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Original Article

Association of left atrial deformation indices with left atrial appendage thrombus in patients with non valvular atrial fibrillation

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ABSTRACT

Aim: Assessment of the value of left atrial deformation indices for prediction of left atrial appendage functioning patients with non-valvular atrial fibrillation.

Method: The study included 250 patients with non-valvular atrial fibrillation and normal left atrial dimension. Trans-thoracic and trans-esophageal echocardiography were performed. Patients were divided into two groups; patients with LAA thrombus (group I) and patients without LAA thrombus (group II), a correlation between trans-esophageal and trans-thoracic data was analyzed.

Results: Group I included110 patients (44%) and Group II 140 patients (56%). By TDI mean LA strain and strain rate were lower in group I (21.89 ± 7.75% vs 35.14 ± 9.28%; $p < 0.001$) and (1.15/sec, IQR 0.12−3/sec versus 2.1/sec, IQR 0.21−3/sec, $p < 0.001$) respectively. By speckle tracking PALS and strain rate were lower in group I (24.79 ± 7.78% vs 37.63 ± 8.64%; p value < 0.001) and (0.95 ± 0.32/sec. Vs 1.27 ± 0.32/sec p, value < 0.001) respectively. By TEE; group I had lower LAA EF (39.2 ± 13.55% vs 53.86 ± 12.7%); $p < 0.001$, and lower LAA emptying velocity (17.53 cm/s, IQR 9.54−77.4 vs 63.5 cm/s, IQR 7.89−86.4; $p < 0.001$). There was a good correlation between LA TDI and speckle tracking PALS and PALSR and LAA EF% and velocity $p < 0.001$. TDI and PALS and PALSR were found to be significant predictors for LAA thrombus ($P < 0.05$) with good sensitivity and specificity.

Conclusion: Left atrium deformation indices are predictors of LAA thrombus or SEC in patients with non-valvular AF with accepted sensitivity and specificity.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia that affects 1%−2% of the general population.[1] AF is a public health challenge associated with high comorbidity and increased mortality.[2]

When AF is managed by rate control strategy leads to fibrosis and remodeling of left atrial (LA) wall. Structural atrial remodeling in AF is manifested by lower myocardial velocities and lower compliance.[3] The contractile dysfunction of atria during arrhythmia leads to decreased blood flow velocity and favors the creation of thrombi. Most commonly, thrombi develop in LA appendage (LAA) and the gold-standard technique for detecting flow stasis, spontaneous echo contrast, and LAA thrombus is transesophageal echocardiography (TEE).[3]

There are several established methods of LA echocardiographic quantification as anteroposterior and superoinferior diameter, area in four-chamber view and volumes by area−length formulas in single or biplane views,[4] but the utility of linear measurements is limited because LA enlarges in an asymmetrical way.[4] Conventional echocardiography enables mainly morphological (anatomical) assessment but deformation indices by tissue Doppler and speckle tracking strain and strain rate allow a more comprehensive assessment of the function of the LA.

Many studies reported the association between LA and LAA function[5] but most of them included patients with abnormal LA by conventional echocardiography parameters, so our study aims to highlight the value of deformation imaging in the detection of LA dysfunction even with normal morphology and its correlation with TEE indexes of LAA dysfunction and measure its prediction for LAA thrombus or SEC.

1.1. Patients and methods

Study Design: This single-center case−control study was conducted at Bena University Hospital from May 2015 to January 2019,

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the study was approved by the local ethical committee and all patients signed informed consent.

Patients: A total of 268 patients with non-valvular AF for at least 3 months who were referred to the echocardiography unit for TEE evaluation. Trans-thoracic echocardiography was performed followed by TEE examination. Patients were divided into those with LAA thrombus or shadow (group I) and a control group of patients without LAA thrombus or shadow (group II).

Inclusion criteria: Patients with non-valvular AF for at least 3 months who were referred to Bena university hospital for TEE evaluation for a clinical indication as:

1-Scheduled carryoversion.

2-Routine evaluation before AF ablation procedures.

3-Assessment of intracardiac shunts.

4-Assessment of intracardiac mass.

5-Assessment of pathologies of the thoracic aorta: Aortic dissection, aortic atherosclerosis, and its complications.

1.2. Exclusion criteria

- Patients with abnormal LA dimension as measured by conventional echo parameters (according to the ASE criteria).[6]
- Patients with absolute contraindications of TEE: Esophageal spasm, stricture, laceration, perforation, or diverticulitis.
- Patients with relative contraindications of TEE: Large diaphragmatic hernia, Atlanto-axial disease, and severe generalized cervical arthritis, extensive radiation to the mediastinum, and upper gastrointestinal bleeding.
- Patients with excluded left atrial appendage.
- Inappropriate endocardial border definition of the left atrium.

2. Methods

- Review of medical history: demographic data (age, sex), risk factors (smoking, DM, and hypertension), history of valvular heart disease (native valvular heart disease, prosthetic valves), cardiac medications and evaluation of the CHA2DS2-VASc score.
- Conventional Trans-thoracic Echocardiography[6]:

Patients were imaged in the left lateral decubitus position using Philips Epic 7 with a multi-frequency transducer with ECG-gated. Routine grey-scale images of the left ventricle and left atrium were acquired from the apical views. Grey-scale imaging of the left atrium was undertaken in the 4-chamber and 2-chamber apical views with care taken to ensure none foreshortening of the chamber. All images were acquired during AF so; five cardiac cycles were stored in cine-loop format for further offline analysis. Echocardiographic measurements were done for consecutive beats and thereafter averaged for assessment of:

Left atrial diameter; was measured from the leading edge of the anterior LA wall to the leading edge of the posterior wall at the end ventricular systole (i.e., just before the mitral valve opening) along para-sternal long axis view from the 2D guided M-mode tracing (upper normal value = 40 mm).[6]

Left atrial function; was estimated by Simpson's biplane method of discs at end-systole, just before the opening of the mitral valve (at the end of the T-wave on the ECG) which is the LA maximum volume (LAV max) measured. At end-diastole, just before mitral valve closure (at the beginning of the QRS complex on the ECG) which is the minimum LA volume (LAV min) measured, then

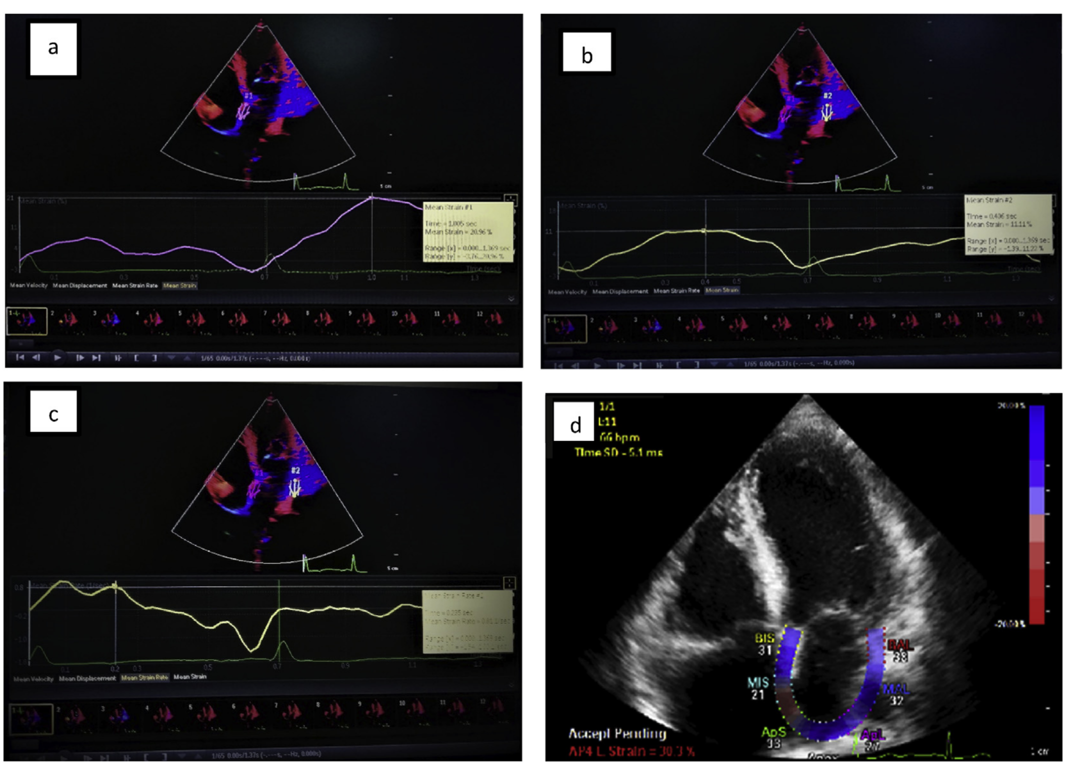

Fig. 1. (a) TDI strain of the septal wall of the LA, (b) TDI strain of the lateral wall of the LA (C) TDI strain rate of the septal and latral wall of the LA, (d) speckle tracking strain of the LA

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software calculate LA total emptying fraction = (LAV max − LAV min)/LAV max (normal value = 54 ± 7%).[7]

- Deformation imaging of the LA:

2.1. TDI echocardiography

- For tissue Doppler imaging of the left atrium, color tissue Doppler was applied in the apical 4-chamber and 2-chamber views at frame rate greater than 100fps. Echocardiographic data over 3 cardiac cycles were stored in digital format for offline analysis.
- For offline color tissue Doppler image analysis of the left atrium, region of interest (10 × 2 mm) was placed superiorly in each wall in the apical 4-chamber and 2-chamber projections. From these, mean LA strain and strain rate were measured as the average mean of three cardiac cycles (Fig. 1).

2.2. Speckle tracking echocardiography (STE)

- Longitudinal LA speckle-tracking strain was measured by applying a speckle-tracking algorithm to the narrow-sector apical LA images. LA endocardial border is traced in both four- and two-chamber views, and the tracking sector width minimized owing to the thinness of the LA myocardium thus delineating a region of interest (ROI), composed by 6 segments. Then, after the segmental tracking quality analysis and the eventual manual adjustment to achieve optimal tracking of the ROI, The cardiac cycle was demarcated by indicating QRS onset. The longitudinal strain curves are generated by the software for each atrial segment (peak longitudinal systolic strain), and by separately averaging values observed in 4- and 2-chamber views (average peak longitudinal systolic strain), This measurement thus represents the total distention of the left atrium during the cardiac cycle. In addition, using the mean of these two views, atrial strain rate was also measured by speckle-tracking,[8] (Fig. 1).
- Trans-esophageal Echocardiography[9]:

Acquired with a multi-plane transesophageal probe (2.9–7.0 MHz). Patients fasted for at least 6 h, received local anesthesia using lignocaine spray and, if necessary, intravenous midazolam (3–5 mg) for sedation. With the patients in the left lateral decubitus position, the transducer was slowly advanced through the mouth guard into the esophagus. If any resistance was met, the direction of the probe was carefully shifted and advancement was resumed. If it was not possible to advance the probe, the procedure was stopped. TEE was performed for evaluation of:

LAA thrombus: thrombus was defined as a fixed or mobile echogenic mass clearly distinguishable from the wall of the LA or LA appendage. Spontaneous echo contrast was diagnosed as dynamic or "smoke-like" echo signal inside the LA that could not be eliminated by changing the gain settings.

LAA flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the LAA into the body of the LA. The maximum emptying velocity was estimated from an average of three well-defined emptying waves.

LAA ejection fraction calculated from planimetry of the maximum and minimum areas of LAA, obtained in appendicular diastole and systole, using the following relation:

- Diastolic area − systolic area/diastolic area x 100 (%)

2.3. Reproducibility

Interobserver variability and intraobserver variability for LA strain and strain rate were studied twice by one operator and by two investigators who were unaware of the previous results. The coefficient of variation for positive strain in the four-chamber view was 9.2% (intraobserver) and 17.2% (interobserver) and for positive strain rate in the four-chamber view was 10.2% (intraobserver) and 14.3% (interobserver).

2.4. Statistical analysis

Data management and statistical analysis were done using SPSS vs. 25 (IBM, Armonk, New York, United States). Numerical data were summarized as means and standard deviations or medians and IQR. Categorical data were summarized as numbers and percentages. Numerical data were compared using independent *t*-test or Mann Whitney *U* test for normally and non-normally distributed variables respectively. Normality was assessed using normality tests and direct data visualization methods. Categorical data were compared using Chi-square test. Correlation analysis was done between tissue Doppler, speckle tracking parameters, and trans-esophageal parameters using Pearson's and Spearman's correlation (when appropriate). "r" is the correlation coefficient. It ranges from −1 to +1. −1 indicates a strong negative correlation. +1 indicates strong positive correlation while 0 indicates no correlation. ROC analysis was done for trans-esophageal, tissue Doppler and speckle tracking parameters for prediction of LAA thrombus or SEC. Area under curve (AUC) with 95% confidence interval and diagnostic indices were calculated. Multivariate logistic regression analysis was done for the prediction of LAA thrombus or SEC. Odds ratio with 95% confidence interval was calculated for predictors. All P values were two sided. P values less than 0.05 were considered significant.

3. Results

Patients' demographics and clinical data: Of the 268 patients enrolled during the study period only 250 patients fulfilled the inclusion criteria; the mean age was 48 ± 15 years. 130 patients

Table 1
Correlation between TDI, STE parameters and LAA function.

		TDI		2D speckle tracking	
		Mean strain	Mean strain rate	PALS	PALSR
LAA EF%	R	.653**	.660**	.699**	.446**
	P value	<0.001	<0.001	<0.001	<0.001
LAA emptying velocity	R	.735**	.753**	.738**	.758**
	P value	<0.001	<0.001	<0.001	<0.001

TDI: tissue Doppler image, STE: speckle tracking echo, LAA: left atrial appendage, PALS: peak atrial longitudinal strain, PALSR: peak atrial longitudinal strain rate, EF: ejection fraction.
* means significant.

Table 2
Clinical and echocardiographic characteristics of patients with and without LAA thrombus or SEC.

		Group I (n=110)	Group II (n=140)	P value
Age	Mean ± SD	47 ± 14	48 ± 16	0.606
Sex	Males	63 (57.3%)	67 (47.9%)	0.139
	Females	47 (42.7%)	73 (52.1%)	
Smoking	n (%)	45 (40.9%)	63 (45.0%)	0.517
Body mass index	Mean ± SD	27.86 ± 4.13	27.12 ± 4.89	0.198
Hypertension	n (%)	66 (60.0)	86 (61.4)	0.818
Diabetes	n (%)	40 (36.4)	47 (33.6)	0.645
CHA2DS2-VASc score	Mean ± SD	3.4 ± 2.0	3.2 ± 1.6	0.08
2D echocardiography				
LA diameter (mm.)	Mean ± SD	38.2 ± 2.5	37.1 ± 3.6	0.137
LA empty fraction (%)	Mean ± SD	55.5 ± 12.2	57.8 ± 10.9	0.124
Tissue Doppler parameters				
TDI strain (%)	Mean ± SD	21.89 ± 7.75	35.14 ± 9.28	<0.001
TDIstrain rate(/sec.)	Median (IOR)	1.15 (0.12–3)	2.1 (0.21–3)	<0.001
Speckle tracking parameters				
2D PALS (%)	Mean ± SD	24.79 ± 7.78	37.63 ± 8.64	<0.001
2D PALSR (/sec)	Mean ± SD	0.95 ± 0.32	1.27 ± 0.32	<0.001
Trans-esophageal parameters				
LAA EF EF (%)	Mean ± SD	39.2 ± 13.55	53.86 ± 12.7	<0.001
LAA emptying velocity	Median (IOR)	17.5 (9.54–77.4)	63.5 (7.89–86.4)	<0.001

Independent *t* test and Mann Whitney *U* test were used based on normality testing, Chi-square test was used for categorical data.
SEC: spontaneous echo contrast, LA: lest atrium, LAA: left atrial appendage, TDI: tissue Doppler image, PALS: peak atrial longitudinal strain, PALSR: peak atrial longitudinal strain rate, EF: ejection fraction.

(52%) were male, 120 patients (48%) were female, 87 patients (34.8%) were diabetic, 152 patients (60.8%) were hypertensive, 108 patients (43.2%) were smokers, none of the patients had an ischemic stroke or TIA, and all patients had persistent or permanent AF with anticoagulation therapy (warfarin) with insignificant difference in the level of INR between the two studied groups (2.1 ± 0.31 vs 2.21 ± 0.44, $p > 0.05$).

3.1. Echocardiography

By transthoracic echo:the mean LA diameter was 35.6 ± 4.6 mm and the mean LA empty fraction was 56.7 ± 11.5%. The mean value of the TDI strain was 29.31 ± 10.86%, median (IQR) of TDI strain rate was 1.44 (0.12–3) seconds. The mean value of 2D peak atrial longitudinal strain (2D PALS) using speckle tracking was 31.98 ± 10.44% and the mean value of 2D peakatrial longitudinal strain rate (2DPALSR) was 1.13 ± 0.36/sec. According to the results of TEE, mean LAA EF% was 47.41 ± 14.95% and the median (IQR) of LAA emptying velocity was 20.42 (7.89–86.4) cm/s. 110 patients (44.0%) had LAA thrombus or SEC.

3.2. Correlation between left atrial deformation and LAA EF%

LA strain and stain rate measured by tissue Doppler and speckle tracking were found to correlate well with LAA EF% and LAA emptying velocity with p value < 0.001 (Table 1).

3.3. Patients were classified into 2 groups

- Group I: 110 patients (44%) had LAA thrombus or SEC (63 patients with thrombus and 47patients with SEC).
- Group II: 140 patients (56%) without LAA thrombus or SEC.

Both groups were comparable regarding age (p value = 0.606), distribution of gender (p value = 0.139) and risk factors and CHA2DS2-VASc score (p value = 0.08) Table 2.

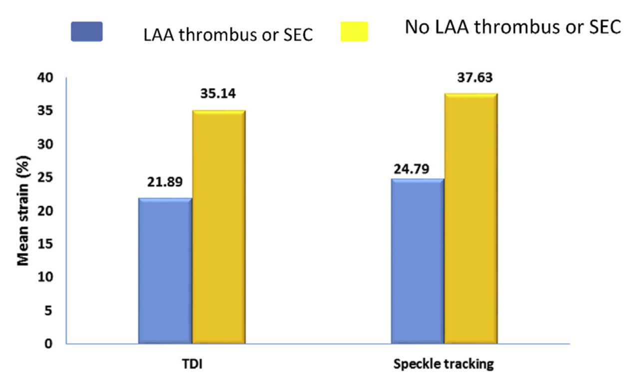

Fig. 2. Mean TDI strain and speckle tracking strain in both groups of patients with & without LAA thrombus or SEC.

3.4. Echocardiographic parameters of patients with and without LAA thrombus or SEC

2D echocardiography revealed that both groups had similar LA diameter (38.2 ± 2.5 mm Vs 37.1 ± 3.6 mm; P value 0.137) and similar left atrial empty fraction (55.5 ± 12.2% vs 57.8 ± 10.9%; p value 0.124) (Table 2).

Mean LA TDI strain and strain rate were lower in group I than group II (21.89 ± 7.75% vs 35.14 ± 9.28%; p value < 0.001) and (1.15/

Table 3
Multivariate binary logistic regression analysis for the predictors of LA thrombus or SEC.

Variable	β	OR	95%CI	P
Velocity	−2.18	9.1	1.58–33.3	0.012
TDI mean strain (%)	−2.45	12.5	2.12–25.0	0.007
TDI mean strain rate (/sec.)	−2.10	8.3	1.51–50.0	0.015
2D PALS (%)	−2.39	10.98	1.29–20.0	0.01
2D PALSR (/sec.)	−1.94	7.14	1.13–43.5	0.021

β = regression coefficient, negative sign means negative effect; increased parameters leads protection against thrombus formation).

Table 4
ROC analysis of TEE & TTE parameters in prediction of LAA thrombus or SEC.

	AUC (95% CI)	SE	Cut-off	Sensitivity	Specificity	P value
LAA EF (%)	0.784 (0.728–0.839)	0.028	46.5	70.9	77.9	<0.001
LAA emptying velocity	0.828 (0.775–0.881)	0.027	20.45	88.2	77.9	<0.001
TDI mean strain (%)	0.839 (0.785–0.892)	0.027	23.42	85.5%	82.1%	<0.001
TDI mean strain rate (/sec.)	0.819 (0.693–0.875)	0.028	1.45	84.3%	78.6%	<0.001
2D PALS (%)	0.833 (0.779–0.887)	0.027	31	88.2%	77.9%	<0.001
2D PALSR (/sec.)	0.811 (0.754–0.867)	0.029	1.16	87.3%	75.7%	<0.001

AUC = Area Under Curve 95% CI = 95% Confidence Interval SE = Standard Error.
TEE: trans-esophageal echo, TTE: transthoracic echo, LAA: left atrial appendage, SEC: spontaneous echo contrast, EF: ejection fraction, TDI: tissue Doppler image. PALS: peak atrial longitudinal strain, PALSR: peak atrial longitudinal strain rate.

sec with IQR0.12–3/sec. Versus 2.1/sec with IQR 0.21–3/sec.) *p* value < 0.001 respectively (Table 2) (Fig. 2).

2D PALS measured by STE is found to be lower in group I than in group II (24.79 ± 7.78% versus 37.63 ± 8.64%) *p* value < 0.001. Also, 2D PALSR was lower in group I than in group II (0.95 ± 0.32/sec. Versus 1.27 ± 0.32/sec.), *p* value < 0.001 (Table 2) (Fig. 2).

TEE examination revealed that; group I has lower LAA EF% than group II (39.2 ± 13.55% versus 53.86 ± 12.7%) *p* value < 0.001 and LAA emptying velocity was lower in group I than group II (17.53 cm/s with IQR 9.54–77.4 versus 63.5 cm/s with IQR7.89–86.4); *p* value < 0.001 (Table 2).

3.5. *Multivariate binary logistic regression analysis for prediction of LAA thrombus or SEC*

Multivariate binary logistic regression analysis was run using blocking technique to show if the studied parameters would add to the model when added one after one starting with velocity. They were found to increase the variation in model from (32%–53%) in block I to (45%–79%) in block 5. TDI and 2D PALS and 2D PALSS were found to be significant negative predictors for LA thrombus formation (increasing values of strain and strain rate are associated with lesser risk of thrombus ($P < 0.05$) (Table 3).

3.6. *Diagnostic value of LA deformation parameters in the prediction of LAA thrombus or SEC*

ROC curve was used to test the diagnostic value (overall accuracy) of LA deformation parameters measured by TDI and STE in predicting LAA thrombus or SEC.

LA TDI strain cutoff value of <23.42% haddiagnostic accuracy (sensitivity = 85.5% & specificity = 82.1%) in predicting LAA thrombus or shadow [AUC 0.839, 95% CIs (0.785–0.892), $P < 0.001$]. LA TDI strain rate cutoff value of <1.45/sec had diagnostic accuracy (sensitivity = 84.3% & specificity = 78.6%) in predicting LAA thrombus or shadow [AUC 0.819, 95% CIs (0.693–0.875), $P < 0.001$] (Table 4). and (Fig. 3A).

2D PALS cutoff value of <31% had diagnostic accuracy (sensitivity = 88.2% & specificity = 77.9%) in predicting LAA thrombus or shadow [AUC 0.833, 95% CIs (0.779–0.887), $P < 0.001$]. 2D PALSRcutoff value of <1.16 haddiagnostic accuracy (sensitivity = 87.3% & specificity = 75.7%) in predicting LAA thrombus or shadow [AUC 0.811, 95% CIs (0.754–0.867), $P < 0.001$] (Table 4) (Fig. 3B).

4. Discussion

LA function has significant clinical and prognostic implications. Evaluation of the LA function by deformation strain and strain rate is a simple, accurate, reproducible, and more sensitive than conventional echocardiography and also, can demonstrate LA functional alterations even before alterations in LA volumes.[10]

The present study included 250 patients with non-valvular AF divided into two groups (group I) patients with LAA thrombus or shadow and (group II) patients without LAA thrombus or shadow, all patients had normal LA dimensions and empty fraction by conventional echocardiography.

Group I included 110 patients (44%) and Group II included 140 patients (56%), both groups were of comparable age, gender, risk factors, CHAD-VASc score, LA diameter, and empty fraction. Group I

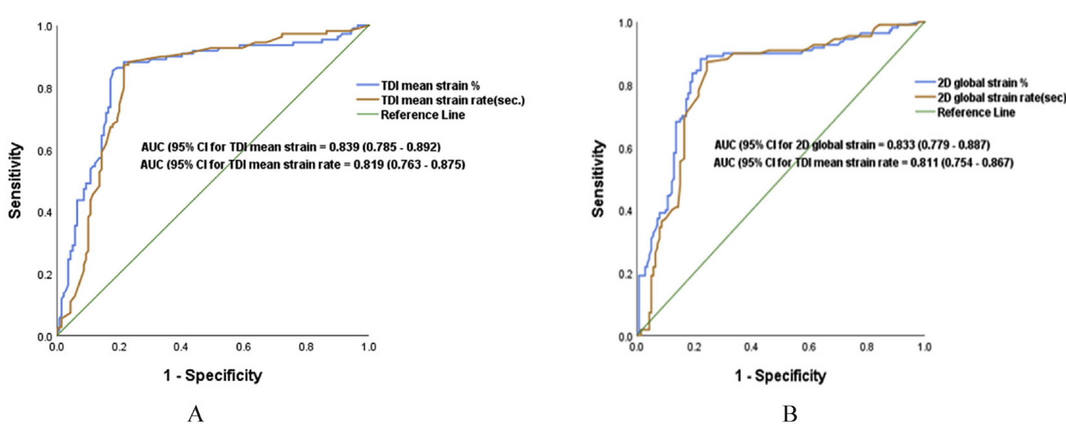

Fig. 3. (A) ROC analysis for the prediction of LAA thrombus or SEC using TDI mean strain &TDI mean strain rate measured by TTE (B): ROC analysis for the prediction of LAA thrombus or SEC using 2D PALS &2D PALSR measured by TTE.

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had lower TDI and speckle tracking strain and strain rate, and lower LAA EF% and empty velocity with good correlation between deformation parameters of the LA and LAA EF% and empty velocity measured by TEE.

Kuppahally et al[11] showed that the LA strain inversely correlates with LA fibrosis in AF patients, suggesting that fibrosis decreases LA compliance. Replacement of healthy atrial tissue with fibrotic tissue in AF leads to a reduction in the atrial contractile function and blood stasis, which results in the process of thrombus formation.

LAA plays important role in maintaining LA pressure as an actively contracting structure. As result of the intravascular volume status and remodeling in AF, LAA has become the primary location for the formation of thrombus.[12]

Predicting LAA thrombus in chronic nonvalvular atrial fibrillation remains challenging even thoughseveral predictive models have been proposed to date; Handke et al.[13]; found that increased LA diameter was independent predictors of LAA thrombus in patients with cerebral ischemia, whereas Tuluce et al.[14]; found that increased LA volume indexin patients with hypertrophic cardiomyopathy was correlated with LAA SEC also Left atrial strain was documented as a predictor of LAA thrombus in patients with sinus rhythm with suspected cardioembolic stroke.[15]

Thepredictive value of tissue Doppler and speckle tracking in patients with non-valvular AF with normal LA parameters for the detection of LAA thrombus or SEC is not well studied.

Our results are in agreement with Kupczynska et al, who studied 87 patients with AF retrospectively with LA longitudinal strain, systolic and early diastolic strain rate in four-chamber and two-chamber apical views. All patients underwent TEE disclosing LAA thrombus in 36 (41%) patients and concluded that; Speckle-tracking allowed the identification of patients with a higher risk of LAA thrombus.[16]

In our study, the mean CHA_2DS_2-VASc score was comparable in both groups, and less than the score predictive of thromboembolic event in previous studies which is 4,[17] so, the score alone in our study cannot be used to predict the presence of LAAthrombus in patients with non-valvular AF.

These results are in agreement with Do Van Chien et al,[18] who suggested that the diagnostic performance for LAA thrombus in patients with chronic nonvalvular AF may be higher when using the combination of LA deformation parameters than when using the CHA_2DS_2-VASc score alone.

Also Obokata et al.[19] found that LA strain provided incremental diagnostic information over that provided by the CHA_2DS_2-VASc score, suggesting that LA deformation could improve the currentrisk stratification of embolism in patients with AF.

Another study by Cameli et al.[20] who studied the correlation between PLS of the LA and presence of LAA thrombus, they concluded that; LA diameter and volume plays minor role in the prediction of LAA thrombus (despite dilated LA in the study population) and PLS were significantly lower in patients with reduced LAA emptying velocity and/or thrombus.

A recent study by Wang et al.[21] found that the addition of the CHA2DS2-VASc score and LAEF to PALS offered no further discrimination in the detection of LAA dysfunction to that offered by PALS alone, which suggests that in real-world practice, when an AF patient cannot undergo TEE, the PALS can alternatively be used to rule out the possibility of thrombus and to determine the subsequent needs for other imaging assessments.

The results of our study indicated that LA deformation parameters can provide clinically useful information concerning LAA function before structural remodeling occurs and also provide additional diagnostic value for patients with LAA thrombus with accepted sensitivity and specificity.

5. *Study limitations*

The main limitation is being single-center study, we the software used for evaluating the left ventricle, not the LA. Also, speckle tracking parameters vary across ultrasound machine manufacturers.

6. Conclusion

Left atrium deformation parameters arepredictors of LAA thrombus or SEC with accepted sensitivity and specificity.

Declaration of competing interest

All authors have none to declare.

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