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Effect of Exercise on Left Atrium Mechanics in Mild Mitral Stenosis

Hafif Mitral Darlıklı Hastalarda Egzersizin Sol Atriyum Mekaniği Üzerindeki Etkisi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: A significant number of individuals with mild mitral stenosis (MS) experience exertional symptoms that are disproportionate to the hemodynamic severity of their condition. This study aims to determine whether exercise-induced left atrial (LA) dysfunction occurs in these patients and whether it is related to the development of symptoms.

Methods: In this observational study, we recruited 46 patients with mild MS. Echocardiographic measurements were initially taken at rest, followed by a maximal exercise stress test. Patients were then returned to the echocardiography laboratory for post-exercise measurements.

Results: Our study cohort exhibited considerably higher left atrial volume index (LAVI) values (mean: 40.52 ± 18.27) compared to those of a healthy population. Furthermore, the LA reservoir strain (mean: 17.1 ± 8.33) was reduced relative to reference values. Following exercise, there was no change in the LA reservoir strain. However, trans-mitral pressure gradients and systolic pulmonary artery pressures increased. The post-exercise mean trans-mitral gradient was identified as the sole predictor of symptom development in patients with mild MS.

Conclusion: The LA reservoir strain is already reduced in individuals with mild MS, and exercise does not lead to further decline in LA reservoir function in these cases. To our knowledge, this study is the first to explore the effects of exercise on LA mechanics in MS.

Keywords: Exercise stress test, left atrium strain, mitral stenosis

ÖZET

Amaç: Hafif mitral darlığı olan hastaların önemli bir kısmında hastalığın hemodinamik ciddiyeti ile uyumsuz, efor ile ilişkili semptomlar mevcuttur. Mevcut çalışmada; bu hastalarda egzersize bağlı sol atriyum (SA) disfonksiyonu olup olmadığını ve semptom gelişiminin SA disfonksiyonu ile ilişkili olup olmadığını belirlemeye çalıştık.

Yöntem: Çalışmaya hafif mitral darlığı olan 46 hasta alındı. İstirahat halinde ekokardiyografik ölçümler alındıktan sonra hastalara maksimal egzersiz stres testi uygulandı. Daha sonra hastalar ekokardiyografi laboratuvarına geri götürüldü ve egzersiz sonrası ölçümler kaydedildi.

Bulgular: Çalışma kohortumuz sağlıklı popülasyona göre oldukça yüksek LAVI değerlerine (ortalama: 40,52±18,27) sahipti. Ayrıca, SA rezervuar strain değeri (ortalama: 17,1±8,33) referans değerlere göre azalmış olarak bulundu. Egzersiz sonrasında SA rezervuar strain değerinde anlamlı değişiklik gözlenmedi. Bununla birlikte, trans-mitral basınç gradientleri ve sistolik pulmoner arter basıncı artmış olarak saptandı. Semptom durumu ile ilişkili tek parametre; egzersiz sonrası ortalama trans-mitral basınç gradienti olarak saptandı.

Sonuç: SA rezervuar strain'i, hafif mitral darlıklı hastalarda dahi azalmaktadır. Egzersiz, hafif mitral darlığı olan hastalarda SA rezervuar fonksiyonunda ilave bozulmaya yol açmamaktadır. Bildiğimiz kadarıyla, bu çalışma mitral darlığında egzersizin SA mekanikler üzerindeki etkisini inceleyen ilk çalışmadır.

Anahtar Kelimeler: Egzersiz stres test, sol atriyum straini, mitral darlık

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Mitral stenosis (MS) results from a restriction of blood flow into the left ventricle due to structural abnormalities in the mitral valve apparatus. The most prevalent cause of MS is rheumatic fever. Despite the global decline in the prevalence of rheumatic fever, rheumatic MS is still a significant source of morbidity and mortality in developing countries.[1]

MS leads to an increase in left atrial (LA) pressure, resulting in chronic pressure overload on the LA, which in turn causes atrial dysfunction, reduced atrial compliance, and ultimately an increase in pulmonary capillary wedge pressure.[2] Previous research using speckle tracking imaging (STE) has addressed LA dysfunction and reduced atrial compliance in patients with severe MS.[3,4] Furthermore, abnormalities in LA mechanics have been reported even in asymptomatic patients with mild MS. Recently, LA reservoir strain has gained recognition as a measure of LA compliance and has shown a strong association with the clinical status of MS patients.[5,6]

Patients with MS typically experience symptoms when the mitral valve area (MVA) narrows to 1.5 cm^2, at which point it becomes hemodynamically significant. However, a significant number of individuals with mild stenosis (MVA > 1.5 cm^2) may develop exertional symptoms that are inconsistent with the hemodynamic severity of their condition. Whether the development of symptoms is related to exercise-induced LA dysfunction remains unclear.

In this prospective observational study, we aimed to examine whether exercise affects LA mechanics in individuals with mild rheumatic MS. We also sought to identify the clinical and echocardiographic factors related to symptom status in these individuals.

Materials and Methods

Patient Selection

In this prospective observational study, we recruited 57 patients with mild MS at our institution's outpatient cardiology clinic from April 2014 to April 2016. Patients who exhibited New York Heart Association (NYHA) class 4 symptoms, severe mitral, tricuspid, or aortic regurgitation, moderate to severe aortic or tricuspid stenosis, severe mitral valvular calcification, a history of surgical commissurotomy, or who developed ischemic symptoms and/or electrocardiographic changes during exercise stress tests were excluded from the study. A final total of 46 patients were included in the analysis.

The Ankara University Faculty of Medicine Clinical Research Ethics Committee (Date: 10/10/16, Decision No: 15-774-16) approved the study, and all patients provided written consent for participation in the registry. The study was conducted in accordance with the ethical standards and principles of the Declaration of Helsinki.

We did not use artificial intelligence-assisted technologies, chatbots, or image creators during the production of the submitted work.

Echocardiographic Evaluation

a) Conventional Measurements

Echocardiographic examinations were performed using the General Electrics Vivid S5 ultrasound machine (GE, Horten, Norway), in accordance with the guidelines.[7] Left atrial and ventricular diameters, fractional shortening (FS), tricuspid annular plane systolic excursion (TAPSE), and systolic pulmonary artery pressure (sPAP) were calculated. The LA volume was calculated using the apical 4 chamber (A4C) and apical 2 chamber (A2C) views with the following formula:

$$\text{Left Atrium volume} = \frac{A1 \times A2}{L} = 0.85$$

Where A1 is the maximum planimetric LA area in the A4C view, A2 is the maximum planimetric LA area in the A2C view, and L is the distance between the left atrial posterior wall and the plane across the mitral valve hinge points.

Accompanying valvular insufficiencies were evaluated semi-quantitatively. Mitral lateral e' and medial e' rates, and tricuspid lateral annular systolic velocity (s') were calculated. All calculations were performed both at rest and post-exercise. Planimetric MVA, as well as mean and maximum mitral valvular gradients, were measured at both stages. For patients in sinus rhythm, three consecutive beats were recorded and averaged, whereas for patients with atrial fibrillation, five consecutive beats were recorded and averaged.

b) Speckle Tracking Echocardiography

Left Atrial Strain Analysis

Apical 4 and 2 chamber grayscale images were obtained both at rest and post-exercise, at a frequency of 60-80 Hz. The recorded images were analyzed using EchoPAC (GE Healthcare). The LA endocardial line was manually tracked, and an additional epicardial line was automatically drawn by the software program, forming a region of interest (ROI). The software then divided the LA into six segments and generated a longitudinal strain curve (Figure 1). The onset of the QRS wave was used as the zero strain point for both patients with atrial fibrillation and those in sinus rhythm. LA reservoir strain was calculated as the peak atrial longitudinal strain during ventricular systole, averaging the values from all twelve segments. The average value was taken from three consecutive beats in patients with sinus rhythm and from five consecutive beats in patients with atrial fibrillation.

Left Ventricle Strain Analysis

The frequency was set at 60-80 Hz, and apical 4, 3, and 2 chamber grayscale images were recorded both at rest and post-exercise. These images were analyzed offline using EchoPAC (GE Healthcare). The left ventricular endocardial line was manually tracked at the end-systole, and the software drew an additional epicardial line, creating an ROI. The ROI was manually

ABBREVIATIONS

AF	Atrial fibrillation
FS	Fractional shortening
LA	Left atrial
LAVI	Left atrial volume index
MS	Mild stenosis
MVA	Mitral valve area
sPAP	Systolic pulmonary artery pressure
STE	Speckle tracking imaging
TAPSE	Tricuspid annular plane systolic excursion

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corrected, after which the software program automatically divided the left ventricle into segments, calculating the peak systolic longitudinal strain value by averaging the values of all 18 segments (Figure 2).

Exercise Stress Test

Following the echocardiographic measurements at rest, a maximal exercise stress test was conducted using the standard Bruce protocol. The maximal heart rate was defined as at least

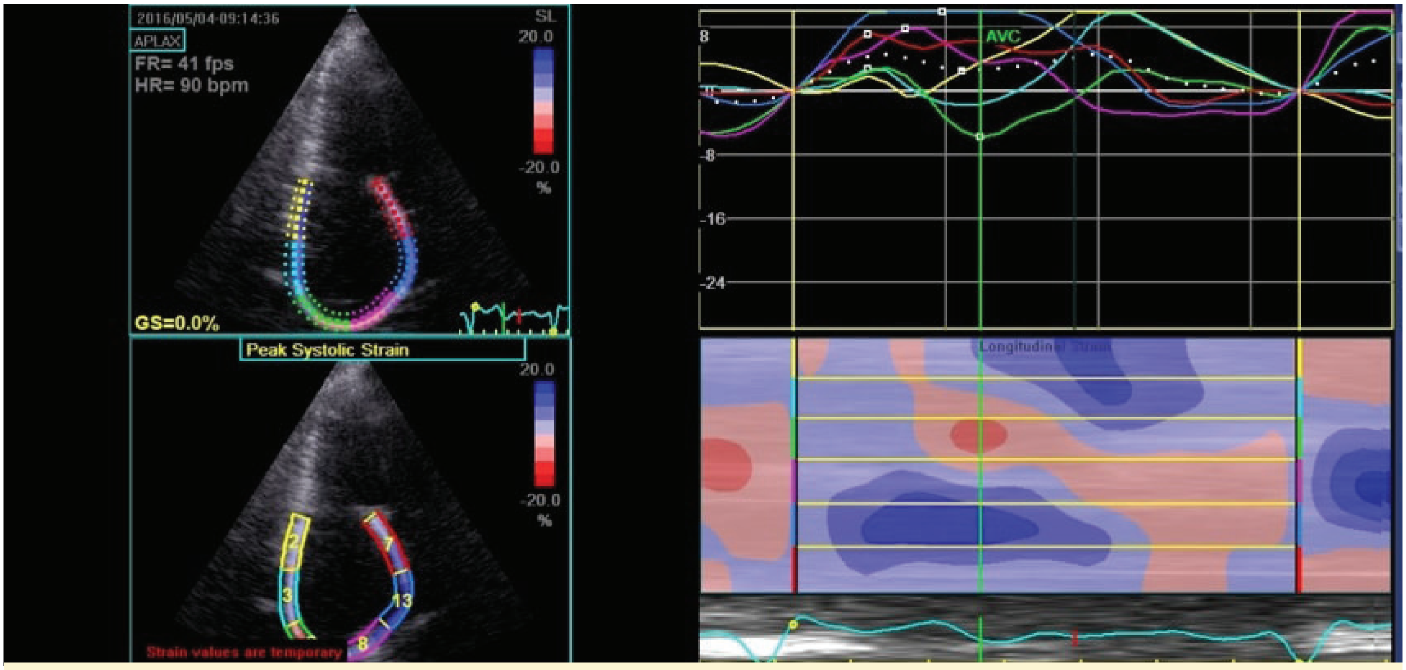

Figure 1. Left atrium strain analysis.

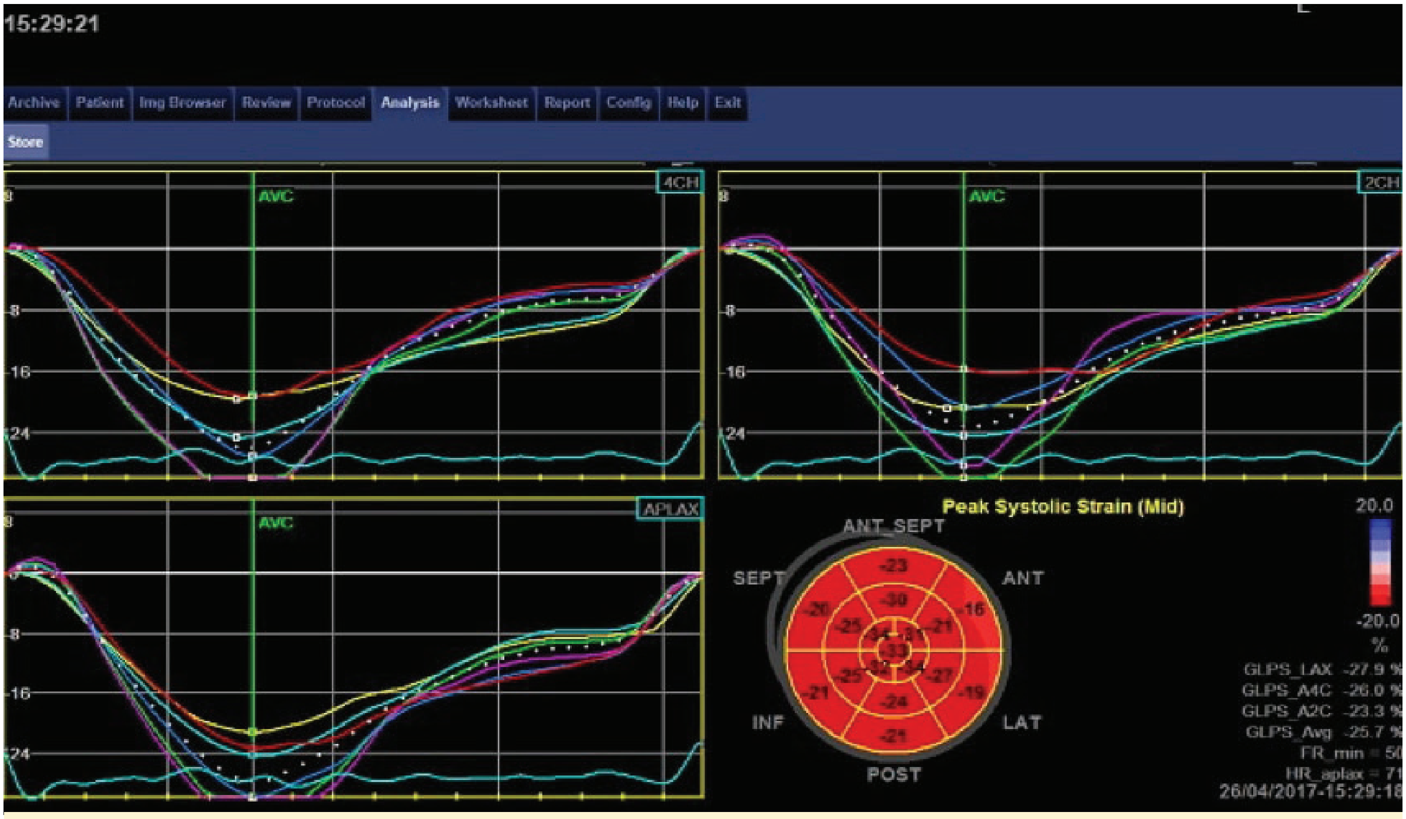

Figure 2. Left ventricle strain analysis.

85% of the value calculated by the formula "220 - age." All patients successfully completed the test. Immediately after the test, patients were returned to the echocardiography laboratory for post-exercise measurements.

Statistical Analysis

The Statistical Package for the Social Sciences version 10.0 (SPSS 10.0, for Windows, IBM, New York, USA) was utilized for statistical analysis. A p-value of less than 0.05 was considered statistically significant. Patient characteristics and the normal distribution of the examined parameters were assessed using the Kolmogorov-Smirnov test. The Student T test was employed for paired data, while the Wilcoxon T test was used for data that were not normally distributed, comparing rest and post-exercise values. The Pearson correlation test was applied to evaluate the relationship between variables under parametric conditions, and the Spearman Rho test was used for data not meeting parametric conditions. The point-biserial correlation analysis was utilized for assessing the association between dichotomous and continuous variables. The relationship between independent variables and the outcome variable was initially evaluated with univariate analysis. Logistic regression analysis was performed to examine categorical outcome data. Variables selected through univariate analysis with a p-value less than 0.3 were included in the multivariable analysis.

Results

We included 46 patients, of whom 78% were female. The mean age of the study group was 52.4 years. Ten patients were symptomatic, while 36 were asymptomatic. Nineteen patients had hypertension, twenty had hyperlipidemia, and six had diabetes mellitus. The demographic and echocardiographic characteristics of the patients at baseline are shown in Table 1.

There was no significant difference in left atrial volume index (LAVI) between rest and post-exercise (*P* = 0.199). sPAP was significantly higher post-exercise (*P* = 0.001). Both mean and maximum trans-mitral gradients were significantly higher post-exercise. No significant difference was observed in LA reservoir strain following exercise compared to baseline (Table 2).

LA reservoir strain at rest was significantly associated with LAVI, age, hypertension, heart rhythm, severity of mitral regurgitation, sPAP, and global longitudinal strain of the left ventricle both at rest and after exercise (Table 3).

Table 1. Baseline Characteristics of the Patients

Variables	n (%) or Mean ± SD
Age (years)	52.4
Sex (Female/Male, %)	36 (78) / 8 (12)
Presence of Symptoms (Yes/No, %)	10 (21) / 36 (79)
History of MBV (Yes/No, %)	5 (11) / 41 (89)
Cardiac Rhythm (Sinus/AF, %)	40 (87) / 6 (13)
Hypertension (%)	19 (41.3)
Hyperlipidemia (%)	20 (43.4)
Diabetes (%)	6 (13)
MVA (cm^2)	2.06 ± 0.068
FS (%)	38.84 ± 1
Tricuspid Lateral S Velocity (m/s)	0.137 ± 0.0059
TAPSE (mm)	23.2 ± 0.68
LVEDDI (mm/m^2)	28.2 ± 0.355
LVESDI (mm/m^2)	17.1 ± 0.3595
Lateral e' Velocity (m/s)	0.09 ± 0.0036
Medial e' Velocity (m/s)	0.07 ± 0.0039
E Velocity (cm/s)	1.33 ± 0.32
E/Mean e'	31.36 ± 10.86
Accompanying TR (Trace/Moderate/Absent)	38 (83) / 8 (17) / 0 (0)
Accompanying MR (Trace/Moderate/Absent)	25 (54) / 21 (46) / 0 (0)
Accompanying AR (Trace/Moderate/Absent)	31 (67) / 12 (26) / 3 (7)
LAI (cm/m^2)	2.45 ± 0.0447

AF, Atrial Fibrillation; AR, Aortic Regurgitation; FS, Fractional Shortening; LAI, Left Atrium Diameter Index; LVEDDI, Left Ventricular End-Diastolic Diameter Index; LVESDI, Left Ventricular End-Systolic Diameter Index; MBV, Mitral Balloon Valvuloplasty; MR, Mitral Regurgitation; MVA, Mitral Valve Area; SD, Standard Deviation; TAPSE, Tricuspid Annular Plane Systolic Excursion; TR, Tricuspid Regurgitation.

Table 2. Changes in Echocardiographic Parameters During Exercise

	Rest	Post-Exercise	*P*
LAVI	40.52 ± 18.27	39.34 ± 17.14	0.199
Mean Trans-Mitral Gradient	4.52 ± 1.84	6.46 ± 3.26	**<0.001***
Maximum Trans-Mitral Gradient	11.1 ± 4.20	15.7 ± 6.78	**<0.001***
sPAP	34 ± 7.01	37.65 ± 10.74	**0.001***
LA Reservoir Strain/A4C	16.9 ± 7.58	18.6 ± 11.39	0.074
LA Reservoir Strain/A2C	17.2 ± 10.00	13.7 ± 7.65	0.121
LA Reservoir Strain (Average)	17.1 ± 8.33	16.8 ± 9.10	0.708
GLS-LV (Average)	-18.1 ± 3.8	-17.9 ± 5.1	0.854

GLS-A2C/LA, Global Longitudinal Strain-Apical 2 Chamber/Left Atrium; GLS-A4C/LA, Global Longitudinal Strain-Apical 4 Chamber/Left Atrium; GLS-avg/LA, Global Longitudinal Strain-Mean/Left Atrium; LAVI, Left Atrial Volume Index; sPAP, Systolic Pulmonary Artery Pressure.

LA reservoir strain following exercise was significantly correlated with age, diabetes mellitus, sPAP at rest, TAPSE, and global longitudinal strain of the left ventricle post-exercise (Table 4).

Table 3. Correlation Analysis of Left Atrial (LA) Reservoir Strain at Rest

	r	*P*
LAVI	-0.463	0.007*
Age	-0.518	0.002*
HT	-0.366	0.039*
Cardiac Rhythm	-0.353	0.044*
MR	-0.368	0.042*
sPAP	-0.454	0.020*
GLS-LV at Rest	-0.369	0.035*
GLS-LV Post-Exercise	-0.383	0.033*

GLS-LV, Global Longitudinal Strain-Left Ventricle; HT, Hypertension; LAVI, Left Atrial Volume Index; MR, Mitral Regurgitation; sPAP, Systolic Pulmonary Artery Pressure.

Potential parameters related to symptom development were examined using univariate analysis. Subsequently, a multivariate logistic regression analysis was conducted, including all parameters associated with symptom status in the univariate analysis. Only the post-exercise mean trans-mitral pressure gradient was identified as a predictor of symptom development (Table 5).

Table 4. Correlation Analysis of Left Atrial (LA) Reservoir Strain Post-Exercise

	r	*P*
Age	-0.433	0.019*
DM	-0.382	0.045*
sPAP at Rest	-0.531	0.011*
TAPSE	0.395	0.046*
GLS-LV Post-Exercise	-0.418	0.014*

DM, Diabetes Mellitus; GLS-LV, Global Longitudinal Strain-Left Ventricle; sPAP, Systolic Pulmonary Artery Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Table 5. Predictors of Symptom Development in Mitral Stenosis (MS)

	Univariate Analysis		
	OR	**95% CI**	***P***
sPAP at Rest	1.007	0.899-1.129	0.904
sPAP Post-Exercise	1.005	0.934-1.082	0.884
TAPSE	1.072	0.893-1.287	0.456
GLS-LV at Rest	1.015	0.847-1.217	0.868
GLS-LV Post-Exercise	1.047	0.905-1.212	0.535
MVG at Rest (Mean)	0.866	0.558-1.343	0.519
MVG at Rest (Max)	1.019	0.867-1.197	0.822
MVG Post-Exercise (Mean)	0.746	0.553-1.007	0.056
MVG Post-Exercise (Max)	0.929	0.824-1.047	0.228
LA Reservoir Strain (at Rest)	0.908	0.801-1.028	0.128
LA Reservoir Strain (Post-Exercise)	0.971	0.882-1.069	0.543
MVA	1.206	0.213-6.845	0.832
MR	1.160	0.348-3.872	0.809
MBV	1.083	0.098-11.917	0.948
Cardiac Rhythm	1.812	0.280-11.750	0.533
HT	1.385	0.331-5.787	0.656
DM	0.600	0.062-5.841	0.660
LAVI	1.003	0.965-1.042	0.892
Age	0.993	0.928-1.063	0.849
Sex	0.347	0.038-3.178	0.349
GLS-LV (at Rest)	1.015	0.847-1.217	0.868
GLS-LV (Post-Exercise)	1.047	0.905-1.212	0.535
Multivariate Analysis			
MVG Post-Exercise (Mean)	**0.366**	**0.148-0.905**	**0.030***
MVG Post-Exercise (Max)	1.450	0.987-2.130	0.058
LA Reservoir Strain (at Rest)	0.915	0.807-1.037	0.165

LAVI, Left Atrial Volume Index; MBV, Mitral Balloon Valvuloplasty; MVA, Mitral Valve Area; MVG, Mitral Valve Gradient; sPAP, Systolic Pulmonary Artery Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Discussion

In this prospective cohort study, we aimed to determine the effect of exercise on LA mechanics using STE in patients with mild rheumatic MS. Our study cohort had considerably higher LAVI values (mean: 40.52 ± 18.27) than those of a healthy population. Additionally, the LA reservoir strain (mean: 17.1 ± 8.33) was reduced relative to reference values.[8] Following exercise, the LA reservoir strain did not change significantly. However, trans-mitral pressure gradients and sPAP increased. Notably, only the post-exercise mean trans-mitral pressure gradient was associated with symptom status in patients with mild MS.

A mitral valve area of 1.5 cm^2 or less is indicative of hemodynamically significant MS.[1] However, it has been demonstrated that MS is dynamic and can become hemodynamically significant even with larger valve areas, particularly during exercise. This phenomenon is evidenced by the presence of symptomatic patients with mitral valve areas greater than 1.5 cm^2. During exercise, an increase in trans-mitral pressure gradients and pulmonary capillary and artery pressures occurs in patients with MS, leading to exertional symptoms.[9] Similarly, our study observed a considerable increase in both trans-mitral pressure gradients and sPAP following exercise.

The LA, through its reservoir, conduit, and contractile functions, plays a central role in the hemodynamic alterations associated with mitral valve disorders. Consequently, non-invasive evaluation of LA anatomy and function has gained prominence in recent research.[10-12] Rheumatic MS may impair LA functions due to pressure and volume overload, inflammation, and fibrosis.[13] Vriz et al.[4] reported reduced LA reservoir strain (LASr) values (11%) in patients with severe MS. In a study involving 29 patients undergoing percutaneous balloon mitral valvotomy (BMV), Reddy et al.[14] demonstrated that global LA strain improves following BMW, albeit not reaching normal values. Kono et al.[15] found that impairment in LA mechanics is evident even in patients with mild stenosis. Similarly, our study found reduced LASr (mean: 17.1 ± 8.33) in individuals with mild MS.

The exercise stress test is fundamental in assessing the hemodynamic effects of mitral valve diseases, particularly in patients whose functional status does not align with their symptom status.[16] Sugimoto et al.[17] reported decreased LA reservoir function during exercise in patients with mitral regurgitation. To our knowledge, this study is the first to investigate changes in LA mechanics with exercise in patients with MS. We did not observe a significant change in LASr after exercise.

Symptoms do not always correlate with the severity of stenosis in individuals with mitral valve disease.[18] Some patients with advanced disease do not develop symptoms or atrial fibrillation, while patients with mild stenosis can experience severe exertional dyspnea or paroxysmal atrial fibrillation. The reasons for this divergence are not fully understood, although several hypotheses have been proposed. Thiedemann et al.[2] suggested that varying degrees of LA remodeling may account for the different clinical outcomes. LV diastolic dysfunction and decreased LV compliance may also contribute to symptom development in these patients.[19] Furthermore, the LA strain rate has been associated with symptom status and the development of atrial fibrillation (AF) in patients with mild MS.[20,21] Bouchahda et al.[22] reported a strong association between LASr and severe symptoms across all clinical stages of MS patients. They noted that LASr reflects LA compliance and helps modulate symptoms by absorbing excessive upstream pressure. However, while mean pressure gradients and LASr were associated with symptom status in univariate analysis, only the post-exercise mean trans-mitral pressure gradient was related to symptom status in multivariate analysis in our study. Similarly, Reis et al.[23] found that the mean trans-mitral pressure gradient at peak exercise was the best predictor of clinical events in patients with moderate MS. We believe that, if we had a higher number of patients in the cohort, we could obtain similar results for LASr.

Limitations

The main limitation of our study was the small sample size. Additionally, information regarding other phases of LA function, specifically the conduit and contractile phases, is lacking. Due to the absence of a semi-supine bicycle in our laboratory, we were unable to perform echocardiographic examinations during peak exercise. Finally, we did not utilize a grading scale to evaluate dyspnea.

Conclusion

LA reservoir strain is an important measure of LA compliance and is central to symptom development in MS. We hypothesized that exertional symptoms in patients with mild MS may be related to exercise-induced impairment of the LA reservoir strain. However, while we found that LA reservoir strain at baseline is decreased in individuals with mild MS, no further decline in LA reservoir strain was observed following exercise. Nonetheless, we acknowledge that if we had been able to perform echocardiographic measurements during peak exercise, the results may have differed.

Despite the study's small sample size, it is valuable for demonstrating impaired LA reservoir strain even in patients with mild stenosis. To our knowledge, no other study has examined the effect of exercise on LA mechanics in MS before. Future studies with larger sample sizes and more detailed evaluations of LA mechanics provide a better understanding of the role of LA function in MS and symptom development.

Ethics Committee Approval: Ankara University Faculty of Medicine Clinical Research Ethics Committee approved the study (Approval Number: 15-774-16, Date: 10/10/16).

Informed Consent: All patients provided written consent for participation in the registry.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.T.K; Design – C.T.K., D.M.G.U.; Supervision – C.T.K., D.M.G.U.; Resource – C.E.; Materials – T.S.T.; Data Collection and/or Processing – M.A., T.S.T., D.M.G.U.; Analysis and/or Interpretation – T.S.T.; Literature Review – M.A.; Writing – M.A.; Critical Review – C.T.K., C.E.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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