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Prognostic Contribution of Bidimensional Left Atrial Strain in Patients with Asymptomatic Mitral Stenosis: About a Tunisian Population

Conflict of interest: nothing to declare.
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Abstract

Introduction. The two-dimensional strain is an objective echocardiographic technique allowing the quantification of myocardial deformation.
Purpose. To specify prognostic contribution of left atrial strain in patients with asymptomatic mitral stenosis.
Materials and methods. We included consecutive patients followed for severe or moderately severe rheumatic Mitral Stenosis (MS), asymptomatic, during the period from January 2015 to June 2020 in military hospital of Tunis. The patients followed were divided into two groups according to one criterion of judgment composed of: Cardiac mortality, The occurrence of hospitalization for cardiac reasons, The occurrence of atrial fibrillation (AF), The occurrence of a thromboembolic event and the need for cardiac surgery or mitral valvuloplasty.
Results. 53 patients were divided into two groups: 30 patients had at least one event and 23 patients had no event according to the occurrence of the major endpoint of the study. In a univariate study and for conventional echocardiographic parameters, we determined that if Left Atrium Area (LAA) is larger than 30 cm^2 and left atrium volume (LAV) more than 100 ml/m^2, the risk of occurrence of an event increased respectively significantly (LAA: 69% vs 10%; p=0.01; OR=6.6; 95% CI [1.5–28] and LAV: 71.4% vs 39%; p=0.002; OR=4; 95% CI [1.1–13]). The same for left atrium deformation parameters, both Peak Atrial Longitudinal Strain (PALS) <25% and Peak Atrial Contraction Strain (PACS) <10% were predictive of events in univariate study with these following respective odds ratios (ORs) (PALS: 83% vs 30.4%; p=0.0001; OR=11.4; 95% CI [3–42] and PACS: 90% vs 47%; p=0.001; OR=9.8; 95% CI [2.3–41]). In a multivariate study, the only independent parameter of the occurrence of an event was PACS <10% (p=0.013; OR=44; 95% CI [2.19–80]).
Conclusion. PACS have prognostic value in asymptomatic MS as it predicts occurring of pathologic events in the following of patients with asymptoms.
Keywords: mitral stenosis, prognosis, speckle tracking, cardiac echography, left atrium

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Прогностическое значение двумерной деформации левого предсердия у пациентов с бессимптомным митральным стенозом: на примере тунисской популяции

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Резюме

Введение. Двумерная деформация – это объективный эхокардиографический метод, позволяющий выполнить количественную оценку деформации миокарда.
Цель. Определение прогностических возможностей деформации левого предсердия у пациентов с бессимптомным митральным стенозом.
Материалы и методы. В исследование были включены произвольно отобранные пациенты с тяжелым или умеренно тяжелым ревматическим митральным стенозом (МС), протекающим бессимптомно, проходившие лечение в военном госпитале Туниса в период с января 2015 по июнь 2020 года. Наблюдаемые пациенты были разделены на две группы на основании единого критерия оценки, включающего в себя такие показатели, как смертность от сердечно-сосудистых заболеваний, количество случаев госпитализации в связи с сердечно-сосудистыми заболеваниями, частота возникновения фибрилляции предсердий (ФП), развитие тромбоэмболических состояний и показания к кардиохирургическому вмешательству или митральной вальвулопластике.
Результаты. 53 пациента были включены в исследование и затем разделены на две группы: у 30 пациентов имел место по крайней мере один сердечно-сосудистый случай, а у 23 пациентов отсутствовали какие-либо случаи, соответствующие основной конечной точке исследования. На основании однофакторного анализа и обычных эхокардиографических параметров было установлено, что при площади левого предсердия (ПЛП) более 30 см^2 и объеме левого предсердия (ОЛП) более 100 мл/м^2 значительно увеличивался сердечно-сосудистый риск (ПЛА – 69% по сравнению с 10%, p=0,01, ОШ=6,6, 95% ДИ [1,5–28] и ОЛП – 71,4% по сравнению с 39%, p=0,002, ОШ=4, 95% ДИ [1,1–13]). Аналогичным образом в отношении параметров деформации левого предсердия как пиковая продольная деформация предсердия (PALS) <25%, так и пиковая деформация сокращения предсердия (PACS) <10% были прогностически значимыми показателями в однофакторном анализе при следующих отношениях шансов (ОШ): PALS – 83% по сравнению с 30,4%, p=0,0001, ОШ=11,4, 95% ДИ [3–42], PACS – 90% по сравнению с 47%; p=0,001; ОШ=9,8; 95% ДИ [2,3–41],

соответственно. При исследовании методом многофакторного анализа единственным независимым показателем сердечно-сосудистого риска являлась PACS <10% (p=0,013; ОШ=44; 95% ДИ [2,19-80]).
Заключение. PACS имеет прогностическое значение при бессимптомном митральном стенозе, поскольку позволяет предсказать возникновение патологических событий у пациентов с бессимптомным течением заболевания.
Ключевые слова: митральный стеноз, прогноз, спекл-трекинг, эхокардиография, левое предсердие

■ INTRODUCTION

Rheumatic mitral stenosis (MS) is a frequent acquired valve pathology in our country and in developing countries [1]. Speckle Tracking is an ultrasound technique that is particularly effective in terms of spatial and temporal resolution. The exploration of the atrial function in 2D strain has been proposed by several authors as an additional tool to the classic parameters of the left atrial function [2–6]. Mitral stenosis is associated with significant morbidity and mortality. Treatment modalities and timing should be guided by both morphological and functional characteristics of the left atrium (LA) [7]. Although there is an agreement to treat patients with symptomatic moderate and severe MR, an investigation of asymptomatic patients is necessary in order to assess the risk of complications and therefore treat in time before they occur [2].

■ PURPOSE OF THE STUDY

To clarify the prognostic contribution of atrial 2D strain in asymptomatic patients with mild and moderate MS.

■ MATERIALS AND METHODS

Our study included patients followed for mild or moderate rheumatic MS, asymptomatic, in sinus rhythm, collected at the cardiology department of the military hospital of Tunis (monocentric study in a university department) during the period from January 2015 to June 2020. Fifty-three patients were followed for 5 years. The patients were followed for a variable period starting from their inclusion. All echocardiographic examinations were performed and analyzed by qualified senior practitioners in echocardiography. The same patient was examined by the same examinator. We had not changed the echocardiographer during study which was VIVID-9 machine associated to a GE-ECHOPACK analysis program. These patients followed were divided into two groups (event group and no event group) according to a composite endpoint consisting of: cardiac mortality, the occurrence of hospitalization for cardiac reasons, the occurrence of atrial fibrillation (AF), the occurrence of a thromboembolic accident, and the need for heart surgery or percutaneous mitral valvuloplasty (PMV).

Inclusion Criteria

Asymptomatic patients with moderate or severe MS, with a sinusal rhythm without a history of paroxysmal AF.

Exclusion criteria

Patients with: another severe valvopathy, congenital MS, degenerative MS, coronary artery disease, severe renal failure, a left ventricular systolic dysfunction (Left ventricular ejection fraction (LVEF) <50%), hypertension, diabetes, or with poor echogenicity. Symptomatic patients and/or presenting a complication of MS as: stroke, embolic accident, AF patients were excluded.

Statistical study

Statistical analysis was performed using SPSS version 22 software. Only results with $p \leq 0.05$ were considered statistically significant. Continuous quantitative variables are expressed as mean±standard deviation and dichotomous variables as frequency (%). The comparison of the quantitative variables was carried out by the student t test. For the qualitative variables, the Khi2 or Fischer tests were used. To study the impact of the LA strain on the endpoint of the study, the odds ratio was calculated. The ROC curves were used for the study of the different statistical relationships of the quantitative parameters. In order to determine the predictive factors independent of the event, including the strain, we conducted a multivariate study by binary logistic regression by introducing the factors whose p is less than 20%. This multivariate analysis made it possible to specify adjusted Odds ratio. The Kaplan Meier survival curve was used to study the evolution of the endpoint of the study over time.

■ RESULTS

53 patients were divided into two groups: 30 patients had at least one event and 23 patients had no event according to the occurrence of the major endpoint of the study. Table 2 summarizes the prevalence of the study's composite endpoint. Thirty patients (56.6%) from the general population had an event during the five-year follow-up. Among them 22 (30%) had a stroke or AF. In our study, as presented in Table 2, the epidemiological data are comparable. Table 4 presents the conventional echocardiographic parameters of

Table 1
Studies that aimed to determine strain implication in asymptomatic MS

Year of study Publication	Authors	Judgement criteria	Prevalence of Judgement criteria	Methodology	Main result
2009	Caso and al. [4]	Heart surgery Mitral valvuloplasty The occurrence AF or hospitalization The occurring of heart symptoms	41% (11,3% AF)	53 patients with MS (Asymptomatic) Three years follow-up	LA strain is altered in MS population even asymptomatic
2013	Roberta Ancona and al. [5]	AF occurrence	20%	101 patients MS Asymptomatic or paucy-symptomatic Follow-up with Holter monitor to AF detection	PALS less than 17.5% Predicted AF

Table 2
The prevalence of the events of the composite endpoint of the study. Epidemiological characteristics of the two groups

Events: 30 patients with event		**Number of events**		
PMV and OR MVR		25		
Stroke		8		
AIL Acute ischemia of limb		2		
AF		14		
Death		3		
Factor	Population, n=53	Event, n=30	No event, n=23	P
Age	52 ±10	53 ±10	49 ±10	0,22
Gender: men/women	32/21 60% / 40%	16/14 53,3% / 46,7%	16/07 69,6% / 30,4%	0,23
Dyslipidemia	3 5,7%	3 10%	0 0%	0,11
Current smoking	10 19%	7 23,3%	3 13%	0,34
Heart rate	78 14	77± 14	79± 13	0,57

Table 3
Echocardiographic parameters of the two groups

Standard echocardiographic parameters	**Population, n=53**	**Event, n=30 (56.6%)**	**No event, n=23 (43.3%)**	**P**
Mitral area (cm^2)	1.3± 0.3	1.3± 0.37	1.4± 0.35	0.4
Transmitral gradient (mmHg)	8.6± 4.5	8± 4	9± 4	0.4
LA AREA (cm^2)	30± 6	32± 6	26± 5	0.005
Volume LA (ml/m^2)	113.3± 27	120.7± 30	101± 17	**0.002**
LVEF%	60± 5	59± 6	62± 5	0.13
LV EDD (mm)	50± 5	51± 6	48± 4	0.22
LV ESD (mm)	32± 6.4	34± 7	29± 3	0.05
TAPSE (mm)	19± 4	20± 4	18± 2	0.2
SVD (cm/s)	11± 2	11± 2	11± 2	0.6
SPAP (mmHg)	38± 12	40± 13	35± 11	0.22
PALS%	20± 8	17.5± 8.5	24± 7	0.002
PACS%	8± 3	7± 2	10± 4	0.001

Notes: SAPS – Systolic Pulmonary Arterial Pressure; SVD – right ventricular systolic S wave velocity; TAPSE – Tricuspid Ring Plane Excursion; LV EDD – Left ventricle end diastolic diameter; LV ESD – Left ventricle end-systolic diameter; LVEF – Left ventricular ejection fraction.

Table 4
Result of univariate study

Factor	Population, n=53	Event, n=30	No event, n=23	P	OR	CI 95%	
						Inferior limit	Superior limit
LA Surface >30 cm^2	19 35.8%	16 69%	03 10%	0.01	6.6	1.5	28
PALS <25%	32 60%	25 83.3%	7 30.4%	<0.0001	11.4	3	42
PACS <10%	38 71%	27 90%	11 47%	0.001	9.8	2.3	41
Volume LA (ml/m^2)	27 50.9%	20 71.4%	7 39%	0.002	4	1.1	13

Table 5
Result of multivariate study I

Factor	P	OR ajusted	CI 95%	
			Inferior limit	Superior limit
PACS <10%	0.013	44	2.19	80
PALS <25%	0.9	20.8	0.9	1.5
LA surface >30 cm^2	0.9	20.7	0.7	1.2
Volume LA (ml/m^2)	0.17	1.05	0.97	1.12

the population studied. Mitral area assessed by planimetry was increased in the event group without reaching the significance threshold (1.3±0.37 vs 1.4±0.35 cm^2, p=0.4). Both the left atrial area and volume were significantly higher in the event group respectively (32 cm^2 ± 6 vs 26±5 cm^2, p=0.005) and (120 ml/m^2 ± 30 vs 101 ml/m^2 ± 17, p=0.002). Left atrial strain parameters (Table 3) were significantly reduced in the positive event group. We found that: The PALS was 17.5±8.5% in the event group vs 24±7% in the no event group with p=0.002.The PACS was 7±2% in the event group vs 10±4% in the no event group with p=0.001.

From the ROC curves cut-offs, we determined that when Left Atrium Area (LAA) larger than 30 cm^2 and left atrium volume (LAV) more than 100 ml/m^2, the risk of occurrence of an event increased respectively significantly (LAA: 69% vs 10%; p=0.01; OR=6.6; 95% CI [1.5–28] and LAV: 71,4% vs 39%; p=0.002; OR=4; 95% CI [1,1–13]).

We have demonstrated from the ROC (Fig. 1) curves cut-offs that it was the same for left atrium deformation parameters, both Peak Atrial Longitudinal Strain (PALS) <25% and Peak Atrial Contraction Strain (PACS) <10% were predictive of events in univariate study with these following respective odds ratios (ORs) (PALS: 83% vs 30.4%; p=0.0001; OR=11.4; 95% CI [3–42] and PACS: 90% vs 47%; p=0.001; OR=9.8; 95% CI [2.3–41]) (Table 4).

The only independent predictor of the occurrence of an event in the follow-up of our patients was the PACS (Table 5) (p=0.013; OR=44; 95% CI: [2.18–80]).

From the survival curve of KAPLAN MEIER (Fig. 2 and 3), we found that patients with a dilated atrium with a surface greater than 30 cm^2 or LA volume more than 100 ml/m^2, PACS <10% and PALS <25% presented significantly (Log Rank = 0.001; respectively for the three parameters) more events over the 5 years of follow-up than the rest of the patients.

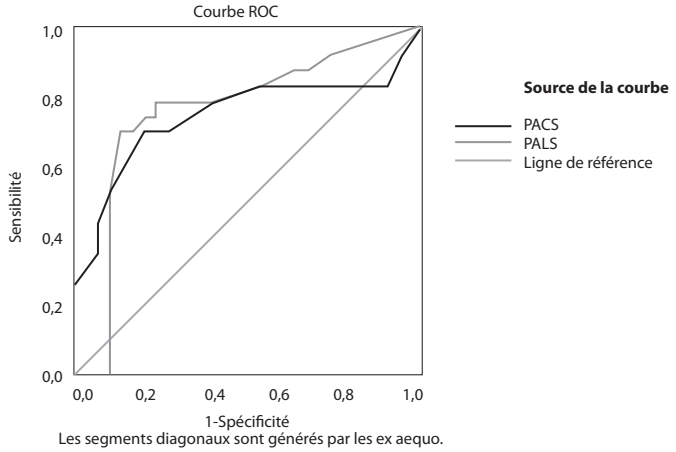

Fig. 1. ROC curve Event / PALS and PACS

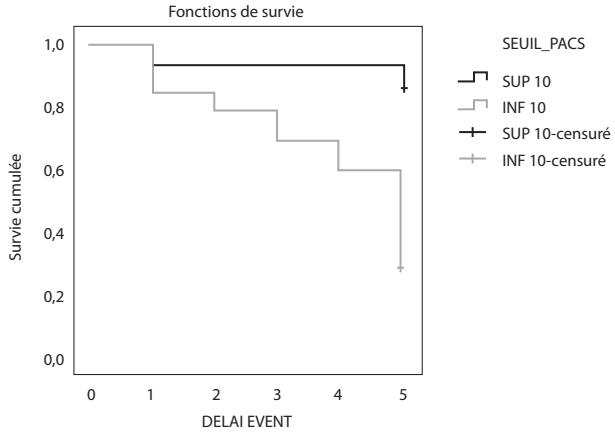

Fig. 2. Kaplan – Meier curve of occurrence of the composite endpoint of the study according to the PACS

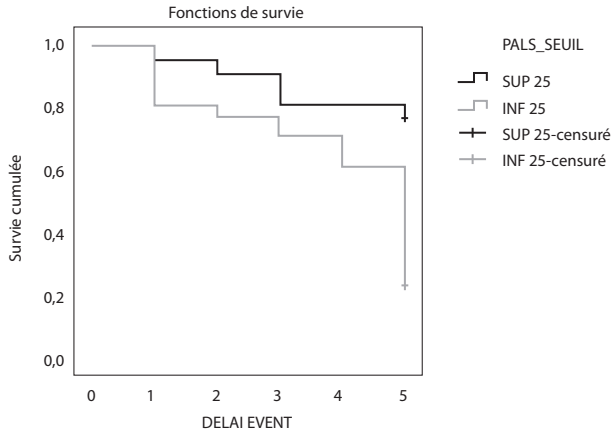

Fig. 3. Kaplan – Meier curve of occurrence of the composite endpoint of the study according to the PALS

■ DISCUSSION

Left atrium deformation parameters seem to have prognostic value in patients with mitral stenosis. Changes in atrial myocardial deformity properties may be due to disorganization of atrial muscle bundles and atrial fibrosis [8]. Thus, the alteration of the left atrial function evaluated by the parameters of the myocardial deformation would explain the thrombogenesis, the intra-atrial stasis and the occurrence of atrial fibrillation.

Two studies in the literature aimed to determine the prognostic impact of LA strain in asymptomatic patients with MS (Table 1).

The prevalence of the primary endpoint (41% vs 56.6%), AF (11.3% vs 26.4%), surgery or PMV (16% vs 47%) in the Caso study are lower compared to our results.

This could be explained by our longer study period (5 years) also our patients have a more severe MS and a more dilated LA than the patients of the Italian series of Caso et al.: LA volume (55±25 ml/m^2 vs 61±21 ml/m^2 in our study) and mitral surface (1.5 cm^2 ± 0.5 vs 1.3 cm^2 ± 0.3 in our study). That's why mitral surface is considered as a determining parameter in the evaluation of a MS: Abel et al. [9] in a hemodynamic study of 314 patients with MS demonstrated that reduced mitral surface significantly increases the occurrence of AF, they demonstrated that patients who developed this arrhythmia had more dilated LA and pulmonary pressures (studied in hemodynamic) which were higher. In the same context Selzer et al. [10], in a second hemodynamic study which included 67 patients with MS including 19 in AF, explained that the decrease in cardiac output in patients with AF with MS compared to those in sinus rhythm is essentially due to a lower mitral surface in the MS group. However, Unverferth et al. [11] in a study of 80 patients with MS invalidated the correlation between severity of mitral stenosis, high trans-mitral gradient, pulmonary hypertension and the occurrence of AF. The only predictive parameter of AF was the anteroposterior diameter of the LA greater than 45 mm.

Also Caso et al. [2] demonstrated that the peak of the atrial strain rate is significantly lower in the group of patients who presented an event without specifying threshold values (1.9%/s±0.8 vs 3.2%/s±0.8; p=0.005). Ancona et al. [5] had proved that the PALS is significantly lower in patients with MR and that a PALS <17.5% is predictive of AF (p<0.001).

The differing prognoses of patients with MR can be predicted by detecting the varying degrees of atrial muscle bundle disorganization and atrial fibrosis that causes atrial stiffness and atrial reservoir dysfunction [12].

Twenty percent of the patients in Roberta Ancona et al. study [5] – presented AF which is lower than what we found in our population (26%). This could be explained (as for the study conducted by Caso et al. [2]) by a smaller mitral surface [9, 10] in our population, a longer follow-up period and also a greater dilation of the LA in our patients: the LA volume is 55.6 ml/m^2 ±6 in this study is lower than that of our patients which is 61±21 ml/m^2.

Regarding the higher prevalence of the occurrence of AF [13] in our study (26%), it can be explained, in addition to the factors previously mentioned, by an older population of patients

The association of AF with age in patients with mitral stenosis has been frequently reported [14]. It has been concluded that the patient's age is associated with an established AF, this is secondary to a longer duration of hemodynamic aggression by the MS. Since mitral stenosis is a progressive disease, it has been postulated that aging leads to worsening of rheumatic lesions leading to an increased prevalence of AF which

is not only due to the simple mechanism of LA overload but to a continuing and aging rheumatic cardiomyopathy [15].

In the literature, the prevalence of AF in patients with MS is ranging between 20% and 40%: Wood et al. [16] reported that association between AF and MS is about 40% which is due to selection of patients presenting mitral regurgitation grade I to grade IV associated to MS so the overload of LA was greater in his patients by MR [17].

Limitations of the study

Our study had some limitations. The need to manually track the LA wall and reposition the region of interest on each of the five LA walls frame by frame. This manual task is time-consuming per patient and decreases reproducibility.

In addition, the small sample size limited the power of our conclusions, a multicentric study with a larger population is necessary to confirm our results.

■ CONCLUSION

Even asymptomatic patients with MS should be examined by echocardiography using in addition to conventional parameters the speckle tracking technology whose utility to predict cardiac events has been proven in some study such ours.

More large series must be realized to have a strong recommendation for this practice which is not yet mentioned in last new heart valve recommendations [18].

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