


# Increased Left Atrial Stiffness is Significantly Associated with Paroxysmal Atrial Fibrillation in Diabetic Patients

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**Purpose:** Atrial fibrillation (AF) and diabetes mellitus (DM) are common pathogenic diseases. Diabetes is an independent risk factor for AF, and coexisting AF is a risk factor for the diabetic patient's progression. The purpose of this study was to see if two-dimensional-speckle tracking echocardiography (2D-STE) might provide valuable criteria for determining the risk of AF in diabetic patients.

**Patients and Methods:** This retrospective study compared 30 adult diabetic patients with documented paroxysmal atrial fibrillation (PAF) with 30 age- and sex-matched diabetic patients without PAF. Inclusion criteria were: age  $\geq 18$  years, sinus rhythm, diabetes mellitus type 2, and the ability to sign the informed consent. Exclusion criteria included: moderate or severe valvular disease, previous myocardial infarction, left ventricular ejection fraction (LVEF)  $< 50\%$ , congenital heart disease, a history of cardiac surgery, paced atrial or ventricular rhythm, inadequate echocardiography imaging. The medical history, clinical, biochemical data and the results of the transthoracic cardiac ultrasound examination were registered during their evaluation at the outpatients cardiology clinics.

**Results:** The mean age of the patients was  $62.5 \pm 1.7$  years, 60% were men. Diabetic patients who experienced PAF episodes demonstrated significantly impaired left atrial (LA) deformation patterns, with decreased LA strains and increased LA stiffness ( $p < 0.05$ ).

**Conclusion:** The present study demonstrates that LA strains and LA stiffness are significantly associated with the occurrence of PAF in diabetic patients. As 2D-STE of the LA is more sensitive than routine echocardiographic examination, it should be performed in patients suspected of being suffering from PAF.

**Keywords:** diabetes mellitus, paroxysmal atrial fibrillation, 2D-speckle tracking echography, left atrial strains, left atrial stiffness

## Introduction

With a current incidence of 2–4%, atrial fibrillation (AF) is the most prevalent persistent cardiac arrhythmia in people around the world.<sup>1</sup> It is expected that one in every three Europeans over the age of 55 will have this disorder.<sup>2</sup> AF patients have a 5-fold risk of having a stroke, a higher prevalence of heart failure, and a higher death rate.<sup>3</sup>

AF is frequent in patients with type 2 diabetes, with a prevalence rate estimated to be at least twice compared to nondiabetic individuals.<sup>4</sup> Diabetes mellitus (DM) has been linked to an increased risk of cardiovascular disease and, when this condition is present, it doubles the chance of a fatal event.<sup>5</sup> Diabetes, independent of hypertension or diastolic function, is also associated with an increase in the size of the left atrium (LA); it also induces sympathetic and parasympathetic denervation of the latter.<sup>1</sup>

AF prevalence is approximately three times greater in diabetic patients with hypertension, than in AF patients with either diabetes or hypertension.<sup>6</sup>

There is disagreement over whether type 2 diabetes is an independent risk factor for AF.<sup>4,7,8</sup> Several studies, however, have found a link between type 2 diabetes and atrial fibrillation.<sup>5,9</sup> Furthermore, diabetes is one of the risk factors included in the CHA2DS2-VASc-score risk stratification scheme.<sup>10</sup>

LA size is recognized to be a useful predictor of paroxysmal atrial fibrillation (PAF) in the general population as well as in patients with a variety of pathologies.<sup>11,12</sup> Atrial dilatation does not discriminate between valvular and non-valvular AF since it also occurs in left ventricular diastolic failure and arterial hypertension. Nevertheless, PAF has been found in individuals with normal LA dimensions.<sup>13–15</sup> Recent studies have shown that LA function parameters surpass LA size measurements as a predictor of PAF, particularly when investigating deformation anomalies using two-dimensional speckle-tracking echocardiography (2D-STE).<sup>14–16</sup>

The purpose of this study was to see if LA 2D-STE might provide valuable parameters that are significantly linked with the occurrence of PAF in diabetic patients.

## Materials and Methods

### Patients' Selection

From December 2021 to December 2022, 600 Caucasian diabetic patients were referred from the diabetologist for cardiological evaluation at the outpatient's cardiology clinics of Timisoara Institute of Cardiovascular Diseases. Among them, 150 (40%) were referred for the evaluation of palpitations, with suspected PAF. The diabetic patients in whom PAF was documented were enrolled in the study group. Inclusion criteria in the study group were: age  $\geq 18$  years, sinus rhythm, diabetes mellitus type 2, documented PAF, and the ability to sign the informed consent. Exclusion criteria included: moderate or severe valvular disease, previous myocardial infarction, left ventricular ejection fraction (LVEF)  $< 50\%$ , congenital heart disease, a history of cardiac surgery, paced atrial or ventricular rhythm, inadequate echocardiography imaging. The control group consisted of age- and sex-matched diabetic adults without palpitations and without documented PAF, and also without any of the exclusion criteria.

The medical history, clinical, biochemical data and the results of the 12-lead resting electrocardiogram, the 24 hours Holter ECG monitoring were performed during their evaluation at the outpatient's cardiology clinics, before the transthoracic cardiac ultrasound examination.

### Definition of Covariates

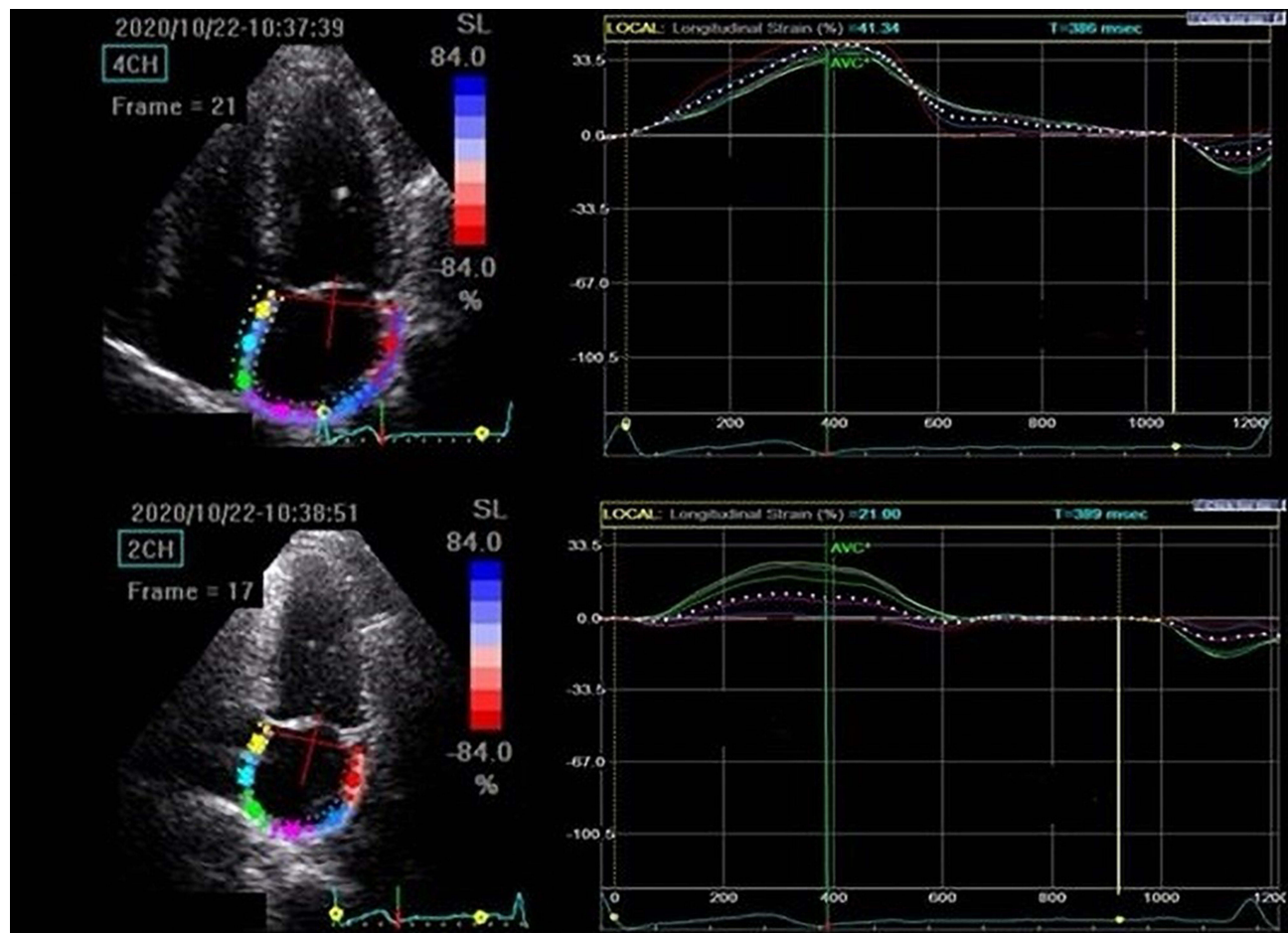
PAF was defined as an AF identified by a 12-lead standard resting electrocardiogram (ECG) or a 24-hour Holter ECG monitoring, with a minimal length of 30 seconds and a spontaneous or therapeutic termination within 7 days.<sup>17</sup> It was documented by reviewing medical records when at least one episode was reported at any point in the patient's history, during the hospitalization, or at the 1-month post-hospitalization assessment.

Diabetes mellitus and systemic arterial hypertension were defined according to the current European Society of Cardiology Guidelines.<sup>18,19</sup>

Heart failure with preserved ejection fraction (HFpEF) was identified in patients with signs or symptoms of heart failure, left ventricular (LV) ejection fraction  $\geq 50\%$  and NT-proBNP levels  $\geq 125$  pg/mL at sinus rhythm.<sup>20</sup>

### Echocardiography

Standard 2-dimensional transthoracic echocardiography (TTE) was performed in all patients according to the American Society of Echocardiography and the European Association Updated Guidelines of Cardiovascular Imaging.<sup>21</sup> A Vivid 5S (General Electric) echocardiograph with a 3.4 MHz transducer was used for standard TTE. The echographer modified machine parameters to improve endocardial and myocardial gray scale definition. The images were taken during an episode of end-expiratory breath-hold. We saved four cardiac cycle loops. The offline analysis was carried out with the help of the Echo PAC 201 software package from GE Healthcare. The LA di-iameter (LAD) was measured in the parasternal long-axis view at the end of systole. During end-ventricular systole, the maximal LA volume was determined using the bi-plane disk approach in apical 4 and apical 2-chamber views, as shown in Figure 1. We assessed the left ventricular end-systolic and end-diastolic volumes, as well as the left ventricular ejection fraction (LVEF), in all subjects.



**Figure 1** Two-dimensional speckle tracking ultrasound of the left atrium.

Mitral flow velocity (E) was measured using pulsed-wave Doppler from the apical 4 chamber view, with the sample volume positioned in diastole between the tips of the mitral leaflets. The peak flow velocities were averaged across five consecutive cardiac cycles.

The mitral annulus' early diastolic velocity (E') was measured using TDI. The E/E' ratio was used to calculate ventricular filling pressures.<sup>21</sup>

Using the offline 2D-STI approach, the maximal LA peak systolic longitudinal strain (LAS) was determined. The LA endocardium was automatically tracked during peak systole, which corresponded to the closing of the aortic valve. If the tracking of the LA endocardium was not acceptable, manual corrections were undertaken. In both 4 and 2 chamber perspectives, LAS was measured by splitting the LA wall into 6 regions. LAS was determined for all segments from the annulus to the LA's roof and then averaged. The peak LA-pool strain was assessed immediately before the mitral valve opened, and the peak LA-pump strain was measured right at the onset of the P wave. LA stiffness was calculated by dividing the E/A ratio by the peak LA-pool strain value. The peak LA-pool strain was measured just before the mitral valve opening, and the peak LA-pump strain just before the P wave. LA stiffness was estimated as the E/A value divided by the peak LA-pool strain.<sup>22,23</sup>

The echocardiographic measurements, including the LA assessment, were done by the same investigator with substantial echocardiography experience that was blinded to all other information and that performed all the echocardiographic evaluations, according to the common approach for the patients with PAF in the echocardiography laboratory.

## Ethics

All study participants gave written informed consent. The study was conducted in accordance with the requirements of the Helsinki Declaration and was authorized by the Ethics Committee of the “Victor Babeș” University of Medicine and Pharmacy Timișoara.

## Statistical Analysis

MedCalc statistical software for Windows, version 20.218, was used for statistical analysis (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2023). Chi square tests for categorical data and Student's t tests for continuous variables were applied to compare differences between study groups. Covariates considered for potential impact with PAF included obesity, smoking status, coronary artery disease, arterial hypertension, heart failure with preserved ejection fraction, dyslipidemia, glycated hemoglobin value, NT-proBNP levels, the CHA2DS2-VASc score, the conventional and two-dimensional echocardiography measurements of the left ventricle and left atrium, the duration of diabetes and the medication of the patients. For assessing the involvement of each variable in the studied outcomes, univariate and multivariate logistic regression models were established. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression models. Multivariate regression analysis with backward stepwise method was used for all parameters that were associated with the occurrence of PAF at univariate analysis. Receiver–operating characteristic (ROC) curves were utilized to determine the sensitivity and specificity of the analyzed parameters. The discrimination ability of the analyzed parameters was estimated by the area under the ROC curve (AUC). A p-value <0.05 was used as the statistical significance level.

## Results

### Characteristics of the Enrolled Subjects

PAF was documented in 35 subjects (5% of all examined patients with DM and 23% of those referred with the suspicion of PAF). Eight patients had to be excluded from the research, 5 from the study group and 3 from the control group, due to inadequate cardiac ultrasound images. Finally, the study and the control group consisted of 30 patients, with a mean age of  $62.5 \pm 1.7$  years, and 60% were males.

Table 1 shows the general clinical features of the recruited diabetic individuals. The diabetic patients with PAF received more frequent oral anticoagulation and anti-arrhythmic medication.

**Table 1** Baseline Clinical Characteristics of Diabetic Patients with and without Atrial Fibrillation

	Diabetes with PAF n = 30	Diabetes without PAF n = 30	P value
BMI (Kg/m <sup>2</sup> )	33.6 ± 5.2	31.8 ± 1.6	0.07
Obesity n (%)	7 (23)	5 (18)	0.63
CAD	20 (68)	17 (57)	0.38
HTN	25 (82)	23 (76)	0.57
HFpEF	13 (43)	12 (40)	0.81
History of stroke/TIA	1 (3)	0 (0)	0.27
Dyslipidemia	17 (56)	16 (53)	0.81
Smoking (current, %)	2 (9)	3 (10)	0.89
Systolic BP (mmHg)	143 ± 15	141 ± 16	0.61
Diastolic BP (mmHg)	85.4 ± 11	82.7 ± 9	0.30

(Continued)

Table 1 (Continued).

	Diabetes with PAF n = 30	Diabetes without PAF n = 30	P value
Heart rate (beats/min)	85.1±13	79.6±13	0.20
ABI	1.09±0.19	1.13±0.17	0.39
Total cholesterol (mg/dL)	174±40	183±62	0.50
HDL (mg/dL)	40.5 ± 10.2	44.0±14.7	0.28
LDL (mg/dL)	129.4±31	130.5±30	0.88
Triglyceride (mg/dL)	172.14±57	158.7±69	0.41
FPG (mg/dL)	153.6±50	161.1 ±61	0.50
HbA1c (%)	7.1±0.9	6.9±0.7	0.34
ASAT (U/L)	24±9	23±5	0.59
ALAT (U/L)	37±7	36±5	0.52
NT-proBNP (pg/mL)	412.2±248	344.0±266	0.24
eGFR	62.5±6	63.7±9	0.54
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score (mean ± 1 SD)	4.6±1.5	4.2±1.2	0.23
0–1	5 (17)	9 (31)	
≥2	25 (83)	21 (69)	0.20
LVEF	48.5±6.2	47.7±6.1	0.64
Duration of diabetes (years)	6.5±4	5.3±2	0.14
Diabetes treatment			
• Oral antidiabetic drugs	21 (70%)	19 (62%)	0.51
• Insulin	8 (25%)	10 (30%)	0.66
• SGLT2i	5 (18)	6 (21)	0.77
Statins	15 (60)	17 (57)	0.81
Beta blockers	24 (82)	24 (80)	0.84
ACE-i/ARB	48 (80)	23 (75)	0.64
CCB	10 (33)	12 (40)	0.57
Diuretics	16 (52)	14 (48)	0.75
ASA	5 (17)	16 (52)	<0.0001
Clopidogrel	15 (51)	14 (48)	0.81
Acenocumarol	30 (100)	0 (0)	<0.0001
Amiodarone	10 (32)	0 (0)	<0.001

**Notes:** The data is given as a mean, standard deviation, or number (percentage).

**Abbreviations:** ABI, ankle brachial index; ACEI, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ALAT, alanine amino transferase; ARB, angiotensin-1 receptor blockers; ASA, Aspirin; ASAT, aspartate amino-transferase; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CHA<sub>2</sub>DS<sub>2</sub>-VAsC, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, sex category (female); FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro- brain type natriuretic peptides; U, units; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TIA, transient ischemic attack.

## Echocardiography Results

The standard echography evaluations of the PAF- and non-PAF patients revealed no disparities in the echocardiographic assessment. However, the LA strain parameters differed significantly between the two groups. Diabetic patients who experienced PAF episodes demonstrated significantly impaired LA deformation patterns (lower strains and increased stiffness), as shown in Table 2 and Figure 2.

## Correlations Between Echocardiography Data and PAF

Both univariate and multivariate logistic regression analysis identified LA global strain, LA-pool strain, LA-pump strain and LA stiffness as independently associated with PAF in diabetic patients (Table 3). The comparison of the ROC curves for these parameters is shown in Figure 3 (LA global strain, AUC = 0.661, 95% CI 0.51–0.78; LA-pool strain, AUC = 0.669, 95% CI 0.56–0.8; LA-pump strain, AUC = 0.700, 95% CI 0.56–0.82; LA stiffness, AUC = 0.703, 95% CI 0.56–0.82).

The parameter that showed a strong positive correlation with PAF was LA stiffness ( $p = 0.005$ ). LAsf was also a strong independent parameter associated with the occurrence of PAF in diabetic patients, with a cut-off value of  $>0.48\%$  (AUC = 0.704, sensitivity 36.7%, specificity 100%,  $P = 0.004$ ), as shown in Figure 4.

## Discussion

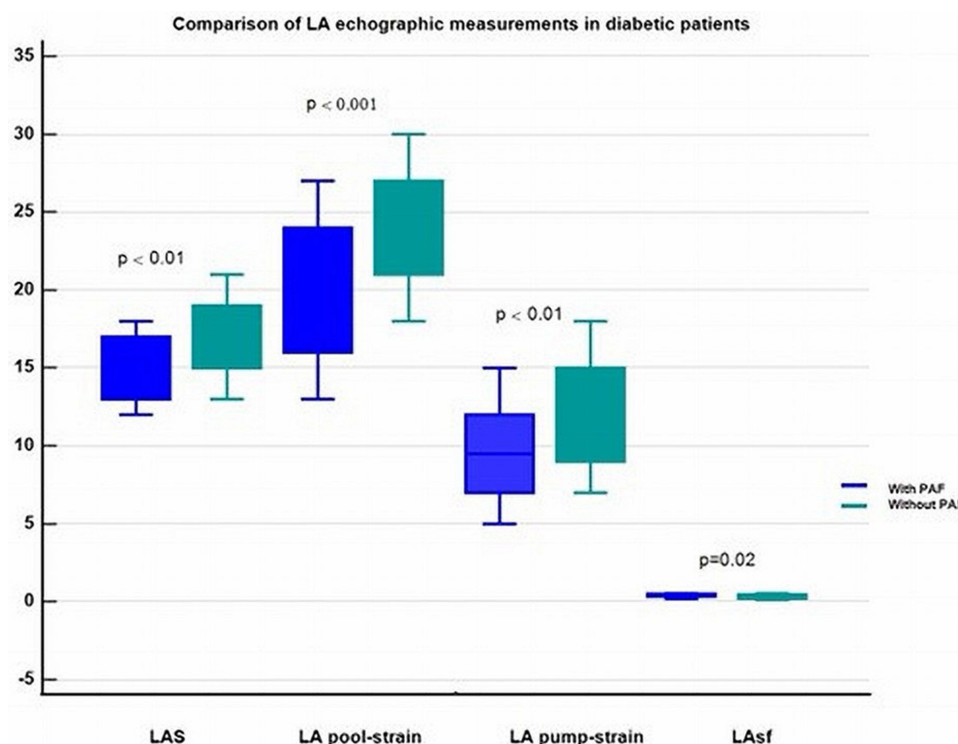
The hypothesis of this study was to verify whether left atrial 2D-speckle tracking echocardiography might predict the occurrence of paroxysmal atrial fibrillation in diabetic patients. This hypothesis was confirmed by our research that found that LA global strain, LA-pool strain, LA-pump strain and LA stiffness are independently associated with PAF in diabetic patients. A strong independent parameter associated with PAF in DM patients was LA stiffness, with a cut-off value  $>0.48\%$

**Table 2** Echocardiography Parameters in Diabetic Patients

	Diabetes with PAF n = 30	Diabetes without PAF n = 30	P value
LVEDV (mL)	97.8±21.0	102.5±17.9	0.34
LVESD (mL)	46.1 ± 10.2	49.3±12.6	0.28
LVMI (g/m <sup>2</sup> )	143 ± 41	139 ± 35	0.68
LVEF (%)	57 ± 2	60 ± 14	0.25
Mitral E/A-ratio	1.3 ± 0.4	1.2 ± 0.2	0.22
Septal E/E' average ratio	13.9 ± 4.2	13.1 ± 3.6	0.43
TAPSE (cm)	2.5 ± 0.43	2.4 ± 0.49	0.40
GLS (%)	−14.4 ± 3.1	−15.2 ± 3.2	0.32
LAVI (mL/m <sup>2</sup> )	42.1 ± 9.3	43.5 ± 10.3	0.58
LAEF (%)	47.7 ± 4.7	49.7 ± 5.9	0.15
LA global strain (%)	14.9 ± 1.9	16.8 ± 2.5	<0.01
LA-pool strain (%)	20.0 ± 4.3	23.8 ± 3.6	<0.001
LA- pump strain (%)	9.6 ± 3.0	12.3 ± 3.4	<0.01
LAsf (%)	0.42±0.09	0.35±0.11	0.02

**Abbreviations:** LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volumes; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; E, peak transmitral early diastolic inflow; A, peak transmitral late diastolic inflow; TAPSE, tricuspid annular plane systolic excursion, GLS, global longitudinal strain, LA, left atrium; LAVI, indexed left atrial volume; LAEF, left atrial total emptying fraction; LAsf, left atrial stiffness.





**Figure 2** Comparison of left atrial echocardiographic measurements in diabetic patients with and without paroxysmal atrial fibrillation.

**Abbreviations:** LA, left atrium; PAF, paroxysmal atrial fibrillation; LAS, left atrial global strain; LAsf, left atrial stiffness.

( $p = 0.004$ ). These results have important practical value, as they allow the early identification of diabetic patients that are at high risk for AF.

Holter-monitoring is commonly used for identifying PAF. Its efficiency is limited, as this arrhythmia is sporadic and frequently not recognized by the patients. Long-term monitoring by insertable loop recorders represents a more efficient method, but it is invasive and expensive and cannot be achieved in all patients.

Ischemic strokes caused by AF are typically severe, recurring, and followed by fatal outcomes or permanent disabilities. Anticoagulation therapy is advised as soon as AF is discovered, regardless of the length of the arrhythmia.<sup>17</sup> If the heart rate in patients with AF is not well controlled, tachy-cardiomyopathy and heart failure may develop, both with high morbidity and mortality rates.<sup>24</sup>

In cardiology, atrial fibrillation (AF) and diabetes mellitus (DM) are frequently associated. About 15% of persons with diabetes mellitus develop AF, and about 30% of AF episodes occur in diabetic patients.<sup>25</sup>

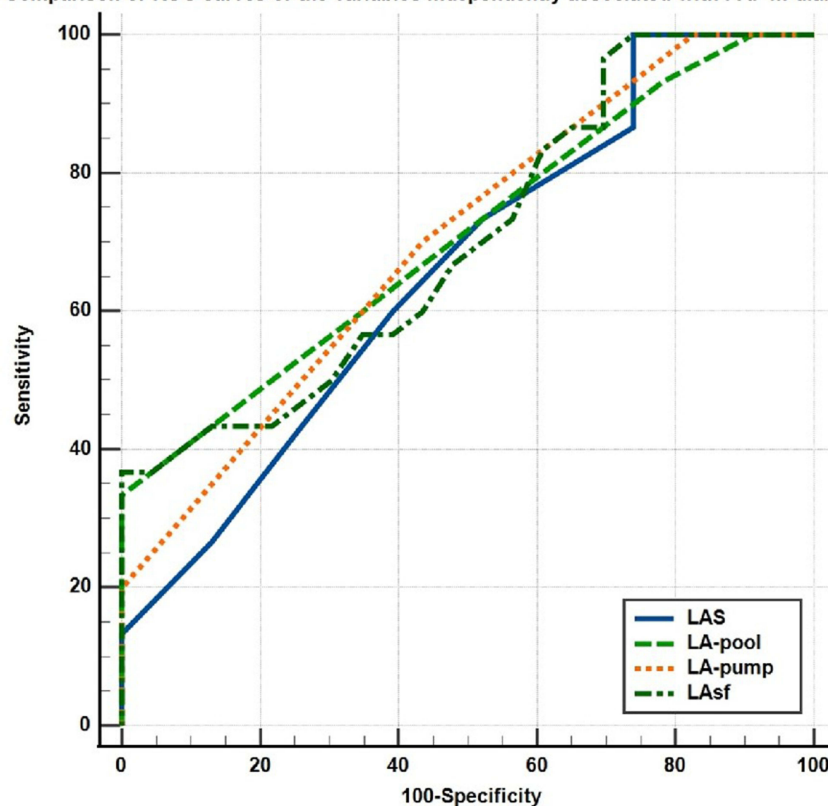
Several studies found that diabetes, particularly type 2 diabetes, is an independent risk factor for the occurrence of AF and that coexisting AF is a comorbidity and a risk factor for the diabetic patient's unfavorable outcome.<sup>5,9</sup> Diabetes can operate as

**Table 3** Predictors of Paroxysmal Atrial Fibrillation in Diabetic Patients

Parameter	Univariate Analysis OR (95% CI)	P value	Multivariate Analysis OR (95% CI)	P value
LAS	0.73 (0.56–0.96)	0.02	0.58 (0.37–0.92)	0.02
LA-pool strain	0.78 (0.64–0.94)	<0.01	0.74 (0.58–1.95)	0.018
LA- pump strain	0.78 (0.64–0.94)	<0.01	0.68 (0.50–0.94)	0.019
LAsf	0.73 (0.56–0.96)	0.01	5.2 (4.05–7.17)	0.007

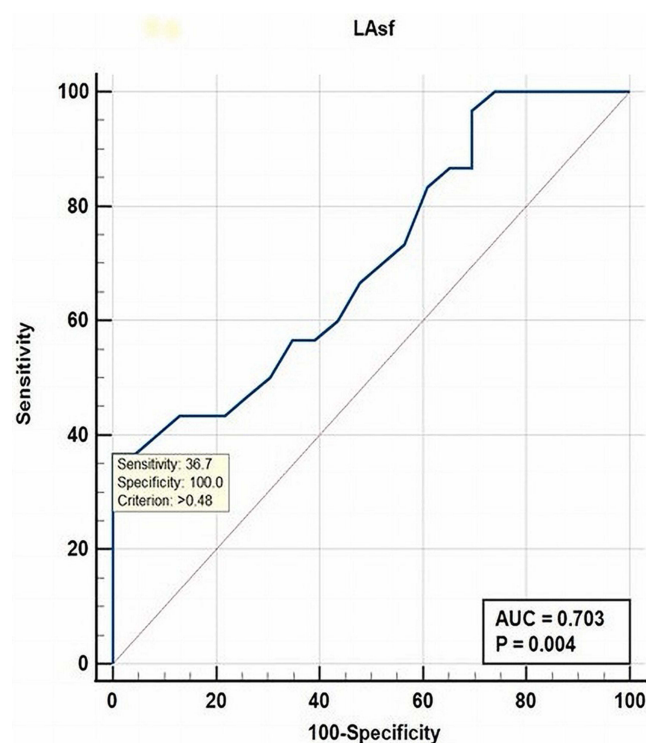
**Abbreviations:** OR, Odds ratio; CI, confidence interval; LAS, left atrial global strain; LAsf, left atrial stiffness.

Comparison of ROC curves of the variables independently associated with PAF in diabetic patients



**Figure 3** Comparison of the ROC curves of LA strain parameters associated with PAF in diabetic patients.

**Abbreviations:** ROC, receiver operating curve; LA, left atrial; LAS, left atrial global strain; PAF, paroxysmal atrial fibrillation.



**Figure 4** ROC curve analysis for LAsf as independent predictor of PAF in diabetic patients.

**Abbreviations:** ROC, receiver operating curve; AUC, area under the curve; LAsf, left atrial stiffness; PAF, paroxysmal atrial fibrillation.



a metabolic determinant at the cell level, alone or in conjunction with other risk factors/comorbidities (hypertension, heart failure, coronary artery disease) that are also implicated in atrial remodeling and generation of atrial tachyarrhythmias. It is recognized that cardiovascular problems are the most serious diabetes-linked complications and the leading cause of death in DM. There are evidences indicating a variety of alterations in diabetic hearts, including interstitial fibrosis of the myocardium, hypertrophy and apoptosis of the cardiomyocytes.<sup>26,27</sup> It has also been proven that functional remodeling occurs prior to structural remodeling, resulting in heart chamber dilatation. The final pathogenic and the underlying mechanism for the occurrence and maintenance of atrial fibrillation is LA remodeling that implies three interdependent forms in diabetes (mechanical, electrical, and neurogenic autonomous).<sup>28</sup>

Our study compared clinical, laboratory, and echocardiographic data in diabetic adults with and without PAF. While clinical, biochemical and conventional echocardiographic parameters such as LA and LV diameters, volumes, and ejection fractions did not differ significantly between the groups, the 2D-STI indicated more frequently aberrant LA deformation patterns in those with PAF. We found a significant association between reduced LA strains and increased LA stiffness and the presence of PAF in diabetic patients. In a previous study, the pattern of myocardial deformation was significantly linked to the degree of myocardial fibrosis as evaluated by cardiac magnetic resonance imaging or on clinicopathologic specimens.<sup>29</sup>

There were several hypotheses that showed mechanisms of type 2 diabetes mellitus influences on LA structure and function.<sup>30,31</sup> First, sustained hyperglycemia induces interstitial fibrosis not only in the LV but also in LA. Second, hyperglycemia is related to enhanced pro-fibrotic signaling molecules that provoke collagen synthesis by cardiac fibroblasts implying that these factors can promote atrial fibrosis in DM.<sup>32,33</sup> In addition, LA stiffness, which is related to LA reservoir function and LV filling pressure, increases with LA remodeling and is recognized as a further indicator of LA performance.<sup>34</sup> Khurram et al reported that LA stiffness is a strong independent predictor AF recurrence after ablation.<sup>35</sup> Additionally, several studies revealed that LA stiffness is associated with poor clinical outcomes in patients with heart failure and reduced ejection fraction.<sup>36,37</sup>

## Limitations of the Study

There are various limitations to our research. This is a retrospective observational study conducted at a single cardiology center with a small number of patients and a single echocardiographer that performed all blinded echocardiographic measurements. We did not determine GAL-3 or other markers of fibrosis in the heart. Moreover, due to the short duration of PAF, the lack of long-term ECG monitoring by insertable loop recorders, as well as the possibility of asymptomatic PAF episodes, many occurrences may have gone unnoticed. Our results need to be validated by larger studies with a prospective design, in order to assess the AF risk in diabetic adults.

## Conclusion

The present study demonstrates that LA strains and LA stiffness are significantly and independently associated with the occurrence of PAF in diabetic patients. As 2D-STI of the LA is more sensitive than routine echocardiographic examination, it should be performed in patients suspected of being suffering from PAF.

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## Disclosure

The authors report no conflicts of interest in this work.

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