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PROGNOSTIC CONTRIBUTION OF TWO-DIMENSIONAL LEFT ATRIAL STRAIN IN PATIENTS WITH ASYMPTOMATIC MITRAL STENOSIS IN THE TUNISIAN POPULATION

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PROGNOSTIČKI DOPRINOS DVODIMENZIONALNOG OPTEREĆENJA LEVE PRETKOMORE KOD PACIJENATA SA ASIMPTOMATSKOM MITRALNOM STENOZOM U TUNISKOJ POPULACIJI

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ABSTRACT

Objective. The two-dimensional strain is an objective echocardiographic technique allowing the quantification of myocardial deformation. The aim of this study was to specify prognostic contribution of left atrial strain in patients with asymptomatic mitral stenosis.

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 the 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. Initially eighty patients were selected, but only 53 were followed and then divided into two groups: 30 patients had at least one event and 23 patients had no events 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 cm² and left atrium volume (LAV) more than 100ml/m², the risk of occurrence of an event increased significantly respectively (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 was true 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 the 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 the occurrence of pathologic events in the followup of asymptomatic patients.

Key words: *mitral valve stenosis; heart atria; ultrasonography.*

SAŽETAK

Cilj. Dvodimenzionalna tehnika merenja opterećenja je objektivna ehokardiografska tehnika, koja omogućava kvantifikaciju deformacije miokarda. Cilj ovog istraživanja bio je da se precizira prognostički doprinos opterećenja leve pretkomore kod pacijenata sa asimptomatskom mitralnom stenozom.

Metode. Uključili smo pacijente koji su praćeni zbog asimptomatske, teške ili umereno teške reumatske mitralne stenoze (MS), u periodu od januara 2015. do juna 2020. godine u Vojnoj bolnici u Tunisu. Praćeni pacijenti su podeljeni u dve grupe prema kriterijumu koji je sastavljen iz sledećih ishoda: srčanog mortaliteta, pojave hospitalizacije iz kardioloških razloga, pojave atrijalne fibrilacije (AF), pojave tromboembolijskog događaja i potrebe za kardiohirurgijom ili mitralnom valvuloplastikom.

Rezultati. Prvobitno je odabrano 80 pacijenata, ali je samo 53 praćeno, a zatim podeljeno u dve grupe: 30 pacijenata je imalo najmanje jedan od navedenih ishoda, a 23 pacijenta nisu imala nijedan od ishoda u skladu sa glavnim kriterijumima studije. U univarijantnoj analizi i za konvencionalne ehokardiografske parametre utvrdili smo da ako je površina leve pretkomore (LAA) veća od 30 cm² i zapremina leve pretkomora (LAV) veća od 100 ml/m², rizik od pojave nekog od ishoda značajno se povećava (LAA: 69% naspram 10%; p = 0,01; OR = 6,6; 95% CI [1,5-28]) i (LAV: 71,4% naspram 39%; p = 0,002; OR = 4; 95% CI [1, 1-13]). Isto, za parametre deformacije leve pretkomore i maksimum longitudinalnog pretkomornog opterećenja (PALS) < 25% i maksimum pretkomornog kontrakcionog opterećenja (PACS) < 10% predviđalo je pojavu nekog od ishoda u univarijantnoj studiji sa sledećim odnosima šansi (OR) (PALS: 83% naspram 30,4%; p = 0,0001; OR = 11,4; 95% CI [3-42]) i (PACS: 90 % vs 47%; p = 0,001; OR = 9,8; 95% CI [2,3-41]). U multivarijantnoj analizi jedini nezavisni parametar pojave ishoda bio je PACS <10% (p = 0,013; OR = 44; 95% CI [2,19-80]).

Zaključak. PACS ima prognostičku vrednost kod asimptomatske MS jer predviđa pojavu patoloških ishoda kod pacijenata sa asimptomatskom bolešću.

Ključne reči: *stenoza mitralne valvule; srčane pretkomore; ultrasonografija.*

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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). Caso and al. published their study in 2009 (4). Their judgement criteria were: heart surgery, mitral valvuloplasty, the occurrence AF or hospitalization and the occurring of heart symptoms. Prevalence of judgement criteria was 41% (11.3% AF). The methodology was characterised by the following: 53 patients with MS (asymptomatic) and three years of follow-up. The main result was LA strain was altered in MS population, even if asymptomatic. Roberta Ancona and al. published their study in 2013 (5). Their judgement criteria inculded AF occurrence with prevalence of 20%. Their methodology was characterised by the following: 101 patients, MS, asymptomatic or paucy-symptomatic, and follow-up with Holter monitor to AF detection. The main result was PALS less than 17.5% predicted AF. Mitral stenosis 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). The aim of our study was to clarify the prognostic contribution of atrial 2D strain in asymptomatic patients with mild and moderate MS.

PATIENTS 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. The 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 such as: stroke, embolic accident, or AF patients were excluded.

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

Initially eighty patients were selected from which only 53 were followed and finally 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. The table (Table 1) 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 1, the epidemiological data are comparable. Table 3 presents the conventional echocardiographic parameters of 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 cm², p = 0.4). Both the left atrial area and volume were significantly higher in the event group respectively (32cm2 ± 6 vs 26 ± 5 cm², p = 0.005) and (120ml/m2±30 vs 101ml/m2± 17, p = 0.002). Left atrial strain parameters (Table 2) 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.

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Table 1. The prevalence of the events of the composite endpoint of the study and epidemiological characteristics of the two groups.

Factor	Population (n=53)	With event (n=30)	Without 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

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

Table 2. Echocardiographic parameters of the two groups

Echocardiographic parameters	Population (n=53)	With event (n=30)	Without event (n=23)	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

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 3. Result of univariate study.

Factor	Population (n=53)	With event (n=30)	Without event (n=23)	p	OR	CI 95%	
						Inferior limit	Superior limit
LA Surface >30 cm^2	19 (35.8%)	16 (69%)	3 (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 4: Result of multivariate study I.

FACTOR	p	OR adjusted	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/m2)	0.17	1.05	0.97	1.12

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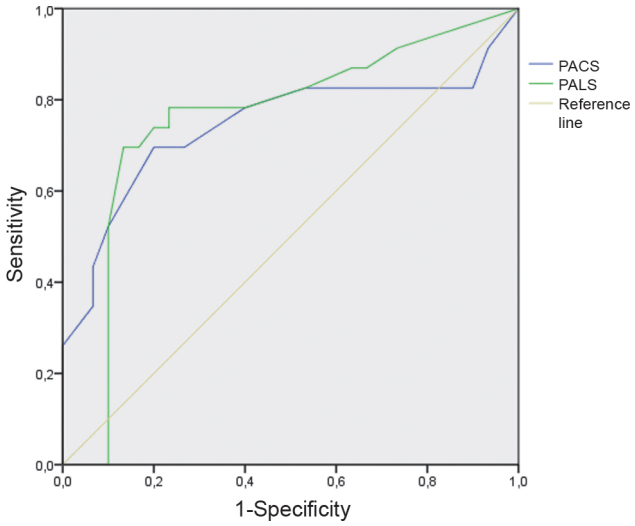

Figure 1. ROC curve Event / PALS and PACS.

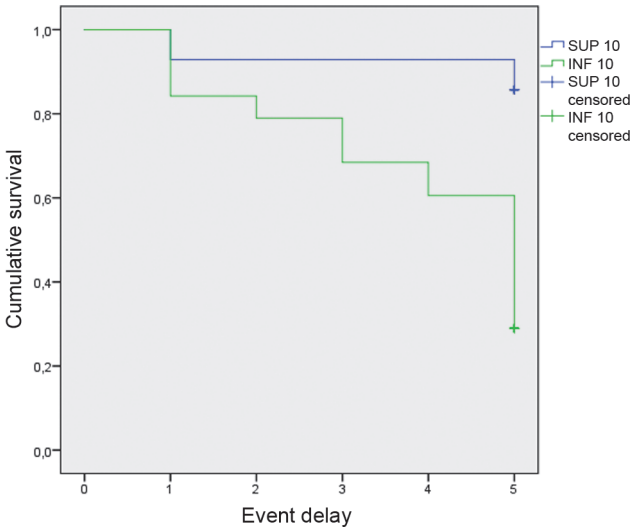

Figure 2. Kaplan Meier curve of occurrence of the composite endpoint of the study according to the PACS.

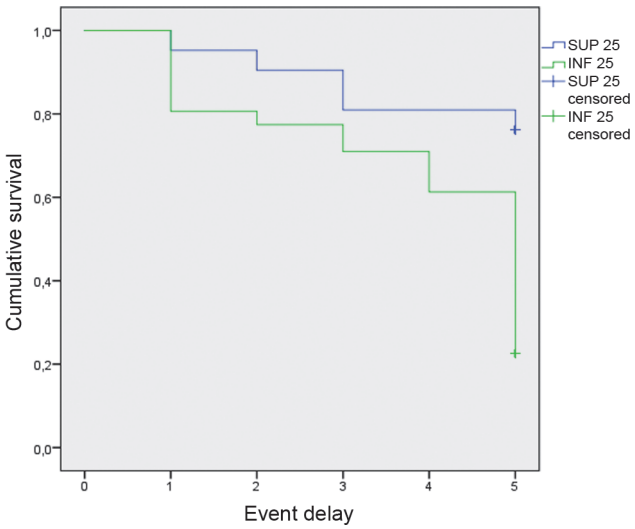

Figure 3: Kaplan Meier curve of occurrence of the composite endpoint of the study according to the PALS.

From the ROC curves cut-offs, we determined that when Left Atrium Area (LAA) was larger than 30 cm2 and left atrium volume (LAV) more than 100ml/m2, the risk of occurrence of an event increased significantly respectively (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 a univariate study with the 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]) (see Table 3). The only independent predictor of the occurrence of an event in the follow-up of our patients was the PACS (Table 4) (p=0.013; OR=44; 95% CI: [2.18-80]). From the survival curve of KAPLAN MEIER (Figure 2 and 3), we found that patients with a dilated atrium with a surface greater than 30 cm2 or LA volume more than 100 ml/m2, 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.

DISCUSSION

Left atrium deformation parameters seem to have prognostic value in patients with mitral stenosis. The 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. 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) as well as the fact that our patients had more severe MS and more dilated LA than the patients of the Italian series of Caso et al. : LA volume (55±25 ml/m2 vs 61±21 ml/m2 in our study) and mitral surface (1.5cm2 ±0.5 vs 1.3cm2 ±0.3 in our study). That is why mitral surface is considered to be a determining parameter in the evaluation of MS: Abel et al. (9) in a hemodynamic study of 314 patients with MS demonstrated that reduced mitral surface significantly increased the occurrence of AF , they demonstrated that patients who developed this arrhythmia had more dilated LA and higher pulmonary pressures (studied in hemodynamic). 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

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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.

Furthermore, Caso et al. (2) also 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 was significantly lower in patients with MR and that a PALS<17.5% was 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 55.6ml/m² ±6 in this study is lower than that of our patients which is 61±21 ml/m².

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).

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.

In conclusion, even asymptomatic patients with MS should be examined by echocardiography in addition to conventional parameters using 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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DECLARATIONS

The authors have no conflicts of interest to declare. The authors declare that this manuscript is not under consideration elsewhere and has not been reported earlier. All authors have made significant contributions to the study and have read and approved the content. No funding to declare. This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. that subjects have given their written informed consent and the study protocol was approved by the committee on human research of the military hospital of Tunis.

ABBREVIATIONS

MS: Mitral Stenosis
AF: atrial fibrillation
LA: left atrium
PMV: percutaneous mitral valvuloplasty
LVEF: Left ventricular ejection fraction
PALS: Peak Atrial Longitudinal Strain
PACS: Peak Atrial Contraction Strain
MVR: mitral valve replacement
AIL: Acute ischemia of limb
EDD: End diastolic diameter
ESD: End-systolic diameter
APD: Anteroposterior diameter
ETT: Trans-thoracic echocardiography
PAH: Pulmonary arterial hypertension
SAPS: Systolic Pulmonary Arterial Pressure
SVD: right ventricular systolic S wave velocity
TAPSE: Tricuspid Ring Plane Excursion