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ORIGINAL ARTICLE

Increased left atrial stiffness in patients with atrial fibrillation detected by left atrial speckle tracking echocardiography

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KEYWORDS

Atrial fibrillation;
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Abstract *Objective:* This study was designed to determine the contribution of left atrial (LA) stiffness to atrial fibrillation (AF) progression by comparing AF patients with normal control subjects, and to evaluate whether LA mechanical function is related to the structural changes of LA.
Background: Abnormalities in the LA structure and function usually develop in patients with AF.
Patients and methods: Twenty paroxysmal and 20 persistent AF patients, were included and studied, using standard, tissue Doppler and speckle tracking echocardiography, and were compared with 20 matched controls. LA maximal volume, mitral annular velocities, and global longitudinal LA strain were measured. The ratio of E/e′ to LA strain was used as an index of LA stiffness.
Results: Study groups were comparable. Paroxysmal and persistent AF patients showed increased LA maximal volume (24.3 ± 3.2, 20.1 ± 5.2 vs. 18.3 ± 1.6, $p < 0.001$) and LV filling pressure (E/e′ = 9.5 ± 1.1, 7.9 ± 1.2 vs. 6.8 ± 1.1, $p < 0.001$), but decreased mitral annular velocities and LA strain (18.1 ± 2.8, 21.5 ± 4.3 vs. 25.9 ± 2.9, $p < 0.001$). LA stiffness was increased in patients with persistent and paroxysmal AF than in the control subjects (0.55 ± 0.12, 0.36 ± 0.09 vs. 0.26 ± 0.02, $p < 0.001$), and was related with LA diameter and LV filling pressure.
Conclusions: Patients with AF have increased LA stiffness in comparison with that of the control subjects and it is higher in persistent than paroxysmal AF. LA volume and LV filling pressure are independent predictors of LA stiffness.

1. Introduction

Atrial fibrillation (AF) is an independent risk factor for mortality across a wide age range in both men and women.[1] It is the most frequently detected arrhythmia in the clinical setting, and it is associated with increased cardiovascular risk.[2]

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AF is a progressive condition that begins with hemodynamic and/or structural changes in the left atrium (LA) and evolves through the paroxysmal and persistent stage.[3]

Better understanding of LA structure and function could lead to improvements in our ability to predict the risk of developing AF and the response to treatment in patients with this arrhythmia. LA enlargement has been widely related to AF, both in patients with persistent and paroxysmal AF.[4]

LA function can be estimated by two-dimensional echocardiography, Doppler analysis of transmitral flow, and tissue Doppler assessment of LV diastolic myocardial velocities. Speckle tracking echocardiography allows the quantification of LA function, and recently, noninvasive estimate of LA strain by speckle tracking has been proposed.[5]

Several studies have shown that LA stiffness increases with atrial remodeling and reflects a deteriorated reservoir function.[6,7] However, to date, little is known with regard to the change in LA mechanical function, including LA stiffness, in patients with AF.[8]

The present study was designed to compare the LA mechanical function, including LA stiffness, in patients with paroxysmal and persistent AF with normal control subjects, and to evaluate whether LA mechanical function, LV filling pressure and LA stiffness are related with the structural changes in LA.

2. Methods

2.1. Study population

We conducted a single center, case-control, cross-sectional study. The study population included 40 patients arranged into two groups: Twenty paroxysmal AF patients (51 ± 13 years, 60% male) and 20 persistent AF patients (49 ± 8 years, 65% male), who underwent echocardiography for the evaluation of cardiac structure and function, between April 2013 and December 2013. Inclusion criteria were as follows; (1) age older than 18 years, (2) recent onset and documented paroxysmal AF on an electrocardiogram or Holter recording in the previous 2 months, and (3) Patients with persistent AF or prior history of AF. Patients were excluded from the study if any of the following were present; (1) LV ejection fraction $< 50\%$, (2) history of ischemic heart disease, (3) dyspnea of New York Heart Association functional class $\geqslant$ II, (4) valvular stenosis or regurgitation $\geqslant$ moderate, (5) hyperthyroidism, acute illness, post-operative status and (6) age > 70 years.

The study protocol was approved by the ethical committee of Assuit faculty of medicine. A written informed consent was obtained from all participants. The consent form was designed with an explanation on the purpose and conduction of this research project. This form was to be explained to each participant; then a written consent was given. Participation was only proceeded after written consent of the participant. The full text of the form was approved by the Ethical Review Committee of Assuit faculty of medicine.

In all subjects, a full medical history was taken, and a complete physical examination was performed. Cardiovascular risk factors were recorded in detail, and all patients underwent standard 12 lead ECG.

Twenty healthy subjects with similar age, gender, and LV systolic function (mean age, 46 ± 8 years; male, 60%; mean LV EF, 64 ± 5.5%) were randomly selected from the subjects who volunteered for general routine health evaluation and underwent echocardiography. None of the controls had any cardiovascular or systemic disease and had sinus rhythm.

2.2. Transthoracic echocardiography

An iE33ultrasound system (Philips xMATRIX echo system, Eindhoven, The Netherlands) was used for the transthoracic echocardio graphic examination. All images and measurements were acquired from the standard views, according to the guidelines of the American Society of Echocardiography[9,10] and were digitally stored for offline analysis with QLAB 9. In the parasternal long-axis views, LA maximum anterior–posterior (A–P) diameter was measured (Fig. 1). In the apical 4-chamber view, LV end-diastolic and end-systolic volumes were measured and LV ejection fraction was calculated by the Simpson method. Pulsed-wave Doppler at the tip of mitral valve leaflets allowed us to measure the early (E) wave velocity and E deceleration time. The LV tissue velocity (e′, a′, s′) was measured by tissue Doppler imaging of the medial mitral annulus and E/e′ was calculated. From the apical 4- and 2-chamber view, the LA maximum volume (before

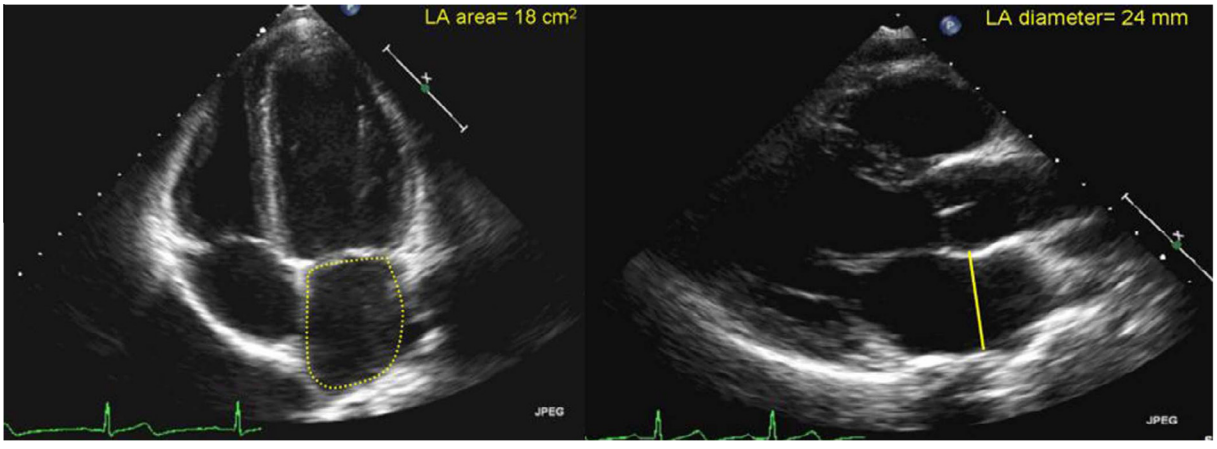

Figure 1 Measurements of left atrial area (before mitral valve opening) in the apical 4 chamber view (on the left side) and left atrial anterior–posterior diameter in the parasternal long axis view (on the right side).

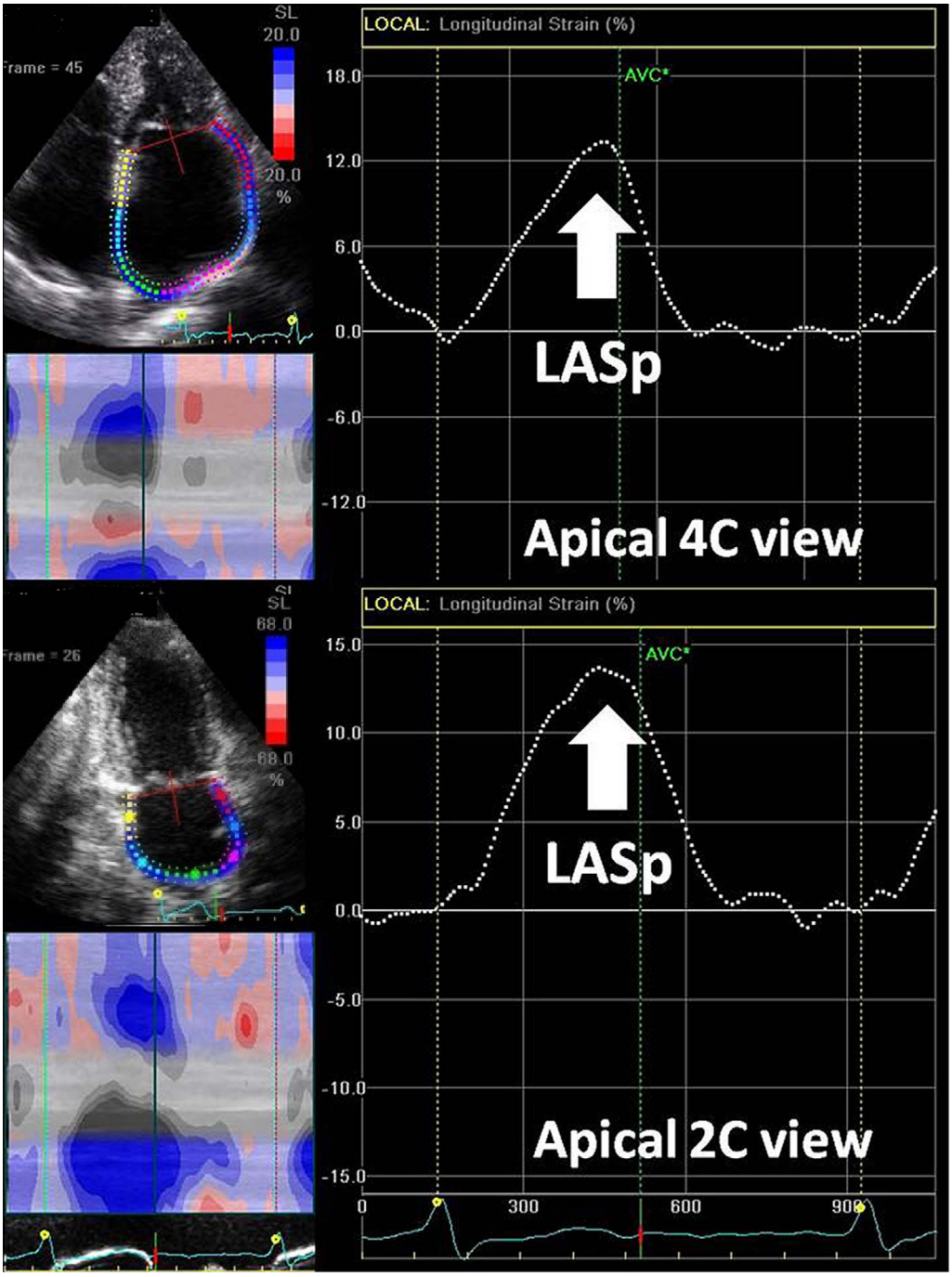

Figure 2 The strain curve from speckle tracking echocardiography of the left atrium in atrial fibrillation patients. Sprecke tracking can be obtained from both apical four-chamber and two-chamber views. White arrows indicate LASp, LA: left atrial, LASp: left atrial speckle tracking.

mitral valve opening) was measured using a biplane area-length method (Fig. 1).

The global systolic LA myocardial strain was measured by 2-dimensional speckle tracking echocardiography.[11] Gray scale image of apical 4-chamber views was obtained with the frame rates of 50–80 Hz (Fig. 2). Recordings were processed with acoustic-tracking software (QLAB 9, Philips Healthcare, Eindhoven, The Netherlands), allowing off-line semi-automated speckle-based strain analyses. Briefly, the lines were manually traced, along the LA endocardium at the time of end-systolic phase. An additional epicardial line was automatically generated by software, which created a region of interest (ROI). After manually adjusting the ROI shape, the global peak LA strain during the whole cardiac cycle was calculated.[12,13] In this study, to derive a noninvasive dimensionless parameter, the ratio of E/e′ to LA peak strain was used to estimate the LA stiffness (strain).[5,11] All echocardiographic analysis was done by a single blinded experienced sonographer.

2.3. Statistical analysis

Continuous variables are expressed as mean and standard deviation, and categorical variables are presented as frequencies and percentages. Study population was divided into 3 groups, two groups according to AF class and a control group. Baseline patient's characteristics were compared using analysis of variance (ANOVA) for continuous variables, a chi-square (X^2) test for dichotomous variables, and fisher exact test for dichotomous variables with fewer than 5 patients in a category. Subgroup post hoc analysis using Bonferroni method was done to clarify if the difference is between control and each AF groups or even paroxysmal vs. persistent AF. Correlation between different variables was evaluated using Pearson correlation coefficient analysis. Univariate analysis was performed using X^2 test with Yates' correction when necessary. Multivariate linear regression analyses were performed using all potentially relevant variables to identify baseline independent predictors of LA stiffness. All p-values were two-tailed, and statistical significance was defined if $p < 0.05$. All analyses were performed with SPSS version 16.0 statistical software (SPSS Inc., Chicago, IL, USA).

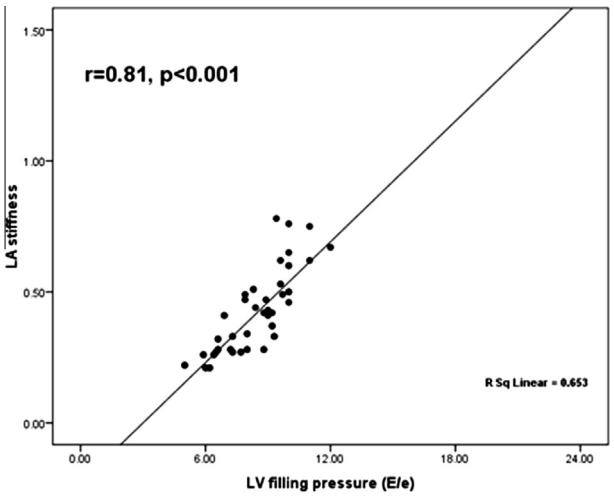

Figure 3 Correlation between left atrial stiffness and left ventricular filling pressure left atrial stiffness showed a strong significant positive correlation with left ventricular emptying pressure. LA: left atrial; LV: left ventricular.

3. Results

The baseline clinical and echocardiographic characteristics of 20 patients with paroxysmal AF, 20 patients with persistent AF and 20 normal control subjects are summarized in Table 1.

There was no significant difference between the study groups with respect to age, gender, heart rate and LV ejection fraction (Table 1). There was a significantly higher number of hypertensive patients in patients with persistent AF compared to other groups ($p < 0.001$). There was a trend toward higher number of diabetics also in persistent AF group however, not statistically significant ($p = 0.06$). There was a significant increase in (E) value in persistent AF group compared with the paroxysmal AF ($p < 0.001$) (Table 1).

Patients with AF showed a significantly increased LA maximal volume, LA antero-posterior diameter and LV filling pressure (E/e′) compared with control group (Table 1). Further post hoc analysis confirmed that the difference is also between paroxysmal and persistent AF groups. On the other hand, there was a significantly lower LA global strain and decreased mitral annular velocities in AF groups compared to control group with more decrease in persistent than paroxysmal AF group (Table 1). LA stiffness was increased in patients with AF than in the control subjects with more significant increase in persistent than paroxysmal AF groups (Table 1).

LA stiffness was increased in patients with AF than in the control subjects also between persistent and paroxysmal AF groups (Table 1). LA stiffness showed a strong significant

Table 1 Clinical and echocardiographic characteristics in patients with paroxysmal and persistent atrial fibrillation and in normal control subjects.

	Control (N = 20 pt)	Paroxysmal AF (N = 20 pt)	Persistent AF (N = 20 pt)	P-value for trend
Age (years)	42.4 ± 10.6	51 ± 13.6	49.6 ± 8.3	0.4[a]
Male sex	12(60%)	12(60%)	13(65%)	0.9[b]
Diabetes mellitus	0	4(20%)	5(25%)	0.06[b]
Hypertension	2(10%)[‡]	8(40%)[†]	15(75%)[#]	<0.001[b]
Heart rate (bpm)	75.70 ± 4.65	75.30 ± 3.44	76.40 ± 4.52	0.913[a]
LV ejection fraction (%)	64 ± 5.5	61.7 ± 8	61.4 ± 5.1	0.37[a]
Transmitral flow(E cm/s)	70.3 ± 13	78.5 ± 14	84.4 ± 7.4[#]	0.002[a]
Annular tissue Doppler (e′ cm/s)	11.6 ± 1.9[‡]	9.1 ± 2.2[†]	8.7 ± 1.4	<0.001[a]
E/e′	6.8 ± 1.1[‡]	7.9 ± 1.2[†]	9.5 ± 1.1[#]	<0.001[a]
LA antero-posterior diameter (cm)	3.6 ± 0.31[‡]	4 ± 0.95[†]	4.5 ± 0.49[#]	<0.001[a]
LA maximal volume (ml/m^2)	18.3 ± 1.6[‡]	20.1 ± 5.2[†]	24.3 ± 3.2[#]	0.000[a]
Global LA strain (%)	25.9 ± 2.9[‡]	21.5 ± 4.3[†]	18.1 ± 2.8[#]	<0.001[a]
LA stiffness	0.26 ± 0.02[‡]	0.36 ± 0.09[†]	0.55 ± 0.12[#]	<0.001[a]

Data are presented as mean ± standard deviation, number (%) of patients.
[a] Compared using ANOVA test for trend.
[b] Compared using Chi-square or Fisher exact test. Results of post hoc analysis using Bonferroni method are presented as.
[†] For $p < 0.001$ comparing paroxysmal with control.
[‡] For $p < 0.001$ comparing persistent with control.
[#] $p < 0.001$ comparing persistent with paroxysmal. AF: atrial fibrillation, E: peak early diastolic filling velocity, e′: peak early diastolic velocity of the medial mitral annulus, LV: left ventricular, LA: left atrium.

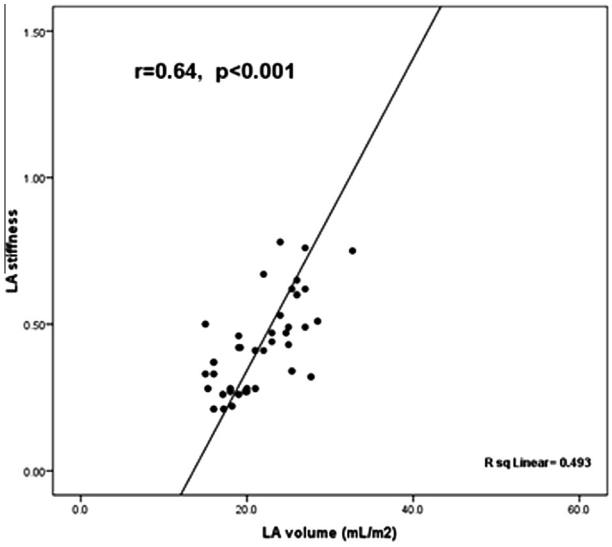

Figure 4 Correlation between left atrial stiffness and left atrial volume left atrial stiffness showed a moderate positive correlation with LA maximal volume. LA: left atrial.

positive correlation with LV filling pressure ($r = 0.81$, $p < 0.001$) (Fig. 3), and moderate positive correlation with LA maximal volume ($r = 0.64$, $p < 0.001$) (Fig. 4), however, weak positive correlation with LA antero–posterior diameter ($r = 0.57$, $p = 0.001$) (Fig. 5).

Multivariate linear regression analysis showed that LA volume (beta = 0.38, 95%CI = 0.003–0.023) and LV filling pressure estimated by E/e′ (beta = 0.68, 95%CI = 0.045–0.073) were independent predictors of LA stiffness. On the other hand, LA diameter, age, male gender, presence of hypertension or diabetes, did not predict LA stiffness (Table 2).

Table 2 Multivariate linear regression analysis for assessment of the predictors of increased left atrial stiffness in patients with atrial fibrillation.

Predictors	Beta	95% CI		*P*
		Lower	Upper	
Age	0.128	0.000	0.004	0.089
Male gender	0.07	−0.022	0.066	0.32
Heart rate	−0.054	−0.005	0.001	0.237
Hypertension	−0.034	−0.06	0.04	0.660
Diabetes mellitus	0.013	−0.53	0.064	0.858
LV ejection fraction	−0.054	−0.005	0.002	0.456
LA diameter (cm)	0.028	−0.053	0.065	0.849
LA volume (m^1/m^2)	0.379	0.003	0.023	0.012*
E/e′	0.677	0.045	0.073	0.000*

AF: atrial fibrillation, E: peak early diastolic filling velocity, e′: peak early diastolic velocity of the medial mitral annulus, LV: left ventricular, LA: left atrium.
* Significant.

4. Discussion

The main finding of the present study is that patients with paroxysmal and persistent AF showed increased stiffness compared to the control subjects. LA stiffness was strongly correlated with LA volume indices and left ventricular diastolic function (E/e′).

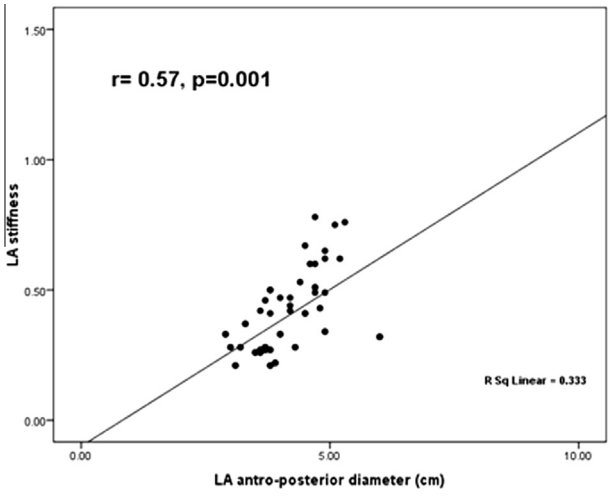

Figure 5 Correlation between left atrial stiffness and left atrial antero–posterior diameter left atrial stiffness showed a weak positive correlation with LA antero–posterior diameter, LA: left atrial.

In our study, we found that LA stiffness was significantly increased in persistent AF compared to paroxysmal AF and to control subjects, also we demonstrated that there is a clear difference in left atrial anatomical and mechanical functions as well as left ventricular diastolic function in patients with persistent AF compared with paroxysmal AF and normal control subjects.

The present study showed that there is a clear relationship between AF and changed ventricular filling patterns; we noticed a significant increase in (E) value as well as (E/e′) ratio in persistent AF group compared with the paroxysmal AF and normal groups. This can be explained for the persistent AF group by the presence of higher number of hypertensive and diabetic patients in this group. However, for paroxysmal AF group this is not the case. The (E) Value represents velocity of blood stream into the ventricle and is largely dependent upon relaxation of left ventricle as well as atrial pressure.[14]

Only few previous studies have tried to assess connection between AF and ventricular diastolic filling patterns. Reant et al. measured parameters of systolic and diastolic function in patients with lone AF after successful ablation[15], and in agreement with our study, they proved the presence of impaired diastolic filling in patients with persistent AF compared with healthy controls. Also Franjo Naji et al.[16] found that in patients with preserved systolic function, presence of persistent AF negatively affects left ventricular filling patterns.

Recently, strain analyses with two-dimensional speckle tracking echocardiography have been applied to the LA.[13] LA myocardial strain has been confirmed as a reliable index that represents the magnitude of atrial deformation.[17] Schneider et al.[18] found that strain rate imaging enables the quantitative assessment of the LA function and can be considered as a potential marker of atrial reverse remodeling. Patients with higher atrial strain rate after catheter ablation appear to have a greater likelihood of maintenance of sinus rhythm.

In agreement with our study, Henein et al.[19] showed that global LA strain and strain rate were significantly reduced in patients with paroxysmal AF, compared with the normal

control subjects. We also found a decreased global LA strain in the paroxysmal AF patients, and with a lower measurement value in persistent AF, suggesting a deteriorated LA function and progression of LA remodeling.

In concordance with our results, Kuppahally et al.[3] found that Patients with persistent AF as compared with paroxysmal AF had more fibrosis and lower midseptal and midlateral strains.

The degree of impairment in atrial compliance, as assessed by longitudinal atrial strain, has been reported to relate to maintenance of sinus rhythm after cardioversion or catheter ablation in subjects with persistent AF.[13] Furthermore, Kuppahally et al.[3] described an inverse relationship between the extent of LA structural remodeling detected by Delayed-enhancement MRI and echocardiographically derived LA strain and strain rate. This relationship was more prominent in patients with persistent AF compared with paroxysmal AF.

The relationship between diastolic abnormalities and the development of non-valvular AF may be mediated through an increase in atrial pressure, atrial stretch, and neuro-hormonal activation, including the release of atrial natriuretic factor.[20] The importance of atrial enlargement in the development of AF is well-known.[4] In accordance with our finding, Sitges et al.[21] found that LA enlargement was observed already in patients with paroxysmal AF.

Parkash et al.[22] evaluated the effect of LA dimension on the occurrence of AF using 2- and 4-year echocardiographic data in a large cohort of patients with new onset AF, they found that the recurrent AF group had a significantly smaller LA dimension at baseline compared to the persistent AF group. In agreement with Yoon et al. [8], we found no significant difference in LA antero-posterior diameter between patients with paroxysmal AF and normal control subjects. We also found a strong correlation between LA volume indices and the E/e′ ratio, and both were strongly correlated with LA stiffness. In agreement with our study, Mori et al.[23] found that paroxysmal AF was associated with greater LA volume than that in controls.

This study has several limitations. Small sample size and higher rate of patients with hypertension and diabetes in persistent AF group also could affect the results. However, aim of our study was to evaluate both paroxysmal and persistent AF, to allow the assessment of LA mechanical function, according to the progression of AF to chronic stage. Second is the lack of gold standard measurement for the LA function. Invasive determination of the LA pressure was not considered feasible, again, it cannot be excluded that differences in medical therapy, especially for the comparison of AF patients and controls, have a potential influence on the atrial strain data. Third is the potential difficulty of accurately obtaining a region of interest close enough to the effective shape of the left atrium, and lack of dedicated software for LA strain analysis. Although the post-processing time in this study was relatively short, it closely depends on the sonographer's experience. Although all analysis was done by a single experienced sonographer, this does not eliminate the effect of intra- and inter-observer variability on our results. Further long-term prospective studies with clinical endpoints and repeated strain measurement over time are required to assess the effects of reverse atrial modeling on strain and stiffness.

5. Conclusion

Patients with AF have increased LA stiffness in comparison with that of the control subjects and it is higher in persistent than paroxysmal AF. LA volume and LV filling pressure are independent predictors of LA stiffness.

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None.

Conflict of interest

We have no conflict of interest to declare.

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