Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.376729.3914 Volume 31, Issue 6, June. 2025
Manuscript ZUMJ-2504-3914
DOI: 10.21608/ZUMJ.2025.376729.3914
ORIGINAL ARTICLE

Role of Galectin-3 on Left Atrial Deformation Relation to Exercise Tolerance in Patients with Mild Mitral Stenosis

Mohamed Arab, Ragab A Mahfouz, Mohamed I Amin, Abdelrahman Ahmed Adel*
Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

***Corresponding author**

Abdelrahman Ahmed Adel
Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Email:
abdelrahmandola@gmail.com
Submit Date 20-04-2025
Accept Date 17-05-2025

ABSTRACT

Background: Despite rheumatic fever becoming less common, rheumatic mitral stenosis (MS) continues to be a major cause of morbidity and death in underdeveloped nations. Herein, we aimed to investigate the influence of Galectin-3 (Gal-3) as a fibrotic marker on left atrial strain and its potential association with reduced exercise tolerance in patients with mild rheumatic MS.
Methods: We performed evaluation of left strain in patients with mild MS using two-D speckle tracking imaging. Also, left and right ventricular strain was performed. All participants performed experience exercises based on the Bruce protocol. Galectin-3 serum concentration was obtained with ELISA.
Results: 87 patients with mild MS were recruited. Compared with 55 healthy controls. Those with mild MS had a higher value of Gal-3 and lower left atrial reservoir (LAS-S%) (P<0.001). Additionally, in patients with mild MS, exercise dramatically reduced both the longitudinal strain of the left ventricle and the longitudinal strain of the right ventricle's free wall (P<0.001). LAS-S% was negatively correlated with Gal-3 concentration (P<0.001). Results revealed that LAS-S%, reduced left ventricular ejection global longitudinal strain (LVGLS)%, reduced right ventricular free wall longitudinal strain (RVFWLS)%, and Gal-3 were independent predictors for reduced exercise tolerance in patients with mild MS. Importantly, ROC curve analysis revealed that LAS-S% ≤17.3 was the best cut-off value to predict reduced exercise tolerance, while a Gal-3 value ≥ 19.95 ng/ml was the cut-off value for prediction of reduced LAS-S% ≤17.3 in patients with mild MS.
Conclusion: Galectin-3 was an independent predictor of a reduced percentage of left atrial strains in patients with mild MS. Furthermore, there was a significant association between LAS-S% and reduced exercise tolerance. Consequently, increased Gal-3 concentration could be a fibrotic marker mediating the association of reduced LAS-S% and reduced exercise tolerance with mild MS.
Keywords: Biomarkers; Left atrium; Mitral stenosis; Strain.

INTRODUCTION

Despite rheumatic fever becoming less common, rheumatic mitral stenosis (MS) continues to be a major cause of morbidity and death in underdeveloped nations [1].

It is often recognized that rheumatic mitral valve stenosis is a gradual condition that worsens over a number of years. Furthermore, abnormalities in left atrium (LA) mechanics have been observed even in asymptomatic subjects, who have mild MS. Studies revealed that left atrial reservoir strain was recognized as a measure of left atrial compliance and has a robust correlation with the clinical presentation of patients with rheumatic MS [2,3].

Patients with MS usually experience symptoms when the mitral valve area (MVA) narrows to 1.5 cm^2 or less. At such an area size, hemodynamic consequences become significant. Still, a notable number of persons with mild MS (MVA > 1.5 cm^2) might experience exertional symptoms that are unexplained with the hemodynamic severity of their state. Inflammatory burden and fibrosis

could be essential players in the pathogenesis of rheumatic heart disease [4].

Galectin-3 (Gal-3), which is released by macrophages, is a member of the lectin family that binds β-galactosides. Importantly, Gal-3 is found in many types of cells: macrophages, neutrophils, mast cells, fibroblasts, and osteoclasts. In other words, it is found mainly in cells involved in inflammatory and fibrotic processes [5]. Moreover, the circulating levels of galectin-3 can be simply assessed using the enzyme-linked immunosorbent assay (ELISA). Also, galectin-3 is easily measured, and it is less costly. It has a significant role in inflammatory and fibrotic processes. It is considered a mediator in the conversion of fibroblasts to activated myofibroblasts and collagen I production. As a consequence, it enhances the release of matrix proteins that play a role in fibrogenesis [6].

An opposing immunological response is sparked by the molecular simulation that takes place between the streptococcal M protein and other cardiac proteins, including myosin, tropomyosin, keratin, laminin, and vimentin. The myocardium and heart valves contain a large number of mononuclear cells that release inflammatory cytokines, which cause inflammation wherever it occurs [7, 8].

Clearly, exercise tolerance in MS patients is significantly impacted by left atrial dysfunction. Even LA is commonly impacted by the rheumatic inflammatory process and, as a result, LA myocardial fibrosis, which develops negative consequences in asymptomatic mild MS people. According to Kono et al. [9], mild MS patients have LA dysfunction even though their left atrial pressure is slightly elevated .

Yet, it isn't clear whether galectin-3 has a role in mediating the relation between LA dysfunction and reduced exercise in patients with mild MS. Accordingly, we conducted the current research to investigate the mediating role of galectin-3 as a measure of myocardial fibrosis on the relationship between exercise tolerance and left atrial mechanics in individuals with mild mitral stenosis.

METHODS

In the current research, 87 patients with mild MS were recruited from the Cardiology Clinic of Zagazig University Hospital, Egypt. Fifty-five with age- and sex-matched healthy subjects were recruited as a control group. Patients who have mitral incompetence, tricuspid, or aortic regurgitation, aortic or tricuspid stenosis, mitral valvular calcification, ischemic electrocardiographic changes during exercise stress tests, and those who underwent valvuloplasty or surgical commissurotomy were not included in the research. The ethics committee and Institutional Review Board (IRB) approved the trial [IRB≠: 915/31-Dec-2024], and each participant completed an informed consent form.

Biochemical analysis

Blood samples were taken and frozen in a fasting state on the morning and frozen for measurement of Gal-3. ELISA (*R&D Systems, Minneapolis, MN; cat. #DGAL30*) was used to test the levels of Gal-3, which were then reported in ng/ml [10]. Additionally, we measured brain natriuretic peptide (BNP), C-reactive protein (CRP), and serum creatinine.

Exercise testing

The modified Bruce procedure was performed to assess exercise tolerance in patients with mild MS. The exercise test was stopped when symptoms appeared, the maximal anticipated heart rate (HR) was reached, there were substantial arrhythmias, an excessive hypertensive or hypotensive response, or a large ST-segment deviation. Metabolic equivalents (METs) were used to measure exercise capacity. Reduced exercise capacity was defined as having METs below 8, whereas maintained exercise capacity was defined as having METs above 8 [11].

Conventional Echocardiography Examination

The GE Vivid i system (*Healthcare, Horten, Norway*) with a 2- to 4-MHz transducer (3S-RS) was used to perform conventional echocardiography. The tricuspid annular plane excursion (TAPSE), pulmonary artery pressure, right ventricular dimensions, left atrial dimensions, left atrial volume index (LAVI),

left ventricle (LV) ejection percent, mitral valve area (MVA), and pressure gradients across the mitral valve (MV) are all taken into consideration .

Every measurement was carried out in compliance with the guidelines set forth by the American Society of Echocardiography (ASE) [12].

Deformation assessment by 2-Dimensional Speckle Tracking

All echocardiographic examinations were performed by one experienced operator, and speckle tracking strain analysis was conducted blinded to the results of the levels of galectin-3.

Left atrial 2D-STE analysis [13]

During processing, the left atrial endocardial surface was manually traced in two-chamber and four-chamber views. The automatic tracking method (*version 10.8, EchoPAC, GE Vingmed Ultrasound, Norway*) was used to track at a frame rate of 40 to 80 frames per second (fps). Six segments made up the epicardial LA boundaries that the software automatically created. The software splits the ROI into six sections after we manually changed its width and shape. Each section's tracking quality is then automatically modified. The software provides the average curve of all segments and the longitudinal strain curve for each segment, which illustrates the pathophysiology of left atrial function. Subjects were eliminated from the study if more than three segments were discarded .

We also used the same program to analyze left ventricular (LV) deformation. The same automatic tracking technique (*version 10.8, EchoPAC, GE Vingmed ultrasonography, Norway*) that we previously described was used to follow the movements of the LV wall frame-by-frame in order to automatically compute the LV global longitudinal stresses (LVGLS) from LV apical images (4CH and 2CH). A small degree of human tweaking is allowed to ensure tracking quality.

Additionally, we assessed the right ventricular free wall longitudinal strain (RVFWLS). RV-focused apical view (>60 frames/s), which has been previously described, was employed to measure systolic 2-dimensional longitudinal strain. The basal, mid, and apical segments are the six divisions of the RV's free wall and septum. After manually tracing the RV endocardial border at an end-systolic frame, a zone of interest was automatically generated. The thickness of the RV wall was then manually incorporated into the breadth and position of the region of interest. RVFWLS was calculated as the average of the RV lateral basal, mid, and apical segments [14, 15].

Statistical analysis

Patient characteristics and the normal distribution of the studied variables were evaluated using the Kolmogorov-Smirnov test, and the Student t-test was employed for paired data. Whereas categorical data were presented as percentages and compared using Chi-square testing, continuous data were provided as mean ± SD and compared using the independent-sample t-test. For correlation analysis, Pearson's correlation coefficient (r) was employed. A multivariate regression analysis was conducted to examine factors influencing exercise tolerance in patients with mild MS. To investigate the diagnostic performance of LAS-S% in predicting exercise capacity, receiver-operating characteristic (ROC) curves were employed. The best cut-off value to forecast a lower LAS-S% in patients with mild MS was also tested using ROC curves. For statistical analysis, IBM SPSS 22 statistical software was utilized. P-values less than 0.5 were considered statistically significant.

RESULTS

A comparison of baseline features between controls and patients with mild MS is shown in Table 1. The findings indicated that in the patient group, Galectin-3 concentration was noticeably greater ($P<0.001$). In addition, BNP and CRP were increased in the patient group ($P<0.05$). LAS-S%, LAS-E%, and LAS-A% were significantly reduced ($P<0.001$) in the patient group. Importantly, LVGLS% and RVFWLS% were comparable among both groups at rest, while they were significantly reduced with exercise ($P<0.001$) in the patient

group, yet these parameters did not change with exercise in controls.

To assess the cut-off value of LAS-S% using MedCal software, a ROC curve based on LAS-S% measurements was created in order to forecast decreased exercise tolerance in MS patients with mild disease. The results indicated that LAS-S% ≤17.3 was the most effective cut-off value for forecasting reduced exercise tolerance. The AUC was 0.83 (CI%: 0.753–0.915, P< 0.001), with 91% sensitivity and 79% specificity (Figure 1).

Patients with mild MS were classified into groups based on the cut-off value (LAS-S% ≤17.3) for predicting reduced exercise tolerance: a group with LAS-S% ≤17.3 and a group with LAS-S%>17.3 (Table 2). We found that the Gal-3 level was significantly higher in the LAS-S% ≤ 17.3 group (P=0.001) compared with the LAS-S%>17.3 group. Furthermore, BNP and CRP were higher in patients with LAS-S% ≤ 17.3 (P<0.05). LAS-S%, LAS-E%, and LAS-A% were significantly reduced (P<0.001) in the LAS-S% ≤ 17.3 group. LVGLS% and RVFWLS% were comparable among both groups at rest; on the other hand, they were significantly reduced with exercise (P<0.01) in the LAS-S ≤ 17.3 group; yet, these parameters were not changed in the LAS-S>17.3 group. Importantly, patients with LAS-S ≤ 17.3 had reduced exercise tolerance (METS = 53±1.1), while those with LAS-S% ≥17.3 had good exercise (METS=11.5±1.9).

Figure 2 demonstrates that, in comparison to patients with LAS-S% ≥17.3 and the control group, those with mild MS and decreased LAS-S% (LAS-S% ≤17.3) had significantly greater Galectin-3 values (P<0.001).

A ROC curve based on galectin-3 level was created using MedCal software in order to assess the predictive value of galectin-3 level for LAS-S ≤17.3. In patients with mild MS, galectin-3 ≥17.95 ng/mL distinguished between those with LAS-S%≤17.3 and those with LAS-S% >17.3 with 87.5% sensitivity and 81.5% specificity. The AUC was 0.85 (95% CI), 0.793–0.905, P <0.001) (Supplementary Figure 1).

Correlation analysis revealed that galactin-3 was the strongest (P<0.001) predictors for reduced exercise tolerance in patients with mild MS (Table 3).

Table 4 shows that galactin-3 was strongly correlated with LAS-S% (P<0.001) in patients with mild MS. Additionally, it was connected with exercise-related LVLGS% and RVFWLS% (P<0.01).

Logistic Regression Analysis

Log-transformed Gal-3 and LAS-S% were initially adjusted to multivariate logistic regression models with each other and then subsequently for BNP, hs-CRP, LVGLS% and RVFWLS% ex. Gal-3 levels ≥17.95 ng/mL (OR: 6.59, 95%CI: 3.08-11.31, P < 0.001) and LAS-S%≥17.3 (OR: 5.95, 95 CI: 1.72-7.83; p<0.001) were the strongest independent predictors for reduced exercise tolerance in patients with mild MS (Table 5).

Table (1): Baseline characteristics of patients with mild mitral stenosis and healthy controls

Variables	Patients (n = 87)	Controls (n = 55)	*P* value
Age (years)	33 ± 7	32 ± 9	0.61
Female, n (%)	49 (56.3%)	27 (49%)	0.26
Body mass index	22.9 ± 3	23.5 ± 3	0.55
Heart rate (bpm)	81 ± 9	79 ± 10	0.42
SBP(mm Hg)	118 ± 9	120 ± 7	0.50
DBP(mm Hg)	68 ± 4	71 ± 3	0.35
METS	7.2±1.3	13.3±1.8	<0.01
Duration of exercise (minutes)	8.3 ± 1.2	12.9 ± 1.8	<0.05
Hs- CRP	3.6 ± 1.2	1.1 ± 0.03	<0.05
BNP (pg/mL)	109 ± 31	27 ± 11	<0.05

Galectin-3 (ng/ml)	19.81±3.3	9.06 ±1.9	<0.001
LA diameter (cm)	4.1 ± 0.2	3.8 ± 0.1	0.07
RV diameter (cm)	2.2 ± 0.4	1.9 ± 0.3	0.19
Mitral valve area—PHT (cm^2)	1.92 ± 0.05	–	–
MVA (cm^2)	1.95 ± 0.04	–	–
MPG (mm Hg)	6 ± 1.2	–	–
LVEF, %	65.9	68.5	0.82
LAVI, ml/m^2	35.7 ± 3.5	32.5 ± 2.7	0.35
LAS-S, %	21.95 ± 8.15	37.13 ± 9.15	<0.001
LAS-E, %	−9.13 ± 4.08	−21.65 ± 5.19	<0.001
LAS-A, %	−8.29 ± 3.17	−12.75 ± 4.1	<0.001
LVGLS, %			
- **Rest**	−20.6 ± 3.9*	−22.5 ± 4.2	<0.01[a]
- **Exercise**	−15.8 ± 2.1	−23.8 ± 5.1	<0.01[b]
RVFWLS, %			
- **Rest**	−21.5 ± 4.4*	−22.9 ± 4.7	0.36[a]
- **Exercise**	−17.2 ± 2.7	−24.1 ± 4.8	0.01[b]

BNP, Brain natriuretic peptide; DBP, Diastolic blood pressure; Hs-CRP, High sensitive C-reactive protein; LA, Left atrium; LAS-A, left atrial longitudinal strain during late diastole; LAS-E, left atrial longitudinal strain during early diastole; LAS-S, peak left atrial longitudinal strain; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVGLS, left ventricular ejection global longitudinal strain; METS, metabolic equivalents; MVA, Mitral valve area; RV, Right ventricle; RVFWLS, right ventricular free wall longitudinal strain; SBP, Systolic blood pressure

* P<0.001 (between LV strain and RV strain at rest and exercise)

[a] P>0.05 (among the three groups at rest)

[b] P<0.01 (among the three groups with exercise)

Table (2): Comparison between patients with mild mitral stenosis with LAS-S ≤ 17.3% versus those with LAS-S >17.3%

Variables	LAS-S ≤ 17.3% (N=48)	LAS-S >17.3% (N= 39)	P value
Age (years)	33.5 ± 8	32.8 ± 7	0.62
Females, n(%)	29 (60.4%)	25 (64%)	0.71
METS	5.3±1.1	11.5±1.9	<0.01
Duration of exercise (minutes)	7.1 ± 1.3	9.9 ± 1.5	<0.05
SBP(mm Hg)	117 ± 6	119 ± 7	0.41
DBP(mm Hg)	65 ± 2	70 ± 2	0.29
BNP (pg/mL)	238 ± 71	35 ± 20	<0.01
Serum creatinine	096 ± 0.03	092 ± 0.03	0.79
Galectin-3 level ng/L	26.8±4.1	11.5±2.6	0.001
LVGLS %	−15.3 ± 3.8	−21.5 ± 5.9	<0.01
LVEF, %	65.9	68.5	0.82
LAVI, ml/m^2	35.7 ± 3.5	32.5 ± 2.7	0.35
LAS-S, %	14.75 ± 2.23	27.93 ± 7.15	<0.001
LAS-E, %	7.71 (3.83, 11.72)	13.02 (11.24, 16.50)	<0.01
LAS-A, %	10.50 (8.76, 14.71)	13.96 (12.62, 17.63)	<0.01
LVGLS, %			
- **Rest**	−19.5 ± 2.5*	−23.1 ± 5.1	<0.01[a]
- **Exercise**	−15.3 ± 1.441	−21.1 ± 5.1	<0.01[b]
RVFWLS, %			
- **Rest**	−20.3 ± 3.9*	−22.08 ± 5.00	0.36[a]
- **Exercise**	−13.1 ± 5.78	−22.05 ± 4.62	0.03[b]

BNP, Brain natriuretic peptide; DBP, Diastolic blood pressure; LAS-A, left atrial longitudinal strain during late diastole; LAS-E, left atrial longitudinal strain during early diastole; LAS-S, peak left atrial longitudinal strain; LAVI, left atrial volume index; LVEF, Left ventricular ejection fraction; LVGLS: Left ventricular ejection global longitudinal strain; METS, metabolic equivalents; RVFWLS, right ventricular free wall longitudinal strain; SBP, Systolic blood pressure.

* P<0.001 (between LV strain and RV strain at rest and exercise)

[a] P>0.05 (among the three groups at rest)

[b] P<0.01 (among the three groups with exercise)

Table (3): Relationship between reduced exercise tolerance and other variables in patients with mild mitral stenosis

Variables	*r*	*P* value
LVGLS%	0.37	<0.05
RVFWLS%	0.48	<0.03
LAS-S%	0.59	<0.001
High sensitive C-reactive protein	−0.21	0.09
Brain natriuretic peptide	−0.37	<0.05
Galectin-3	−0.71	<0.001

LAS-S, peak left atrial longitudinal strain; LVGLS: Left ventricular ejection longitudinal global strain; RVFWLS, right ventricular free wall longitudinal strain.

Table (4): Relationship between galectin-3 levels and other variables in patients with mild mitral stenosis

Variables	r	P value
Left atrial volume index	0.19	0.22
LV ejection fraction%	− 0.16	0.34
Left atrial reservoir strain (LAS-S)	− 0.66	<0.001
LV global longitudinal strain		
- At rest	− 0.29	0.18
- With exercise	− 0.58	<0.01
RVFWLS %		
- At rest	− 0.27	0.26
- With exercise	−0.49	<0.01

LV, Left ventricle; RVFWLS, right ventricular free wall longitudinal strain.

Table (5): Binary Logistic Regression Analysis

Variables	OR value	Lower limit	Upper limit	P value
LVGLS% $^{ex.}$	3.25	1.83	4.72	<0.05
RVFWS$^{\% ex.}$	3.09	1.91	4.05	<0.05
LAS-S%	5.95	1.72	7.83	<0.001
BNP	1.06	0.79	1.05	0.13
hs-CRP	1.27	1.02	1.39	0.09
Galectin-3	6.59	3.08	11.31	<0.001

LVGLS% ex., Left ventricular ejection longitudinal global strain with exercise; RVFWS% ex.: right ventricular free wall strain with exercise, LAS-S%: Peak LA longitudinal strain; BNP: Brain natriuretic peptide, CRP: C-reactive protein.

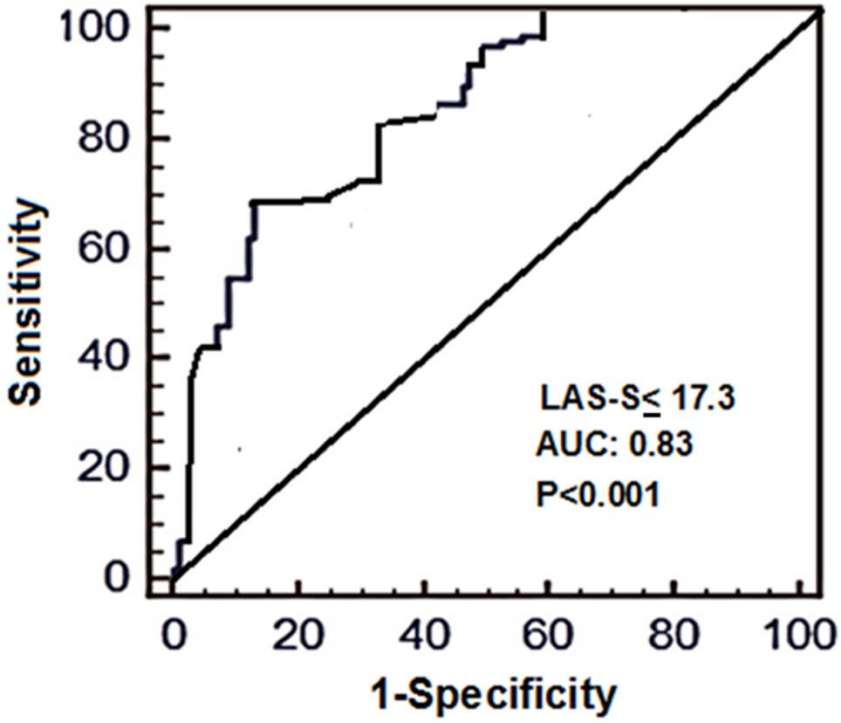

Figure (1): Receiver Operating Characteristic (ROC) curve analysis of LAS-S% cut-off values for prediction of reduced exercise tolerance in patients with mild MS. ROC curve analysis revealed that the LAS-S% cut-off value of ≤ 17.3 could be an excellent predictive test of reduced exercise tolerance in patients with mild MS. The AUC was 0.83 (CI%: 0.753–0.915, P < 0.001), with 91% sensitivity and 79% specificity.

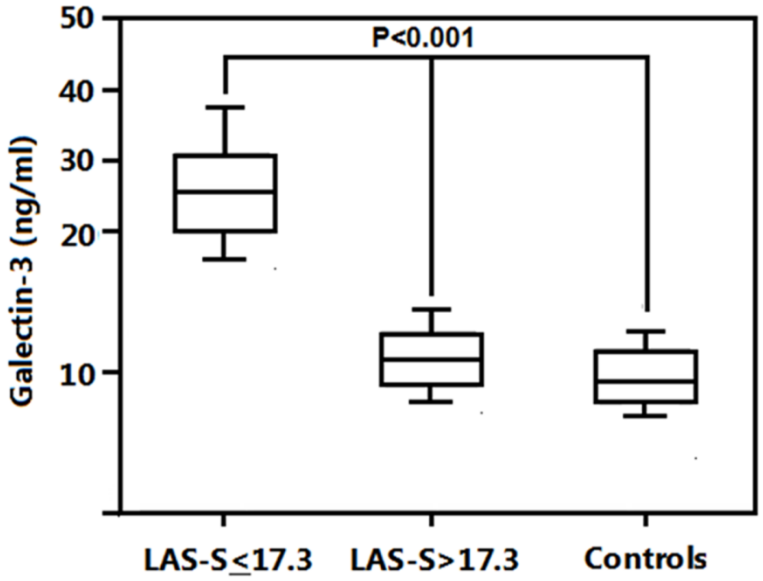

Figure (2): Comparison of galectin-3 concentrations in patients with mild MS and controls. A highly statistically significant higher concentration (p<0.001) was observed in the patient group with LAS-S% ≤ 17.3 compared with patients with LAS-S% ≥ 17.3 and controls. Whereas, galectin-3 concentration was comparable between patients with LAS-S% ≥ 17.3.

DISCUSSION

The degree of MS is typically unrelated to the presentation of people with the condition. Some persons who have severe MS do not develop symptoms, whereas many patients with mild MS might develop symptoms or atrial fibrillation. Explanations for this discrepancy are not fully understood [16]. Trying to explore this disparity, we investigated the relationship between galectin-3 level and left atrial function in patients with mild MS.

Reduced left atrial strain indicates altered left atrial reservoir function, might reflect fibrotic changes in atrial myocardium, and consequently augmented LA stiffness. These changes predict symptom development and subsequently adverse cardiovascular outcomes. In previous research, it was provided that left atrial compliance improvement has a vital role in the prediction of functional status, regardless of other hemodynamic data [17].

Left atrial functions, including reservoir, conduit, and contractile functions, have a crucial role in hemodynamic changes related to mitral valve diseases. For that, anatomical and functional assessment of LA gained great importance [18-19].

In patients with rheumatic MS, pressure and volume overload and inflammatory processes, as well as fibrosis, are the contributing factors to impaired LA functions [20].

Whereas higher galectin-3 concentrations have been formerly recounted in subjects with rheumatic diseases, the current research is perhaps the first one exploring the impact of serum galectin-3 levels on left atrial deformation in mild MS patients .

Left atrial strain in mild MS

We found that LAS-S% was reduced significantly in patients with mild MS compared with controls. In addition, patients with mild MS, who had reduced exercise tolerance, had a pronounced reduction in LAS-S% compared with those with good exercise tolerance .

The current research revealed that LAS-S% ≤ 17.3 was the best cut-off point for identifying patients with mild MS who would have less tolerance to exercise. Moreover, we found that Gal-3 ≥ 17.95 ng/ml was the cut-off concentration that predicts reduced LA strain (LAS-S% ≤ 17.3). Additionally, we found that galectin-3 was the strongest independent predictor of reduced LAS-S in patients with mild MS.

Vriz et al. [21] revealed that patients with mild MS had significantly lower LA reservoir strain values. Furthermore, Kono et al. [9] revealed that LA mechanics are significantly impaired even in patients with mild MS. Moreover, Reddy et al. [22] found a significant improvement in global LA strain following percutaneous balloon valvuloplasty, although not reaching normal values.

Thiedemann et al. [23] stated that variable remodeling grades of the left atrium might be considered for the varying clinical presentation. Impaired left ventricular compliance and diastolic dysfunction due to myocardial inflammatory status may also play a role in developing symptoms in mild MS [24]. Bouchahda et al. [25] found a robust relation between LA strain reservoir and symptomatic severity across all clinical statuses of subjects with MS. They demonstrated that the LA strain reservoir reflects left atrial compliance and could modify symptoms by nullifying higher upstream pressure.

Ventricular strain in patients with mild MS

Interestingly, our results revealed a significantly reduced exercise RVFWLS% and LVGLS% in mild MS patients, who exhibited elevated galectin-3 levels in comparison to both controls and patients with normal galectin-3 levels, despite good rest right and left ventricular strain. This may be explained by the fact that higher levels of galectin-3 are linked to greater myocardial fibrosis in MS patients. Furthermore, exercise may raise pulmonary artery pressure due to these structural alterations, which could modify the function of the right ventricle. Furthermore, higher levels of galectin-3 might cause fibrotic changes in the right and left ventricular myocardium, affecting the longitudinal function of both ventricles.

Role of remodeling and fibrosis in mild MS

A previous study discovered a crucial role of the activation of the fibrosis pathway, which includes boosting collagen synthesis and extracellular matrix remodeling through the TGF-β1 pathway. Additionally, this route is linked to tissue fibrosis, scar tissue formation, and the left atrial collagen volume fraction in individuals with RHD [26]. Elen et al. [27] revealed that 16.6% (5.5–55.8%) of patients with rheumatic MS had changes in the left ventricle's volume of fibrotic tissue. They claimed that a large drop in LVEF% was linked to the amount of fibrotic tissue. It was discovered that a 0.87% decrease in left ventricular EF% was linked to a 1% increase in cardiac tissue fibrosis. The degree of myocardial fibrosis in patients with MS is correlated with left ventricular function. Yu et al. [6] suggested that myocardial fibroblasts, extracellular matrix, and galectin-3, in addition to activated myocardial macrophages, potentially lead to mast cell and macrophage invasion along with fibroblast activation and proliferation. This causes cardiac fibrosis and remodeling, including the atria, by increasing the amount of type collagen and other myocardial interstitial deposits surrounding the heart and blood vessels. Reduced LAS-S may be explained by this argument.

Galectin-3 and myocardial remodeling

Galectin-3 poses a direct influence on the immune system and inflammatory reactions by modifying cell adhesion of different types of immune cells. The most likely mechanism is that tissue damage, galectin-3, and other biological fluids are actively secreted into the blood, resulting in inflammation and dysfunction of immune reaction and a surge of serum galectin-3 concentration in patients with different rheumatic diseases [28]. Galectin-3 interacts with different cytokines, an important reaction in the development of inflammation. In addition, galectin-3 has a significant role in promoting fibrosis in various tissues, including cardiac tissues [92].

Wu et al. [30] in their cell experimental study revealed that augmented release of galectin-3 with cardiac muscle cell stretching. Also, Sharma et al. [31] and Liu et al. [32] have shown that galectin-3 may increase the infiltration of mast cells and macrophages into cardiac cells, leading to myocardial remodeling, fibrosis, and stiffness of the heart's chambers, particularly the left atrium [33].

Galectin-3 is an increased biomarker that mediates fibrosis in certain fibrotic disorders. It activates and promotes profibrotic factors, fibroblast transformation, proliferation, proapoptotic effects, collagen deposition, and the subsequent myocyte dysfunction and cardiac fibrosis [34]. Elevated levels of the protein have also been reported in the literature as a predictor of recurrence after AF ablation. Galectin-3 levels have been shown to contribute to the development of atrial fibrillation (AF) by facilitating atrial remodeling [35].

Galectin-3 has been shown to be a potential atrial substrate mediator in the development of atrial fibrillation in the Takemoto et al. [36] investigation (AF), and its inhibition has been observed to decrease atrial fibroblast proliferation, atrial dilatation, and atrial fibrosis.

These arguments link LA dysfunction and decreased exercise tolerance in patients with mild MS to the substantial influence of high galectin-3 levels .

Clinical implication

It appears that assessment of circulating levels of galectin-3 in patients with mild MS may represent an effective strategy for early prediction and risk stratification of that population. Circulating galectin-3 levels also show great potential as noninvasive biomarkers for left atrial dysfunction and reduced functional capacity in subjects with mild MS. For that, galectin-3 might be considered a potential biomarker for evaluation of LA function, prognosis, and assessment of treatment response in patients with mild MS.

Limitations

Some limitations were encountered: first, the study was single center and performed on a relatively small sample; second, we did not examine other factors of circulating fibrosis

biomarkers that could be linked to left atrial stiffness and dysfunction; third, we did not undergo non-invasive fibrosis tests such as magnetic resonance imaging; and finally, we did not utilize a grading scale to evaluate dyspnea.

CONCLUSION

We found an independent association between galectin-3 level and left atrial reservoir in mild mitral stenosis patients. Additionally, higher galectin-3 levels are significantly correlated with reduced left atrial strain, exercise reduction, LVLGS%, and RVFWLS%. These results may help to explain how galectin-3 mediates the relationship between decreased exercise tolerance and left atrial dysfunction in patients with mild mitral stenosis. Serum levels of galectin-3 may offer an extra means of identifying high-risk individuals with mild mitral stenosis.

Conflict of interest: None.

Financial disclosures: None.

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Citation

Arab, M., Mahfouz, R., amin, M., Ahmed Adel, A. Role of Galectin-3 on Left Atrial Deformation Relation to Exercise Tolerance in Patients with Mild Mitral Stenosis. *Zagazig University Medical Journal*, 2025; (2335-2345): -. doi: 10.21608/zumj.2025.376729.3914