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Assessment of Right Ventricular Systolic Function with 3-Dimensional Speckle Tracking Echocardiography in Isolated Mild Mitral Stenosis

ABSTRACT

Background: In rheumatic severe mitral stenosis, right ventricular mechanics deteriorate with the increasing severity of mitral stenosis. Therefore, we aimed to investigate right ventricular mechanics in patients with mild mitral stenosis using 3-dimensional speckle tracking echocardiography.

Methods: In total, 40 patients with mild mitral stenosis and 36 age- and gender-matched healthy controls were included. Conventional echocardiographic examination was performed and 3-dimensional data sets were acquired for strain analysis. Besides conventional echocardiographic parameters, right ventricular volume and function and 3-dimensional speckle tracking echocardiography-derived right ventricular free wall longitudinal strain were compared between patients with mild mitral stenosis and healthy controls.

Results: Although 3-dimensional right ventricular volumes and ejection fraction were similar between the groups, 3-dimensional speckle tracking echocardiography-derived right ventricular free wall longitudinal strain was significantly lower in patients with mild mitral stenosis than in controls (25.57 ± 4.39% vs. 27.90 ± 4.71%, $P = .028$). Significant correlations were observed between right ventricular free wall longitudinal strain and mitral valve area and estimated systolic pulmonary artery pressure ($r = 0.597$, $P < .001$; $r = -0.508$, $P = .003$, respectively). Another significant positive correlation was observed between planimetric mitral valve area and 3-dimensional speckle tracking echocardiography-derived right ventricular free wall longitudinal strain ($r = 0.597$, $P < .001$).

Conclusion: The degree of severity of mild mitral stenosis in terms of mitral valve area can help in the early detection of subclinical right ventricular systolic function impairment which can be easily detected by 3-dimensional speckle tracking echocardiography. Right ventricular contractile performance could decrease even in mild mitral stenosis.

Keywords: Mitral stenosis, right ventricle, speckle-tracking echocardiography, 3-dimensional echocardiography

ORIGINAL INVESTIGATION

INTRODUCTION

Rheumatic valvular heart disease is the leading cause of cardiovascular morbidity and mortality, particularly in developing countries.[1] The mitral valve is the most commonly affected valve presenting as mitral stenosis (MS) or mitral regurgitation. Various degrees of atrial remodeling can be seen related to the severity of MS due to mechanical and/or hemodynamical factors. In MS, resistance develops against pulmonary venous forward flow due to increased left atrial pressure. This pathophysiological process affects the pulmonary vascular bed and function of the right side of the heart that determines the prognosis.[2]

In subjects with MS, right ventricular (RV) function plays an essential role in the onset of symptoms and prognosis.[2-4] Previous studies have investigated RV functions in mitral valve stenosis using 2-dimensional speckle tracking echocardiography (2D-STE).[5-6] But, RV analysis using 2-dimensional imaging techniques is challenging due to the unique shape of the RV. Unlike 2-dimensional

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echocardiography, 3-dimensional echocardiography enables complete assessment of RV volumes and systolic function besides its geometry.[7]

Three-dimensional speckle tracking echocardiography (3D-STE) is a relatively new technology used for assessing RV functions in many studies.[8,9] Early detection of subtle RV dysfunction is essential for managing patients with valvular heart disease. As already known, RV free wall longitudinal strain is an independent predictor of RV hemodynamic performance indices.[10] Therefore, we aimed to evaluate RV systolic functions in isolated mild rheumatic MS using 3D-STE.

METHODS

Study Population

A total of 40 consecutive patients with mild MS admitted to our echocardiography laboratory between November 2015 and November 2016 were retrospectively included in the study. Mild MS was defined as having a planimetric mitral valve area of 1.5-2.0 cm^2 with a mean diastolic transmitral gradient <5 mm Hg.[11] Patients who were <18 years old, had left ventricular systolic dysfunction, congenital heart disease, ischemic heart disease, history of cardiac surgery, history of myocarditis, hypertension, diabetes mellitus, chronic pulmonary disease, estimated systolic pulmonary artery pressure > 35 mm Hg, any other degree of valvular disease accompanying mild MS, systemic inflammatory diseases, pregnancy, poor echocardiographic images, and any rhythm other than sinus rhythm were excluded. The control group comprised 36 healthy volunteers who were age- and gender-matched and did not have any cardiovascular risk factors or systemic diseases.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee.

Echocardiographic Evaluation

Image acquisition was performed using a Phillips EPİQ 7C (Philips Healthcare, Andover, Mass, USA) ultrasound system with an X5-1 matrix-array transducer. The examination was performed by an experienced cardiologist who was unaware of the study groups. Standard 2-dimensional transthoracic echocardiography and Doppler imaging were performed according to the recommended guidelines.[12,13] Left ventricular end-diastolic and end-systolic volumes (LV EDV and LV ESV) and LV ejection fraction (LVEF) were measured from the conventional apical 4-chamber (A4C) and 2-chamber (A2C) views using biplane-modified Simpson's method. Left atrial (LA) and right atrial (RA) dimensions were measured from the A4C view. Right ventricular end-diastolic area (EDA) and RV end-systolic area (ESA) were measured from the A4C RV-focused view with border tracing of the RV endocardium.[12] The fractional area change (FAC) was calculated as (RV EDA – RV ESA)/RV EDA × 100. Tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (RV S') were measured from RV free wall. Estimated systolic pulmonary artery pressure (SPAP) was derived from the Bernoulli equation with the maximum velocity of the tricuspid regurgitation by adding an estimated RA pressure according to the size and collapsibility of the inferior vena cava. Three-dimensional right ventricular data were acquired from the A4C RV-focused view adapted to include the entire RV applying the 3D full-volume wide-angle mode during expiratory breath-holding. A minimum of 3 consecutive elect rocardiogram-gated beats were recorded. Temporal resolution was maximized with a volume rate of 20-35 volume/s to obtain 3D-STE analyses with adequate quality. Mitral valve area (MVA) was measured using a 3-dimensional multi-planar reconstruction method. First, the largest early diastolic opening of the mitral valve orifice was found. Then, using a multi-plane reconstruction, 2 orthogonal planes were placed to intersect the tips of the mitral valve, then a third cropping plane was identified at the level of the mitral valve orifice, and MVA was measured using planimetry.

Post-Processing Analysis

Three-dimensional data were transferred offline and analyzed by an experienced cardiologist who was blinded to the study groups. Strain analysis was performed using Tomtec 4D RV software (Tomtec Image Arena 4D RV analysis 4.6 version). Tomtec, is a vendor-independent software quantifying cardiac wall motion in 3D ultrasound data for LV and RV functions. [14] The software (Tomtec Image Arena 4D LV analysis 4.6 version) was used as an automatic detection method to follow the LV endocardium, providing volumetric information automatically. The Tomtec 4D RV software (Tomtec Image Arena 4D RV analysis 4.6 version) was utilized for 3D RV volumetric analysis. Similarly, the software recognized the RV endocardial boundaries automatically in 3D and calculated 3D RV volumes, RV ejection fraction, and RV free wall longitudinal strain (RV FWLS) (Figure 1). If the delineation of the LV and RV endocardial boundaries was insufficient to ensure optimum speckle tracking, manual adjustments were applied.

Statistical Analysis

Statistical Package for the Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as percentages. Depending on the estimated cell value, categorical data were compared using the χ^2 test or Fisher's exact test. The Shapiro–Wilk test was performed to test the normality of the distribution of data. For normally distributed continuous variables, the independent sample *t*-test was applied, whereas for not normally distributed continuous variables, the Mann–Whitney *U* test was applied. Correlation analyses between variables were

HIGHLIGHT

- The degree of mitral stenosis is important in the evaluation of right ventricular systolic functions in patients with rheumatic mitral stenosis. Even in patients with mild mitral stenosis, subclinical right ventricular systolic dysfunction could be observed in correlation with the degree of mitral valve stenosis.

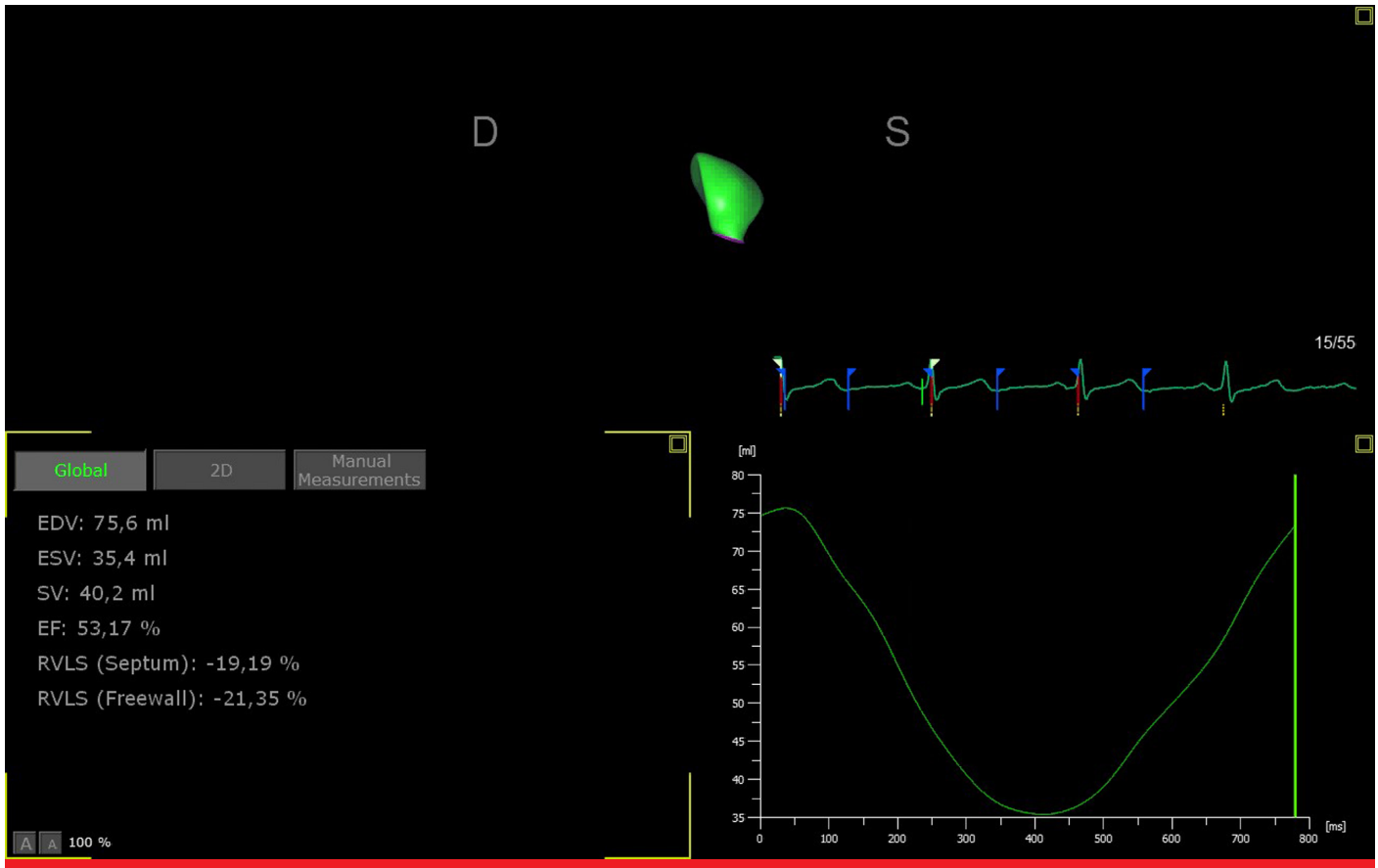

Figure 1. Three-dimensional volume and strain analysis of the right ventricle in patients with mild mitral stenosis. EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; RVLS, right ventricular longitudinal strain.

performed using Spearman's rho or Pearson correlation analyses, depending on whether the variable is parametric or non-parametric.

RESULTS

Baseline Characteristics

Demographic and clinical characteristic data were presented in Table 1. The mean age of the patients with mild MS was 41.07± 10.29. In terms of age, gender, body surface area, systolic and diastolic blood pressure, and heart rate, there was no significant difference between the 2 groups.

Table 1. Demographic and Clinical Characteristic Data in Patients with Mitral Stenosis and Control Group

Variables	Patients with Mild MS (n = 40)	Control Group (n = 36)	*P*
Age (years)	41.07 ± 10.29	40.38 ± 9.39	.763
Female gender (n, %)	23 (57.5)	20 (55.6)	.864
BSA (m^2)	1.79 ± 0.16	1.81 ± 0.21	.722
SBP (mm Hg)	124.92 ± 6.84	123.75 ± 6.39	.443
DBP (mm Hg)	70.02 ± 7.45	68.83 ± 5.13	.425
Heart rate (bpm)	73.15 ± 8.22	75.69 ± 5.40	.120

Data were presented as mean ± standard deviation.
MS, mitral stenosis; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beat per minute.

Conventional Echocardiographic Parameters for the Evaluation of Right Ventricular Function

Two-dimensional and 3-dimensional echocardiographic data in the 2 groups were summarized in Table 2. Three-dimensional LV volumes and LV ejection fraction were found to be similar between the 2 groups. Both left and right atrial diameters and RV basal diameter were found to be higher in the mild MS group. However, RV EDA, ESA, and RV volumes were found to be similar between the 2 groups. Right ventricular systolic function was analyzed with 2-dimensional conventional echocardiographic parameters (TAPSE, RV S', and RV fractional area change) and 3-dimensional echocardiographic parameters of 3D RV ejection fraction were not found to be different between mild MS and control groups. However, SPAP was significantly increased in patients with mild MS patients compared to healthy controls ($P < .001$) (Table 2).

Deformation Parameter

Three-dimensional STE-derived RV FWLS was found to be lower in the mild MS group than in healthy subjects (25.57 ± 4.39% vs. 27.90 ± 4.71%, $P = .028$).

Correlation analyses between the echocardiographic criteria of the severity of MS and RV mechanics were given in Figure 2 and Table 3. Moderate and significant correlations were observed between RV FWLS and MVA and estimated

Table 2. Two-Dimensional and 3-Dimensional Echocardiographic Data in Study Groups

Variables	Mild MS Patients (n = 40)	Control Group (n = 36)	*P*
2D LV EDV (mL)	102.23 ± 24.07	100.98 ± 27.97	.834
3D LV EDV (mL)	105.54 ± 24.17	102.23 ± 26.85	.574
2D LV ESV (mL)	36.52 ± 10.75	35.81 ± 10.28	.771
3D LV ESV (mL)	39.54 ± 11.08	39.01 ± 10.21	.833
2D LV EF (%)	64 ± 4.93	64 ± 5.10	.973
3D LV EF (%)	62 ± 4.40	62 ± 3.63	.283
LA apicobasal diameter (cm)	5.29 ± 0.42	4.70 ± 0.51	<.001
LA mediolateral diameter (cm)	3.72 ± 0.33	3.40 ± 0.34	<.001
RA apicobasal diameter (cm)	4.90 ± 0.30	4.69 ± 0.41	.011
RA mediolateral diameter (cm)	3.20 ± 0.34	3.09± 0.35	.173
Mean transmitral gradient (mm Hg)	3.55 ± 2.13	1.22 ± 0.03	<.001
Planimetric MVA (cm^2)	1.79 ± 0.12	5.12 ± 0.54	<.001
Estimated SPAP (mm Hg)	26.45 ± 8.23	17.98 ± 7.46	<.001
RV basal diameter (cm)	3.14 ± 0.36	2.96 ± 0.26	.015
RV EDA (cm^2)	13.82 ± 2.13	13.19 ± 2.08	.198
RV ESA (cm^2)	7.16 ± 1.13	6.69 ± 1.14	.076
RV FAC (%)	48.17 ± 3.40	49.33 ± 3.14	.127
TAPSE (mm)	21.07 ± 3.19	22.23 ± 2.75	.097
RV S′ TDI (cm/s)	12.78 ± 2.06	13.68 ± 1.96	.055
3D RV EDV (mL)	91.84 ± 25.34	87.76 ± 25.12	.483
3D RV ESV (mL)	38.04 ± 8.45	34.75 ± 7.71	.082
3D RV EF (%)	58 ± 5.39	60 ± 4.50	.131
3D RV FWLS (%)	25.57 ± 4.39	27.90 ± 4.71	.028

Data were presented as mean ± standard deviation.
MS, mitral stenosis; LV, left ventricular; EDV, end-diastolic volume; 2D, 2-dimensional; 3D, 3-dimensional; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricular; EDA, end-diastolic area; ESA, end-systolic area; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; S′, peak velocity of the lateral tricuspid annulus measured by tissue Doppler imaging; LA, left atrium; RA, right atrium; MVA, mitral valve area; SPAP, systolic pulmonary artery pressure; FWLS, free wall longitudinal strain.

SPAP ($r = 0.597$, $P < .001$; $r = -0.508$, $P = .003$, respectively). However, weak and significant correlations were observed between 3D RV FWLS and RV end-systolic volume, TAPSE, RV S′ ($r = -0.434$, $P = .005$; $r = 0.363$, $P = .021$; $r = 0.417$, $P = .008$, respectively). But, there were no correlations between 3D RV FWLS and mean gradient.

Intra-Interobserver Variability

The intraobserver and interobserver variability for 3D-STE-derived RV FWLS was examined. Intra-class correlation coefficients (ICCs) for intra- and inter-observer variability were found to be 0.863 (95% CI: 0.740-0.927) and 0.823 (95% CI: 0.665-0.907) for RV FWLS.

DISCUSSION

Our study's key findings can be stated as follows: (i) RV EDA, RV ESA, and RV FAC measurements were similar in patients with mild MS and healthy controls, (ii) patients with mild MS had reduced 3D RV FWLS despite presenting similar 3D RV ejection fraction and 3D RV volumes with healthy controls, (iii) moderate and significant correlations were observed between RV FWLS and MVA, estimated SPAP, and (iv) the highest correlation was observed between RV FWLS and MVA.

Conventional echocardiographic modalities are inadequate in assessing RV functions due to the unique shape and anatomic features of the RV. While 2-dimensional echocardiography remains incapable in the evaluation of RV volumes and systolic function, 3D echocardiography gets over this limitation by assessing the RV volumes and systolic function.[15] The RV strain has been demonstrated as a prognostic marker for many cardiovascular conditions, including heart failure, diabetes, congenital heart disease, arrhythmogenic right ventricular dysplasia, valvular heart disease, pulmonary hypertension, and chronic obstructive pulmonary disease.[16-18]

In our study, several sensitive RV function measures were examined, although conventional echocardiographic measures of RV function were unable to identify the impairment in RV contractility. Right ventricular contractile performance, as measured by TAPSE, FAC, and RVEF, was comparable between groups, in contrast to reduced RV free wall longitudinal strain in the mild MS group. This finding may be related to the tissue Doppler imaging that has significant limitations due to low spatial resolution, angle dependency, and analysis in only 1 dimension.[10,19] The contribution of RV longitudinal fibers to RV systolic function is higher than RV circumferential fibers. Additionally, the estimated SPAP was found to be higher in the mild MS group than in the controls. Right ventricular enlargement and deterioration in systolic function are most likely attributable to RV afterload changes caused by pulmonary pathology, as the estimated SPAP is higher in individuals with mild MS. The right ventricle is known to be afterload-sensitive, which may explain the nature of this subclinical involvement. Additionally, there is an inflammatory process in rheumatic heart valve disease. Ongoing cardiac remodeling has an impact on myocardial contractility due to myocardial and valvular involvement during the disease process. Multimodality cardiac imaging to assess morphological changes in cardiac chambers is crucial for timing of intervention in patients with MS.[20] The specific etiology of subclinical impaired RV contractility in individuals with mild MS is unknown, as echocardiography does not allow for detailed tissue characterization. Due to the limitations of ultrasonic methods for tissue characterization, the actual pathophysiological processes behind these findings cannot be identified using echocardiography or deformation imaging, and therefore, more research is needed that relates current findings to ultrastructural changes in the myocardium.

Right ventricular longitudinal deformation parameters are closely related to RV systolic performance. In our study,

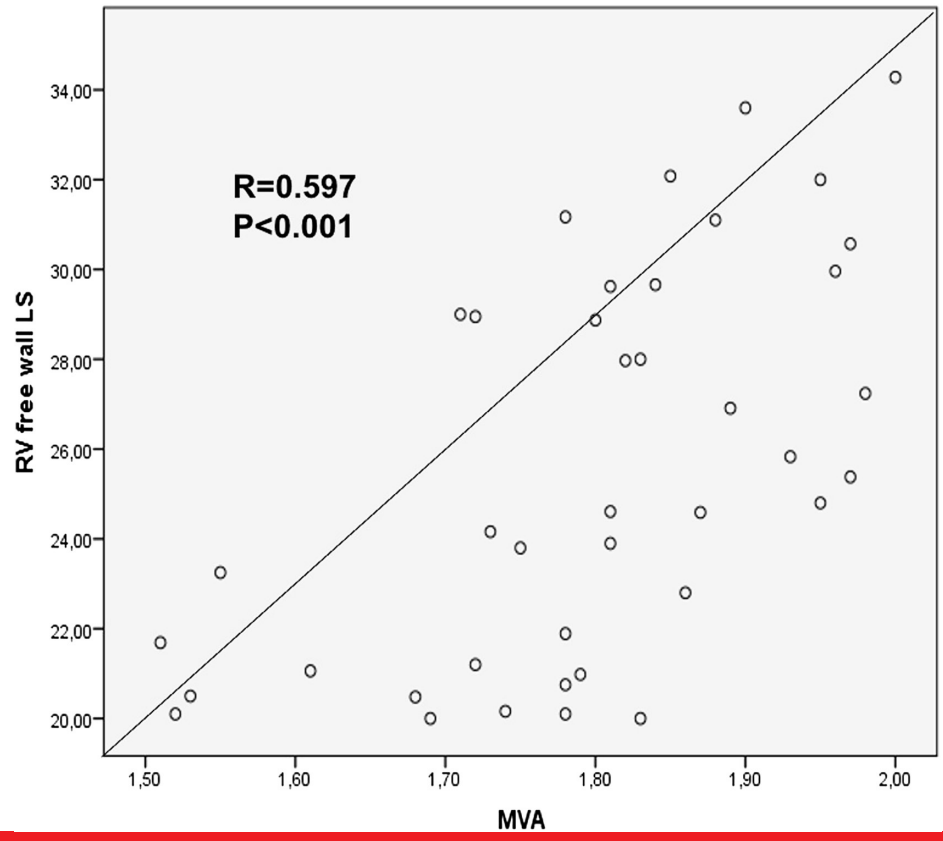

Figure 2. Correlation between mitral valve area (cm²) and right ventricular (RV) free wall LS. The correlation coefficient (R) and statistical significance (P) are indicated.

3D RV FWLS was reduced in patients with mild MS compared to healthy controls. Additionally, positive and moderate correlations were observed between MVA and 3D RV FWLS in our study. Similarly, Tanboga et al[21] found reduced RV GLS and RV-Sr obtained using 2D-STE in subjects with mild MS compared with healthy controls, but they found a weak correlation between RV deformation parameters and MVA in the aforementioned study. Furthermore, they analyzed RV global longitudinal strain not RV FWLS. Recently, RV FWLS has been used as a determinant in predicting the RV systolic function.[22] Another study, which analyzed RV deformation parameters in individuals with mild-to-moderate MS, found that while RV GLS and RV SLS were decreased, no significant change was observed in RV FWLS in patients with mild-to-moderate MS compared to healthy individuals.[23] This result could be elucidated by the direct relationship between the interventricular septum and the mitral apparatus via LV fibers. However, current guidelines recommend measuring only the RV free wall to assess RV systolic function to avoid the potential confounding effect of LV contribution to RV systolic function.[22] Therefore, RV systolic function seems to be preserved in mild-to-moderate MS, since there was no significant change in RV free wall longitudinal strain in their study.[23] Furthermore, the cause of discrepancies between studies can be explained that it might be related to acquisition techniques (2-dimensional vs. 3-dimensional) and different software packages that were used for the analysis. In comparison to 2D-STE, 3D-STE allows for a more comprehensive review of RV geometry, volumes, and systolic function[24] In another study analyzing RV deformation parameters with 3D-STE by a different vendor, Seçkin Göbüt et al[25] obtained similar results as to our study. They found lower RV septal longitudinal strain and RV FWLS in mild MS compared with healthy controls and they found a positive correlation between RV deformation parameters and MVA. But they did not investigate the relationship between RV deformation parameters and the parameters showing the severity of MS other than MVA.[25]

Table 3. The Correlation of 3D Right Ventricular Free Wall Longitudinal Strain and Both Mitral Valve Measurements and Right Ventricular Measurements

	3D RV FWLS	
Variables	***r***	***P***
Mitral valve area (cm²)	0.597	<.001
Mean transmitral gradient (mm Hg)	−0.236	.143
RV ESV (mL)	−0.434	.005
TAPSE (mm)	0.363	.021
RV S′ TDI (cm/s)	0.417	.008
SPAP (mm Hg)	−0.508	.003

3D, 3-dimensional; RV, right ventricular; FWLS, free wall longitudinal strain; ESV, end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; RV S′, right ventricular tricuspid annulus Sm; SPAP, systolic pulmonary artery pressure

The mitral mean diastolic gradient was not found to be correlated with 3D RV FWLS. It would be expected that as the diastolic gradient increases, pulmonary wedge pressure and further pulmonary artery pressure increases, leading to a decrease in RV strain. We have shown that RV systolic functions can be impaired by decreasing MVA independent of gradient increase.

Systolic pulmonary artery pressure was significantly higher in patients with mild MS compared to healthy controls. Negative and moderate correlations were observed between RV deformation parameters and SPAP in our study. Similarly, Tanboga et al[21] found that there was a negative and moderate correlation between RV deformation parameter and SPAP. The right ventricle works against RV afterload. So that, an increase in RV afterload can cause deterioration of RV systolic function in patients with MS.

As the severity of MS increases, an increment in RV afterload occurs.[26] Right ventricular–pulmonary circulation coupling is an important physiological phenomenon. Normally, the RV pumps against a pressure of 30 mm Hg, which is one-quarter that of the LV. The RV free-wall thickness was thinner than LV wall thickness.[27] Thus, compared to LV systolic function, RV systolic function is easier to be affected and worsened against an increase in afterload. An increase in the severity of MS was responsible for decreasing RV free wall longitudinal strain. Therefore, MVA is estimated to be an important criterion in determining RV contractile performance.

Study Limitations

The study findings should be interpreted in the light of some limitations. It was a single-center retrospective study with a limited study population and was not generalizable. Standardized 3D-STE deformation cut-off values have not been determined because there are few studies with a small sample size that have investigated RV functions using 3D-STE-derived RV strain parameters, and their reference values are still unidentified. Therefore, the study's findings should be evaluated in light of these limitations.

CONCLUSION

Before the development of permanent irreversible changes in the pulmonary system, reduced RV mechanics have been shown in patients with mild MS with this study. Reduced RV FWLS in mild MS can also be used to predict the likelihood of overt RV systolic impairment in the future, which influences the prognosis. The MVA indicating the severity of rheumatic MS also predicts subclinical RV systolic dysfunction.

Ethics Committee Approval: The study was conducted with the Declaration of Helsinki and approved by the Institutional Ethics Committee (registration number: HNEAH-KAEK 2021/263).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: EP, LDA, TKO, and SU contributed to conception or design; EP and TKO contributed to acquisition; EP, LDA, and TKO contributed to analysis, or interpretation, drafted the manuscript, critically revised the manuscript. SU contributed to analysis or interpretation and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of Interests: The authors declare that they have no competing interest.

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