

# Left Atrial Deformation Imaging and Atrial Fibrillation in Patients with Rheumatic Mitral Stenosis

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**Background:** Atrial fibrillation (AF) is a frequent complication of rheumatic mitral stenosis (MS) and is associated with worse outcomes. Prediction of new-onset AF by assessing left atrial (LA) mechanics with speckle-tracking echocardiography might be useful for risk stratification and guiding therapeutic strategies. Therefore, the aim of this study was to assess the association of LA reservoir strain (LASr) and strain rate (LASRr) with AF at follow-up in patients with rheumatic MS.

**Methods:** Left atrial reservoir strain and LASRr measured by speckle-tracking echocardiography were assessed in 125 patients (mean age,  $50 \pm 15$  years; 80.8% female) with rheumatic MS and without a history of AF. Patients were followed up for the occurrence of a first episode of AF after the index echocardiogram.

**Results:** During a median follow-up of 32 (9.5-70) months, 41 patients (32.8%) developed new-onset AF. Patients who developed AF had significantly more impaired LASr ( $13.4\% \pm 5.2\%$  vs  $18.9\% \pm 8.2\%$ ;  $P < .001$ ) and LASRr ( $0.72 \pm 0.26 \text{ s}^{-1}$  vs  $0.98 \pm 0.36 \text{ s}^{-1}$ ;  $P < .001$ ) compared with patients who remained in sinus rhythm. On multivariable Cox regression analysis, LASr  $< 21\%$  and LASRr  $< 0.8 \text{ s}^{-1}$  were independently associated with the development of AF at follow-up (hazard ratio = 7.03, 95% CI, 2.08-23.77,  $P = .002$ ; and hazard ratio = 3.42, 95% CI, 1.59-7.34,  $P = .002$ , respectively).

**Conclusions:** LASr and LASRr are impaired in patients with rheumatic MS, and the degree of impairment is associated with new-onset AF at follow-up. (J Am Soc Echocardiogr 2022; ■: ■-■.)

**Keywords:** Atrial fibrillation, Rheumatic mitral stenosis, Left atrial reservoir strain, Left atrial reservoir strain rate

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Rheumatic heart disease (RHD) remains an important preventable cause of cardiovascular death and disability in most low- and middle-income countries and accounts for up to 1.4 million deaths per year.<sup>1,2</sup> In developing countries, rheumatic mitral stenosis (MS) remains the most common valvular heart disease. In industrialized countries, RHD is most frequently observed in the elderly. However, changes in the migratory flows have led to a growing number of young individuals with RHD.<sup>3</sup> Atrial fibrillation (AF) is a common complication of RHD and has been observed in 30%-40% of patients with rheumatic MS.<sup>4</sup> Atrial fibrillation is often the first manifestation of rheumatic MS after an initial course without symptoms, and its presence is associated with an increased risk of thromboembolic events, heart failure, and premature death.<sup>5,6</sup> Furthermore, about 80% of strokes in patients with RHD occur in patients with rheumatic MS and AF.<sup>7</sup> Because AF has a crucial impact on the course and treatment of rheumatic MS, identifying patients at risk of new-onset AF is of clinical interest and may be helpful in improving risk stratification and guiding therapeutic strategies.

Left atrial (LA) strain derived by speckle-tracking echocardiography evaluates LA function and reflects atrial compliance.<sup>8</sup> Previous studies have shown that LA strain correlates well with the extent of atrial fibrosis detected by cardiac magnetic resonance,<sup>9</sup> and it has

**Abbreviations**

<b>AF</b> = Atrial fibrillation
<b>ECG</b> = Electrocardiogram
<b>HR</b> = Hazard ratio
<b>LA</b> = Left atrium, atrial
<b>LAScd</b> = Left atrial conduit strain
<b>LASct</b> = Left atrial contractile strain
<b>LASr</b> = Left atrial reservoir strain
<b>LASRcd</b> = Left atrial conduit strain rate
<b>LASRct</b> = Left atrial contractile strain rate
<b>LASRr</b> = Left atrial reservoir strain rate
<b>LAVI</b> = Left atrium volume index
<b>LV</b> = Left ventricular
<b>MS</b> = Mitral stenosis
<b>MV</b> = Mitral valve
<b>MVA</b> = Mitral valve area
<b>RHD</b> = Rheumatic heart disease

been shown to be a useful diagnostic technique to predict the onset of AF and outcome in patients after AF ablation, cryptogenic stroke, and heart failure.<sup>10-12</sup> However, the prognostic value of speckle-tracking echocardiography to assess LA strain in patients with rheumatic MS has not been thoroughly evaluated. Therefore, the aim of this study was to evaluate the association between LA strain assessed by speckle-tracking echocardiography and development of AF at follow-up in patients with rheumatic MS.

**METHODS****Patient Population**

A total of 259 patients with rheumatic MS referred for echocardiography at the Leiden University Medical Centre (Leiden, the Netherlands), from July 2000 until September 2020, were consecutively selected from an echocardiographic database. Patients with permanent AF or a history of paroxysmal AF, prior surgical

two-dimensional planimetry, whereas continuous-wave Doppler with the velocity-time integral of the MV was used to calculate the peak and mean transmitral gradient.<sup>4,13</sup> Three beats in each view were analyzed and averaged. Concomitant valvular diseases were identified and graded as recommended, using a multiparametric approach based on qualitative, semiquantitative, and quantitative assessment.<sup>4,13-15</sup> Right ventricular areas were measured from a focused right ventricular apical view.<sup>15</sup> To assess right ventricular systolic function, tricuspid annular plane systolic excursion was measured on M-mode recordings of the lateral tricuspid annulus on a focused right ventricular apical view.<sup>16</sup> The systolic pulmonary artery pressure was estimated based on the tricuspid regurgitant jet velocity, adding 3, 8, or 15 mm Hg based on the inferior vena cava diameter and collapsibility.<sup>17</sup>

**Speckle-Tracking Echocardiography**

Left atrial strain and strain rate were measured on the apical four-chamber view with the onset of the QRS complex used as the zero-reference point (R-R gating), according to current guidelines.<sup>18</sup> According to a large meta-analysis, the guidelines recommend measuring LA strain from the apical four-chamber view.<sup>18,19</sup> The mean frame rate was  $60 \pm 10$  fps. A region of interest was manually drawn along the LA endocardial border when the LA was at its minimum volume after atrial contraction. Automatic tracking of the LA wall by the software was visually verified and corrected by adjusting the region of interest or the width of the contour, ensuring appropriate capture of LA motion. The resulting LA strain curve provided two peaks: one peak just before MV opening, representing LA reservoir strain (LASr), and one peak just before atrial contraction, representing LA contractile strain (LASct). The difference between these two peaks represented the LA conduit strain (LAScd; [Figure 1A](#)). In addition, the peak (positive) strain rate during the reservoir phase, the peak (negative) strain rate during the conduit phase in early diastole, and the peak (negative) strain rate during LA contraction phase in late diastole were assessed from the strain rate curve and used to calculate the LASr rate (LASRr), LAScd rate (LASRcd), and LASct rate (LASRct), respectively ([Figure 1B](#)). All values were determined using the averaged longitudinal strain and strain rate curves.

**Follow-up**

Serial follow-up at the outpatient clinic was obtained in all patients every 6-12 months and at any time the patient reported symptoms. At each examination, a standard 12-lead ECG was obtained and symptoms were noted. A 24-hour ECG Holter recording was performed if the patient had symptoms suggesting AF. Data were included up to the last date of follow-up. The endpoint of the study was the occurrence of new-onset AF from the first echocardiogram diagnosing rheumatic MS where LA strain was measured. Atrial fibrillation was documented on standard 12-lead ECG or on 24-hour ECG Holter recording in which AF was defined as irregular R-R intervals in the absence of distinct repeating P waves and irregular atrial activations for at least 30 seconds or during the entire 12-lead ECG.<sup>20</sup>

**Statistical Analysis**

Categorical variables are expressed as numbers and percentages. Normally distributed continuous variables are presented as mean  $\pm$  SD, whereas nonnormally distributed variables are displayed as median and interquartile range. Categorical variables were compared using the Fisher's exact test. Continuous variables were

mitral valve (MV) repair or replacement, suboptimal data to perform two-dimensional speckle-tracking echocardiography analysis, or lack of follow-up data were excluded. Demographic and clinical data were obtained from the departmental electronic medical record (EPD-vision; Leiden University Medical Centre). Echocardiographic data were analyzed retrospectively. The institutional review board of the Leiden University Medical Centre waived the need for written patient informed consent as this study involved the retrospective analysis of clinically acquired data. The data that support the findings of this study are available on reasonable request to the corresponding author.

**Echocardiography**

Comprehensive transthoracic echocardiography was performed using Vivid 7, E9, or E95 ultrasound systems (GE Vingmed, Horten, Norway), equipped with a 3.5 MHz or M5S transducer, with the patient at rest in the left lateral decubitus position. Electrocardiogram (ECG-) triggered echocardiographic data were stored digitally in a cine-loop format for offline analysis (EchoPAC version 203, GE Vingmed Ultrasound, Horten, Norway). Left ventricular (LV) ejection fraction and LV end-diastolic and end-systolic volumes were calculated using the biplane Simpson's method. Left atrial volumes were calculated from the apical four- and two-chamber views using the biplane method of disks and indexed to body surface area. Mitral stenosis severity was assessed with a multiparametric approach, according to contemporary guideline recommendations.<sup>4,13</sup> Mitral valve area (MVA) was evaluated using the pressure half-time method and

## HIGHLIGHTS

- AF is a common complication of rheumatic MS.
- Reduced LA strain is associated with AF at follow-up in rheumatic MS.
- LASr < 21% is associated with AF at follow-up in rheumatic MS.
- Evaluation of LA function improves risk stratification in rheumatic MS.

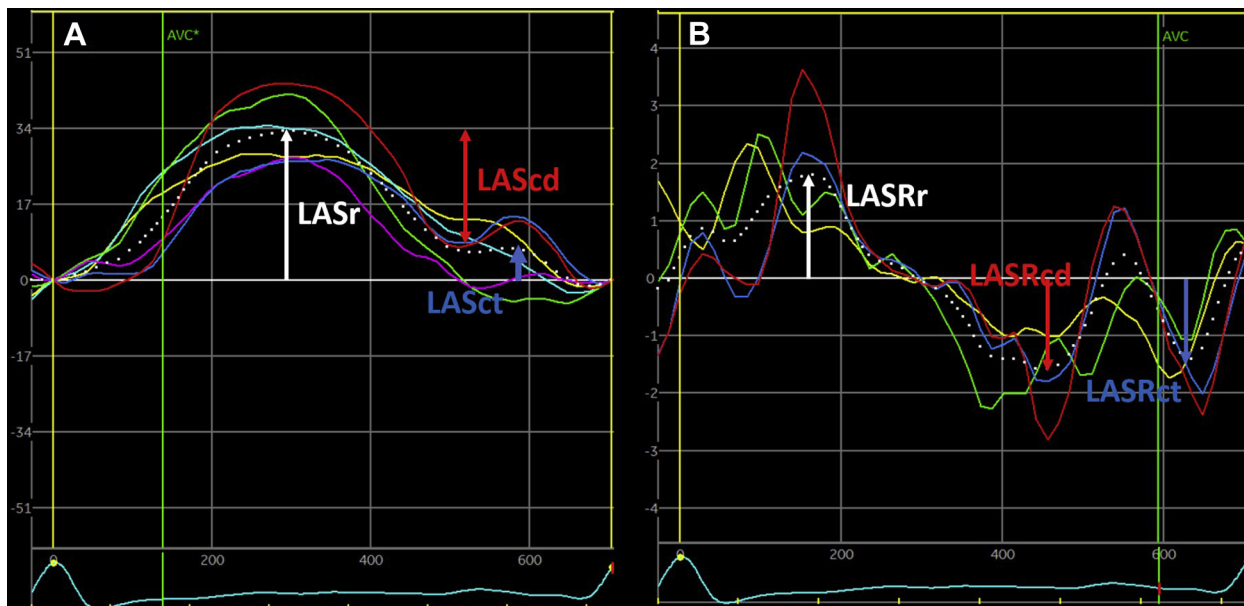
compared using the independent-sample Student's *t* test when normally distributed, whereas the Mann-Whitney *U* test was used to compare continuous variables that did not adhere to a normal distribution. The association between LASr and LASRr with the occurrence of the primary endpoint (new-onset AF) was assessed with fitted spline curves. The population was then divided in two groups based on the cutoff values of LASr and LASRr that were associated with an excess of new-onset AF (i.e., when the predicted hazard ratio [HR] was  $\geq 1$ ). Cumulative survival rates free of AF were calculated using the Kaplan-Meier method, and the log-rank test was used to compare groups. The association between clinical and echocardiographic variables and occurrence of new-onset AF was assessed using uni- and multivariable Cox proportional hazard regression models. Variables with a univariable value of  $P < .10$  were incorporated into the multivariable models. The HRs and 95% CIs were calculated and reported for each variable. The proportional hazards assumption was verified through the evaluation of Schoenfeld residuals. To incorporate nonlinearity in the fitted Cox regression models, as a sensitivity analysis, LASr and LASRr were entered as continuous variables according to the plateau regions of their respective fitted spline curves. To investigate the incremental value of LASr over LA volume index

(LAVI), a likelihood ratio test was performed. The change in global  $\chi^2$  values was calculated and reported. All tests were two sided, and  $P < .05$  were considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of the 259 patients with rheumatic MS, 125 patients met the study inclusion criteria (Supplemental Figure 1). Demographic and clinical characteristics of the overall study population are summarized in Table 1. The mean age of the population was  $50 \pm 15$  years, and 80.8% of the patients were female. A total of 23.9% of patients reported New York Heart Association functional class 3 or 4 heart failure symptoms, and 12% previously underwent percutaneous balloon mitral valvotomy. Table 2 summarizes the echocardiographic characteristics of the study population. Mitral valve peak and mean gradients were  $16.0 \pm 7.6$  mm Hg and  $8.3 \pm 4.9$  mm Hg, respectively. Mean MVA assessed by pressure half-time was  $1.8 \pm 0.8$  cm<sup>2</sup>; 40.2% had severe MS (MVA  $\leq 1.5$  cm<sup>2</sup>).

During a median follow-up of 32 (9.5-70) months, 41 patients (32.8%) developed new-onset AF. Patients who developed new-onset AF during follow-up were more likely to be male (34.1% vs 11.9%,  $P = .007$ ) and had smaller MVA ( $1.6 \pm 0.5$  cm<sup>2</sup> vs  $1.9 \pm 0.9$  cm<sup>2</sup>,  $P = .031$ ) and larger end-diastolic LV volume index ( $73$  [61-91] mL/m<sup>2</sup> vs  $65$  [51-82] mL/m<sup>2</sup>,  $P = .020$ ) compared with patients who remained in sinus rhythm. There were no significant differences in age, heart failure symptoms, treatment with percutaneous balloon valvotomy, MV mean gradient, or LV ejection fraction. When assessing echocardiographic measurements of LA size and function, patients who developed AF during follow-up had



**Figure 1** Assessment of LA strain (A) and LA strain rate (B). Panel A shows an LA strain curve providing two peaks: one peak just before MV opening, representing LASr, and one peak just before atrial contraction, representing LASct. The difference between these two peaks represents the LAScd. Panel B shows an LA strain rate curve providing three peaks: the positive peak representing LASRr, the early negative peak during early diastole representing LASRcd, and the second negative peak during late diastole, representing LASRct. Values are determined using the averaged longitudinal strain and strain rate curves (white dotted line).

**Table 1** Clinical and demographic characteristics

Variable	Total population (N = 125)	AF (n = 41)	No AF (n = 84)	P value
Age, years	50 ± 15	52 ± 14	49 ± 16	.348
Sex, female	101 (80.8)	27 (65.9)	74 (88.1)	.007
Caucasian	53 (46.1)	18 (45.0)	35 (46.7)	>.999
BMI, kg/m <sup>2</sup>	25.6 ± 4.8	25.9 ± 4.3	25.5 ± 5.0	.647
Hypertension	40 (32.8)	11 (26.8)	29 (35.8)	.415
Dyslipidemia	22 (18.3)	6 (14.6)	16 (20.3)	.620
DM	22 (18.3)	4 (9.8)	4 (4.9)	.440
CKD	25 (22.9)	9 (23.1)	16 (22.9)	.979
NYHA class ≥ 3	21 (23.9)	5 (18.5)	16 (26.2)	.598
Previous PBMV	15 (12)	3 (7.3)	12 (14.3)	.382
Beta blocker	50 (41.0)	16 (39.0)	34 (42.0)	.846
CCB	12 (9.8)	3 (7.3)	9 (11.1)	.749
ACEi or ARB	45 (36.9)	14 (34.1)	31 (38.3)	.695
Diuretic	37 (30.3)	12 (29.3)	25 (30.9)	>.999
Spirinolactone	6 (4.9)	1 (2.4)	5 (6.2)	.662
Oral anticoagulation	19 (15.6)	4 (9.8)	15 (18.5)	.292

Values are presented as mean ± SD or n (%).

ACEi, Angiotensin II converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease (defined as eGFR < 60 mL/minute/1.73 m<sup>2</sup>); DM, diabetes mellitus; NYHA, New York Heart Association; PBMV, percutaneous balloon mitral valvotomy.

**Table 2** Standard echocardiographic characteristics

Variable	Total population (N = 125)	AF (n = 41)	No AF (n = 84)	P value
Heart rate, bpm	77 ± 13	75 ± 12	77 ± 13	.343
MV peak gradient, mm Hg	16.0 ± 7.6	16.3 ± 7.5	15.8 ± 7.7	.733
MV mean gradient, mm Hg	8.3 ± 4.9	8.8 ± 5.6	8.1 ± 4.6	.475
MVA by planimetry, cm <sup>2</sup>	1.9 ± 0.8	1.7 ± 0.7	1.9 ± 0.8	.369
MVA by PHT, cm <sup>2</sup>	1.8 ± 0.8	1.6 ± 0.5	1.9 ± 0.9	.031
MVA by PHT ≤ 1.5 cm <sup>2</sup>	49 (40.2)	20 (48.8)	29 (35.8)	.178
Significant MR*	49 (39.2)	15 (36.6)	34 (40.5)	.701
IVS end-diastolic thickness, mm	10.0 ± 2.6	10.2 ± 2.3	9.9 ± 2.7	.543
LV PW end-diastolic thickness, mm	9.8 ± 3.1	10.0 ± 2.2	9.7 ± 3.4	.587
LV end-diastolic diameter, mm	48.9 ± 6.6	50.0 ± 6.9	48.3 ± 6.3	.185
LV end-systolic diameter, mm	34.2 ± 7.9	34.2 ± 8.3	34.3 ± 7.7	.953
LV EDV index, mL/m <sup>2</sup>	67 (55-85)	73 (61-91)	65 (51-82)	.020
LV ESV index, mL/m <sup>2</sup>	28 (21-37)	31 (24-44)	28 (19-35)	.063
LV EF, %	57 ± 10	56 ± 9	57 ± 11	.594
Stroke volume index, mL/m <sup>2</sup>	39 ± 10	39 ± 9	39 ± 11	.910
Pulmonary arterial systolic pressure, mm Hg	35.5 (30.0-46.3)	36.5 (25.8-52.8)	35.0 (30.0-45.8)	.632
RV EDA, cm <sup>2</sup>	19.1 ± 3.8	20.0 ± 4.2	18.8 ± 3.5	.107
RV ESA, cm <sup>2</sup>	11.8 ± 3.2	12.6 ± 4.1	11.5 ± 2.7	.113
TAPSE, mm	22.9 ± 4.1	22.0 ± 4.1	23.4 ± 4.0	.068

Values are presented as mean ± SD, median (interquartile range), or n (%).

EDA, End-diastolic area; EDV, end-diastolic volume; EF, ejection fraction; ESA, end-systolic area; ESV, end-systolic volume; IVS, interventricular septum; LV, left ventricle; MR, mitral regurgitation; PHT, pressure half-time; PW, posterior wall; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

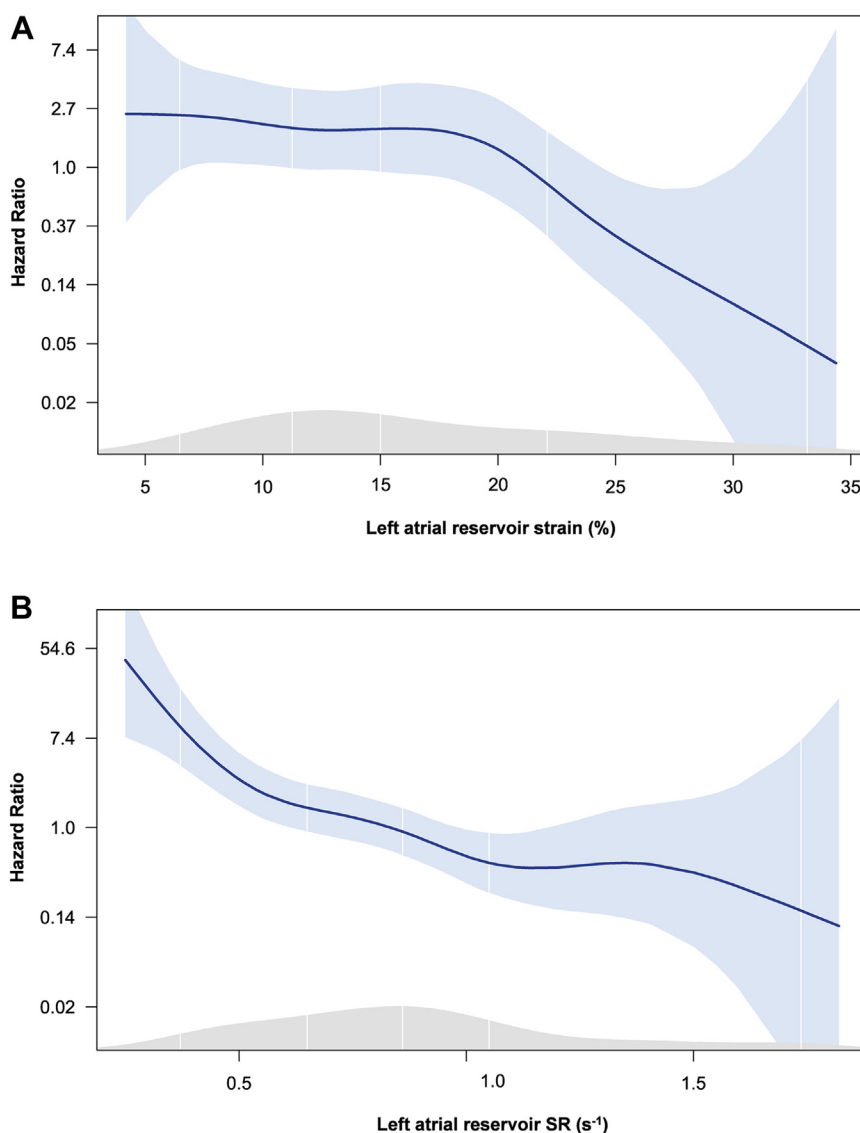
\*Defined as moderate or severe MR.

**Table 3** Echocardiographic measurements of LA size and function

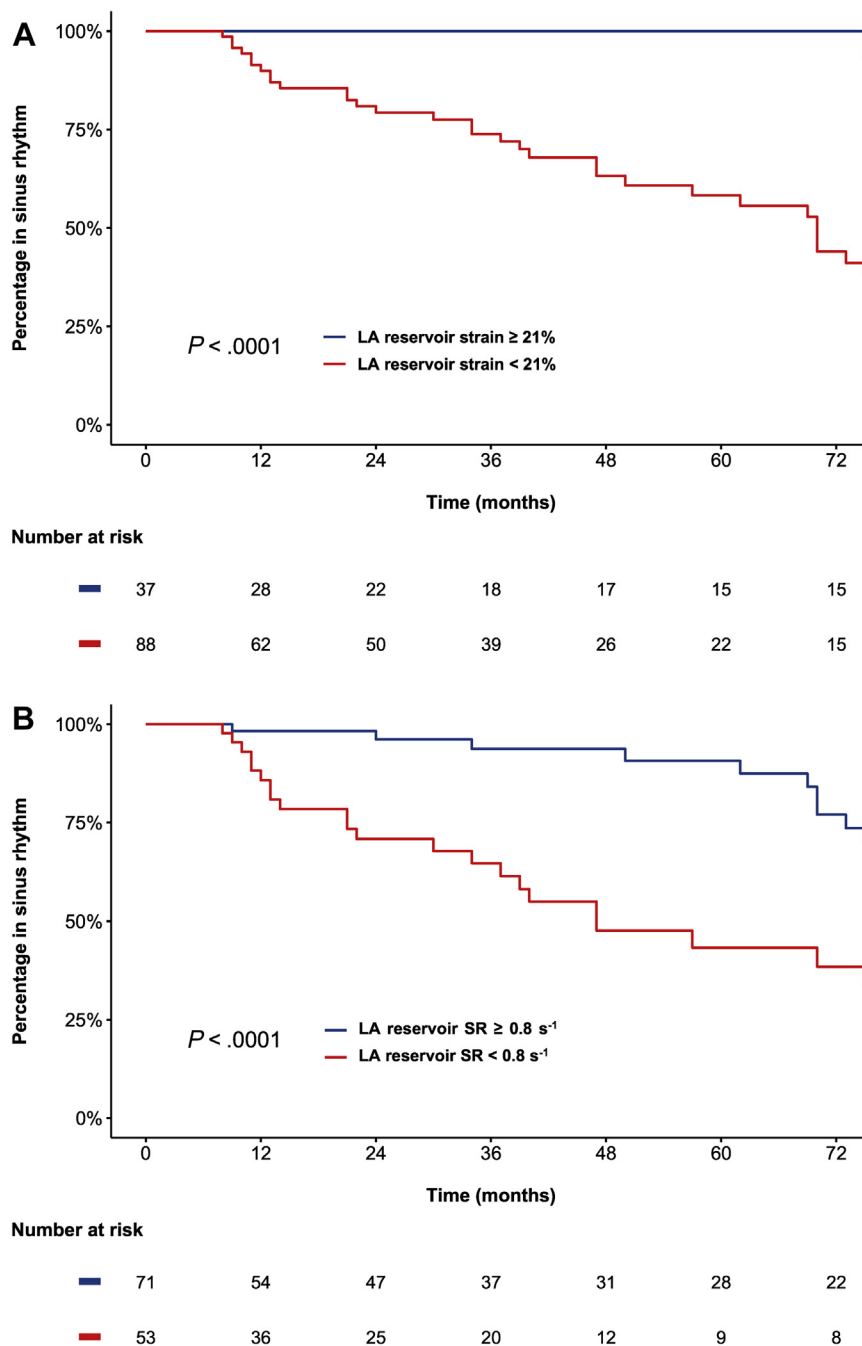
Variable	Total population (N = 125)	AF (n = 41)	No AF (n = 84)	P value
LAVI max, mL/m <sup>2</sup>	59 ± 28	129 ± 61	92 ± 35	.001
LAVI min, mL/m <sup>2</sup>	43 ± 24	55 ± 31	37 ± 18	<.001
LAEF, %	26.4 ± 20.1	22.4 ± 21.3	28.3 ± 19.4	.132
LASr, %	17.1 ± 7.8	13.4 ± 5.2	18.9 ± 8.2	<.001
LAScd, %	-9.6 ± 5.4	-7.6 ± 3.6	-10.6 ± 5.9	.001
LASct, %	-8.1 ± 4.3	-6.5 ± 4.3	-8.8 ± 4.2	.01
LASRr, s <sup>-1</sup>	0.89 ± 0.35	0.72 ± 0.26	0.98 ± 0.36	<.001
LASRcd, s <sup>-1</sup>	-0.58 ± 0.38	-0.45 ± 0.21	-0.65 ± 0.43	.001
LASRct, s <sup>-1</sup>	-0.86 ± 0.22	-0.65 ± 0.38	-0.95 ± 0.48	.001

Values are presented as mean ± SD.

LAEF, LA ejection fraction.



**Figure 2** Spline curves demonstrating the HR for the occurrence of AF at follow-up according to LASr (**A**) and LASRr (**B**). The curve in panel A shows the HR change for occurrence of AF at follow-up with 95% CIs (shaded blue areas) across a range of values of LASr at the time of the index echocardiogram. The curve in panel B shows the HR change for occurrence of AF at follow-up with 95% CIs (shaded blue areas) across a range of values of LASRr at the time of the index echocardiogram.



**Figure 3** Kaplan-Meier curves for occurrence of AF according to LASr (A) and LASRr (B). The Kaplan-Meier curves demonstrate the lower AF free survival rates at follow-up for patients with LASr  $< 21\%$  (A) and LASRr  $< 0.8 \text{ s}^{-1}$  (B).

a larger LAVI ( $129 \pm 61 \text{ mL/m}^2$  vs  $92 \pm 5 \text{ mL/m}^2$ ,  $P = .001$ ) and significantly more impaired LASr ( $13.4\% \pm 5.2\%$  vs  $18.9\% \pm 8.2\%$ ,  $P < .001$ ) and LASRr ( $0.72 \pm 0.26 \text{ s}^{-1}$  vs  $0.98 \pm 0.36 \text{ s}^{-1}$ ,  $P < .001$ ) compared with patients who did not present with new-onset AF (Table 3).

#### Association between LASr and LASRr and New-Onset AF

Based on spline curve analysis, decreasing values of LASr and LASRr were associated with increasing HR of new-onset AF (Figure 2). Left atrial reservoir strain  $< 21\%$  and LASRr  $< 0.8 \text{ s}^{-1}$  were associated with an excess risk of new-onset AF and were used to divide the

population. On Kaplan-Meier analysis, patients with an LASr  $< 21\%$  had a significant reduction in event-free survival for the occurrence of new-onset AF at follow-up compared with their counterparts (73.9% vs 100%, respectively, at 3 years of follow-up,  $P < .001$ ; Figure 3A). Likewise, patients with an LASRr  $< 0.8 \text{ s}^{-1}$  showed a significantly reduced event-free survival compared with patients with an LASRr  $\geq 0.8 \text{ s}^{-1}$  (65.5% vs 93.6%, respectively, at 3 years of follow-up,  $P < .001$ ; Figure 3B).

On univariate analysis, age, sex, MVA by pressure half-time, LV end-diastolic volume, LAVI, LASr, and LASRr were significantly associated with the occurrence of new-onset AF (Table 4). Subsequently, several multivariable models were constructed with a maximum of



**Table 4** Univariable Cox proportional hazard models for occurrence of AF at follow-up

	Univariable analysis	
	HR (95% CI)	P value
Clinical and demographic characteristics		
Age	1.043 (1.018-1.068)	.001
Sex, female	0.503 (0.261-0.970)	.040
BMI	1.040 (0.965-1.120)	.307
Hypertension	1.002 (0.497-2.017)	.997
Dyslipidemia	1.219 (0.505-2.947)	.660
DM	1.298 (0.772-2.182)	.325
Echocardiographic characteristics		
MV mean gradient	1.045 (0.976-1.119)	.210
MVA by PHT	0.550 (0.277-1.095)	.089
LV EDV	1.007 (1.001-1.012)	.016
LV EF	0.993 (0.958-1.029)	.696
Echocardiographic measurements of LA size and function		
LAVI	1.007 (1.000-1.015)	.065
LASr	0.911 (0.866-0.958)	<.001
LASRr	0.036 (0.008-0.156)	<.001
LASr < 21%	8.204 (2.514-26.774)	<.001
LASRr < 0.8 s <sup>-1</sup>	3.473 (1.806-6.676)	<.001

BMI, Body mass index; DM, diabetes mellitus; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricle; PHT, pressure half-time.

four variables incorporated to avoid overfitting. Multivariable Cox regression analyses showed that, after adjusting for age, LAVI and LV end-diastolic volume, LASr < 21% and LASRr < 0.8 s<sup>-1</sup> remained significantly associated with the occurrence of AF at follow-up after adjusting for age, LAVI and LV end-diastolic volume (HR = 7.030; 95% CI, 2.079-23.771; *P* = .002 for LASr < 21%; and HR = 3.417, 95% CI, 1.591-7.339; *P* = .002 for LASRr < 0.8 s<sup>-1</sup>; Table 5). In a sensitivity analysis, these findings were confirmed using a second multivariable model adjusting for age, sex, and MVA (Table 5).

The models with LASr and LASRr as continuous variables can be found in Supplemental Table 1. Models with LASr and LASRr as continuous variables, accounting for the plateau regions of each fitted spline curve (Figure 2A and 2B), can be found in Supplemental Table 2.

To determine the incremental prognostic value of LASr over LA volume, a likelihood ratio test was performed. The addition of LASr to a baseline model with LAVI showed a significant increase in the  $\chi^2$  value ( $\chi^2$  difference = 14.1, *P* < .001), demonstrating the incremental prognostic value of LASr in patients with rheumatic MS.

## DISCUSSION

The main findings of this study can be summarized as follows: (1) LASr and LASRr are independently associated with the development of AF during follow-up in patients with rheumatic MS, and (2) patients with an LASr < 21% and LASRr < 0.8 s<sup>-1</sup> show a significant reduction in event-free survival for the occurrence of new-onset AF at follow-up.

### Pathophysiology of AF in Patients with MS

In MS, the combination of an increase in LA pressure and an intense atrial inflammatory response secondary to the underlying rheumatic carditis is accompanied by a progressive increase in interstitial fibrosis of the atrial wall with disorganization of atrial muscle bundles, LA dysfunction, and eventually LA dilatation.<sup>21,22</sup> Atrial remodeling alters atrial electrical properties, enhancing the risk of AF development.<sup>23</sup> New-onset AF is associated with poor outcomes in patients with rheumatic MS since AF may further impair LA function and abruptly increase LA pressures that lead to pulmonary edema,

**Table 5** Multivariable Cox proportional hazard models for occurrence of AF at follow-up

	Multivariable analysis adjusting for age, LAVI, and LVEDV		Multivariable analysis adjusting for age, sex, and MVA by PHT	
	HR (95% CI)	P value	HR (95% CI)	P value
LASr < 21%	7.030 (2.079-23.771)	.002	8.588 (2.507-29.424)	.001
LASRr < 0.8 s <sup>-1</sup>	3.417 (1.591-7.339)	.002	3.273 (1.648-6.501)	.001

LVEDV, LV end-diastolic volume; PHT, pressure half-time.

pulmonary hypertension, and eventually right ventricle dysfunction. The pathophysiology of MS differs from most other valvular diseases, as it typically causes an isolated increase in LA afterload with much less impact on the left ventricle. Therefore, it seems essential to assess the LA dimension and function to improve risk stratification and optimize the timing of intervention in these patients. Although previous studies have demonstrated the relationship between LA size and AF occurrence,<sup>24-26</sup> LA dysfunction may represent an earlier stage of LA remodeling than LA dilation alone.<sup>27,28</sup> Moreover, LASr more accurately reflects dynamic LV filling pressures, whereas LA size reflects the chronic effects of LV filling pressures over time.<sup>29</sup> Left atrial reservoir function also correlates better with LA fibrosis and compliance than LA conduit and contractile function do since these functions are also influenced by LV relaxation and intrinsic atrial contractility, respectively. Finally, as the extent of atrial fibrosis quantified by late gadolinium enhancement on cardiac magnetic resonance imaging correlates well with LASr measured by speckle-tracking echocardiography,<sup>9</sup> LASr could be a good surrogate of atrial fibrosis and could therefore be useful in the risk stratification of patients with rheumatic MS.

### Risk Assessment of AF in Patients with Rheumatic MS

As AF is the most prevalent arrhythmia with a significant health and socioeconomic impact, increasing attention has been given to the development of prediction models for assessing the risk of new-onset AF, both for the general population and for subgroups of patients with an underlying cardiovascular disease.<sup>30</sup> Previous studies have demonstrated that LASr is associated with the development of AF after cryptogenic stroke or catheter ablation and in patients with heart failure.<sup>10-12</sup> The results in the current study demonstrate that impaired values of LASr and LASRr are also associated with an increased risk of developing AF at follow-up in patients with rheumatic MS. In addition,  $\text{LASr} < 21\%$  and  $\text{LASRr} < 0.8 \text{ s}^{-1}$  are independently associated with incident AF at follow-up. Interestingly, none of the patients with an  $\text{LASr} \geq 21\%$  developed AF during the first 5 years of follow-up. In another study including 101 asymptomatic patients with mild or moderate rheumatic MS followed up for 4 years, Ancona *et al.*<sup>31</sup> demonstrated that assessment of LA strain was more accurate than other clinical and echocardiographic parameters for predicting the development of new-onset AF. Patients with asymptomatic MS and an  $\text{LASr} > 17.4\%$  showed a reduced incidence of new-onset AF compared with those with an  $\text{LASr} \leq 17.4\%$ . In a 5-year follow-up study of 81 asymptomatic patients with mild or moderate rheumatic MS, Candan *et al.*<sup>32</sup> demonstrated similar results, defining  $\text{LASr} < 16.5\%$  as an optimal cutoff value to predict new-onset AF. Differences in patient populations may explain the different reported cutoff values of LASr associated with new-onset AF.

### Clinical Implications

The global burden of RHD remains significant, and 80% of strokes in patients with RHD occur in patients with rheumatic MS and AF.<sup>7</sup> It is estimated that approximately 30%-40% of patients with symptomatic MS develop AF,<sup>4</sup> which is in accordance with the results of our study, where 32.8% of patients developed AF during a median follow-up of 32 months. The presence of AF in patients with rheumatic MS is associated with a poor prognosis, due to an association with an increased risk of thromboembolic events, heart failure, and premature death, even after valve intervention.<sup>5,6,33</sup> Therefore, strategies for reducing the incidence of AF in these patients are needed but

complicated by the fact that RHD is largely limited to populations with little access to primary health care. Echocardiography is an accessible imaging technique that, according to the results of this study, may help to timely identify patients with rheumatic MS at risk of developing AF and who therefore need closer follow-up. In this regard, assessment of LASr may clinically be more comprehensive than assessment of LASRr. The strength of our study is the identification of a subgroup of patients who have a very low risk of developing AF during the first years of follow-up (none of the patients with an  $\text{LASr} \geq 21\%$  developed AF during the first 5 years of follow-up) and in whom the need for anticoagulant treatments can be delayed, whereas the group with an increased risk of developing AF needs close monitoring to implement timely anticoagulant therapy.

Other echocardiographic methods to assess LA function (such as LA expansion index) may also identify patients at risk of developing AF.<sup>34,35</sup> However, the prognostic value of these novel measurements of LA function have not been investigated in patients with rheumatic MS and therefore requires further research.

### Limitations

This study is subject to the limitations of its retrospective, single-center, observational design. A time span of 20 years was used to retrospectively identify patients to acquire the large cohort as presented. Images were not recorded specifically for assessment of LA function (in terms of orientation, depth, gain, and frame rate), potentially influencing the results. In addition, although comprehensive follow-up for new-onset AF was performed, without continuous ECG monitoring it is possible to have missed the development of cases of asymptomatic AF during follow-up. However, because diastolic filling time is significantly reduced with new-onset AF, it is unlikely that many patients with significant MS would have remained asymptomatic. Finally, although this is the largest study on this topic in current literature, the small sample size does limit the power of our conclusions. Larger studies are therefore needed to confirm our data.

### CONCLUSION

Left atrial strain is abnormal in patients with rheumatic MS, and the degree of impairment is associated with the development of AF at follow-up.

### SUPPLEMENTARY DATA

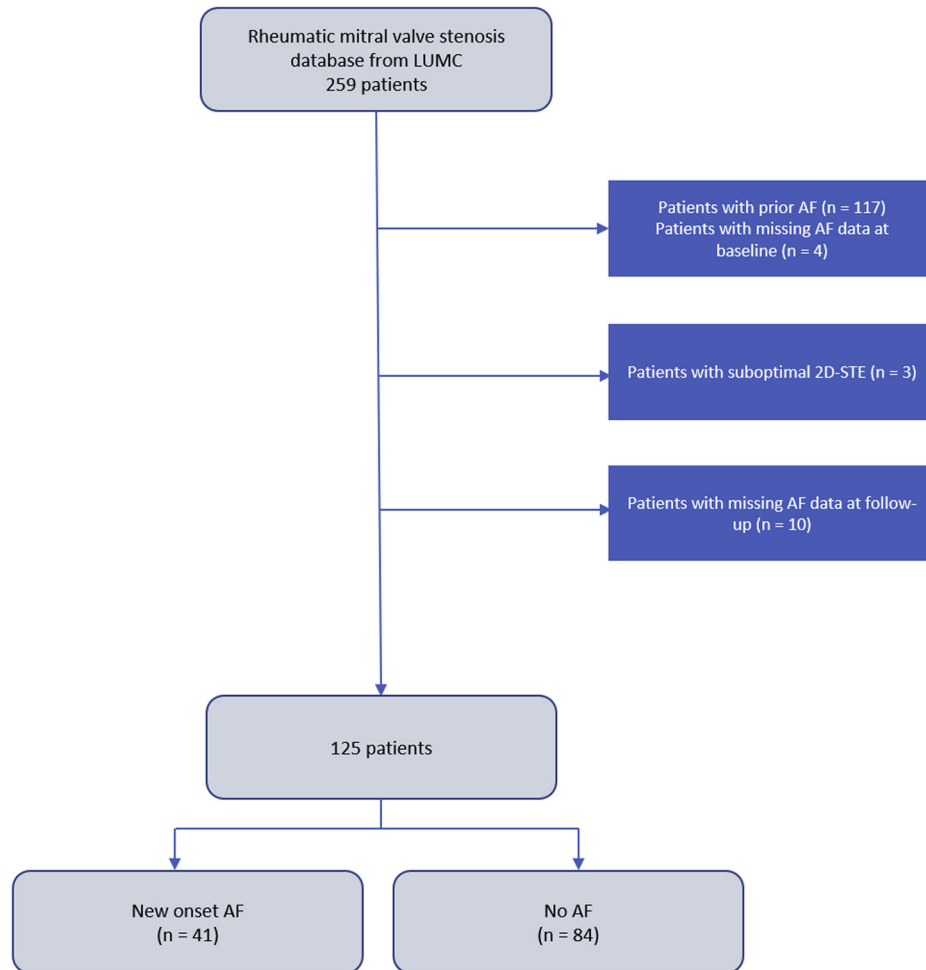
Supplementary data related to this article can be found at <https://doi.org/10.1016/j.echo.2021.12.010>.

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**Supplemental Figure 1** Study flow chart. *2D-STE*, Two-dimensional speckle-tracking echocardiography; *LUMC*, Leiden University Medical Center.

**Supplemental Table 1** Multivariable Cox proportional hazard models for occurrence of AF at follow-up with LASr and LASRr entered as continuous variables

	Multivariable analysis adjusting for age, LAVI, and LVEDV		Multivariable analysis adjusting for age, sex, and MVA	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
LASr	0.894 (0.837-0.955)	.001	0.918 (0.872-0.967)	.001
LASRr	0.066 (0.013-0.329)	.001	0.052 (0.012-0.224)	<.001

LVEDV, LV end-diastolic volume; PHT, pressure half-time.

**Supplemental Table 2** Multivariable Cox proportional hazard models for occurrence of AF at follow-up with LASr and LASRr entered as continuous variables, accounting for nonlinearity

	Multivariable analysis adjusting for age, LAVI, and LVEDV		Multivariable analysis adjusting for age, sex, and MVA	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
LASr, per %, above 18%*	0.702 (0.552-0.894)	.004	0.685 (0.542-0.865)	.002
LASRr, per s <sup>-1</sup> , up to 1.1 s <sup>-1</sup> *	0.031 (0.005-0.185)	<.001	0.027 (0.005-0.137)	<.001

LVEDV, LV end-diastolic volume; PHT, pressure half-time.

\*To incorporate nonlinearity in the fitted Cox regression models, both LASr and LASRr were treated as continuous variables while accounting for the plateau regions of each fitted spline curve (Figure 2A and 2B, extending from <18% for values of LASr and >1.1 s<sup>-1</sup> for values of LASRr, respectively). For LASr, the HR was estimated per %, above values of LASr of 18%. Likewise, the HR for LASRr was estimated per s<sup>-1</sup>, up to a maximum of 1.1 s<sup>-1</sup>.