent of LA fibrosis and the value of LA strain, showing the great sensibility of this new index in comparison with other echocardiographic parameters of LA size and function [27].

The present study confirms that LA dilatation is associated with a poorer prognosis in patients with asymptomatic moderate MR and highlights LA deformation analysis as a more sensitive tool, providing independent and additional prognostic information to other conventional LA measurements, with a good intra- and interobserver agreement. LA strain also proved its utility for risk stratification of these patients, showed by Kaplan–Meier free-of-events survival curves.

Previous studies have already demonstrated that once the patients reach the moderate range of MR, a closer follow-up can be recommended, because with the development of subtle contractile dysfunction, decisions regarding surgical correction may be considered, even with absent or minimal symptoms or preserved LV systolic function, assessed by conventional measures, in order to avoid the development of irreversible myocardial dysfunction.

Hence, our study provides further insight into the influence of LA volume changes and function alterations in patients with chronic moderate MR. Our data suggest that LA function indexes may be considered both diagnostic and prognostic adjuvants that facilitate the unmasking of incipient LA myocardial impairment. With ROC analysis we found that a cut off value of PALS < 35% was the best

to predict cardiovascular events, therefore it could represent a reference echocardiographic index to consider surgical evaluation in asymptomatic patients with MR, which obviously needs to be comprehensive of clinical, anatomic and functional parameters.

Therefore, serial measurement of LA function could be suggested in order to detect the early onset of LA dysfunction and impaired LA compliance, which occurs in advanced stages of the disease, in order to estimate the optimal time for surgical intervention.

Limitations

Although this was a prospective study on consecutive patients with MR, some limitations need to be acknowledged in this study. First of all, it was a single center study so a bigger number of patients could be useful to generalize this research findings. Then, the LA strain methodical itself shows important limitations: an adequate measurement of global PALS requires the presence of optimal 4 and 2-chamber apical views, that can permit an easy delineation of the endocardium border while, at the same time, avoiding LA foreshortening and auricular visualization, so it cannot be used in patients with an inadequate acoustic window; moreover, we used a vendor specific software designed for LV analysis to study the LA strain, since a dedicated software for LA analysis has not yet been released. Although some correlations have been made, the values of strain can be applied only for the vendor software we have used in our study.

Conclusions

Global PALS emerged as the best prognostic marker of cardiovascular events in patients with moderate asymptomatic MR, among first and second level LA and LV echocardiographic parameters. It proved to be a useful index for risk stratification in these subjects, with a value of less than 35% as a predictor of increased events. Thus, it could aid in decision making relative to the timing of mitral valve surgery, before the development of irreversible cardiac dysfunction.

The study of LA function could be crucial to detect subtle myocardial dysfunction in patients with MR. Strain imaging is an advanced novel technique which could help in prediction of LA damage caused by MR. However, the significance of these findings and their possible use will require further prospective studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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