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Using speckle tracking strain of left atrium for risk stratification of embolic stroke in non valvular atrial fibrillation in single cardiac center

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Abstract
Background: Atrial fibrillation (AF) is the most common arrhythmia treated in clinical practice and the most common arrhythmia for which patients are hospitalized. AF is associated with an approximately five fold increase in the risk for stroke and a two fold increase in the risk for all-cause mortality.
Objective of study: To investigate myocardial deformation of the left atrium (LA) assessed by two-dimensional speckle tracking echocardiography in patients with nonvalvular atrial fibrillation and its value for risk stratification of embolic stroke.
Patient and Methods: A prospective cohort study in Baghdad teaching hospital cardiac center from June 2016 to May 2017 We recruited 107 consecutive patients who were referred to echocardiography unit for evaluation by 2D full echocardiographic study with speckle tracking strain of left atrium. These patients were divided into two groups control and AF. those with AF further divided into two groups according to the presence or absence of stroke.
Results: The left atrial strain among patients with AF and stroke had significantly reduced from those patient with AF without stroke(9.8 ±3.0, 18.5±5.6 respectively).P- value= 0.001. Where as left atrial volume index and left ventricular filling index (E/E`ratio) did not show significant differences. After multi-variant analysis, global LA strain were independently associated with stroke in patients with AF. Those with LA GLS <12.8 % had a significantly higher rates of stroke than those with LA GLS > 12.8 %.
Conclusion: This study demonstrated that LA deformation reduced in patients with AF and stroke. Global LA strain measured by speckle tracking echocardiography can be used for risk stratification for stroke in patients with AF and has incremental diagnostic values in addition to clinical risk stratification.

Keywords: atrial fibrillation, left atrial strain, stroke

1. Introduction

Atrial fibrillation is the most common arrhythmia treated in clinical practice and the most common arrhythmia for which patients are hospitalized (33%). AF is associated fivefold increase in the risk for stroke and a twofold increase in the risk for all-cause mortality.AF is also associated with the development of heart failure [1].

Estimates of the actual number of individuals with AF in the United States range between 2.3 and 5 million in most studies. The incidence of AF is age and sex related and ranges from 0.1% per year before the age of 40 years to higher than 1.5% per year in women and higher than 2% per year in men older than 80 years. Heart failure, aortic and mitral valve disease, left atrial enlargement, hypertension, and advanced age are independent risk factors for the development of AF, as are obesity and obstructive sleep apnea [1].

Approximately 20% of is chaemic strokes are due to embolism from the heart. The most common causes are atrial fibrillation, prosthetic heart valves, other valvular abnormalities and recent myocardial infarction. A transthoracic or transoesophageal echocardiogram can be useful, either to confirm the presence of a clinically apparent cardiac source or to identify an unsuspected source such as endocarditis, atrial myxoma, intracardiac thrombus or patent foramen ovale [2]. Although transesophageal echocardiography is a useful method for predicting stroke and deciding on anticoagulation therapy, it is a semi-invasive method and cannot be used as widely as transthoracic echocardiography [3].

A novel approach to quantify regional left atrial (LA) function from routine gray-scale two-dimensional echocardiographic images, known as speckle tracking two-dimensional strain echocardiography, calculates myocardial strain independently of angle of incidence and has recently been validated against sonomicrometry and tagged magnetic resonance imaging. The feasibility of two-dimensional speckle tracking echocardiography for measuring LA deformation in patients with all types of AF was documented in a recent studies, and the LA deformation was inversely related to LA wall fibrosis, as demonstrated by delayed enhancement on magnetic resonance imaging.

Echocardiography is the best method for assessment and follow-up of LA size, because this imaging modality is radiation free and does not require contrast enhancement. It is safe, portable, comfortable for patients, relatively inexpensive, and readily available in large and smaller centers, and it could be used more widely for population screening [3].

LA remodeling refers to a spectrum of complex pathophysiologic changes that occur in response to external stressors. LA dilatation, a hallmark of LA structural remodeling, is often the result of pressure or volume overload. Diastolic dysfunction, tachycardia, ischemia, and valve diseases such as mitral and aortic valves stenosis and regurgitation can lead to LA enlargement. The left atrium may respond with a range of adaptive and maladaptive changes, such as myocyte hypertrophy, apoptosis, necrosis, changes in the composition of extracellular matrix, alterations in cellular energy balance, and neurohormonal disturbances [5]. LA pressure increases to maintain adequate filling of the LV in conditions associated with increased stiffness or decreased compliance of the LV.

A major goal of therapy in patients with AF is to prevent thromboembolic complications such as stroke. The strongest predictors of ischemic stroke and systemic thromboembolism are a history of stroke or a transient ischemic episode and mitral stenosis. When patients with AF and a previous ischemic stroke are treated with aspirin, the risk for another stroke is very high, in the range of 10% to 12% per year. At the other end of the risk spectrum are patients with lone AF, whose cumulative 15-year risk for stroke was reported to be in the range of 1% to 2%. Aside from previous stroke, the best-established risk factors for stroke in patients with nonvalvular AF are diabetes (relative risk, 1.7), hypertension (relative risk, 1.6), heart failure (relative risk, 1.4), and age 70 years or older (relative risk, 1.4 per decade) [1].

A simple clinical scheme to risk-stratify patients on the basis of major risk factors is the CHADS2 (cardiac failure, hypertension, age, diabetes, stroke) score. Each of the first four risk factors is worth 1 point, and a previous stroke or transient ischemic event is worth 2 points. There is a direct relationship between the CHADS2 score and the annual risk for stroke in the absence of aspirin or warfarin therapy. However, recent studies have demonstrated that the CHA_2DS_2-VASc score more accurately discriminates low-risk from intermediate-risk patients [1].

2. Patients

A prospective study conducted in Baghdad teaching hospital department of echocardiography from first of June 2016 to 30thMay 2017.One hundred seven patient included in this study divided into three groups (AF group, AF with stroke group, control group). patients data are recorded including clinical comorbidities and atrial fibrillation types. AF was diagnosed according to the guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology(The diagnosis of AF requires rhythm documentation using an electrocardiogram (ECG) showing the typical pattern of AF: Absolutely irregular RR intervals and no discernible, distinct P waves. an episode lasting at least 30 s is diagnostic) [8, 29].

Stroke was defined by a history of hospital admission and positive image studies from brain computed tomography. The stroke risk of our patients was assessed by assigning one point each for the presence of congestive heart failure, hypertension, age 65-75 years, and diabetes mellitus, female gender and assigning two points for a history of stroke or transient ischemic attack and age more than 75 years old according to (CHA_2DS_2- VASC).[9] and informed consent was obtained from all participants.

Study include the following groups control group (44 patients), atrial fibrillation group (35 patients) and stroke with atrial fibrillation group (28 patients).

2.1 Exclusion criteria

1. Any patient with valvular heart disease including (rheumatic valve disease. mitral annular calcification, mitral valve repair, prosthetic valve replacement, mitral valve stenosis of any degree) [30, 31].
2. All patients with hemorrhagic stroke due to any cause.
3. All patients with intra-cardiac devices or pacemakers.
4. Patients with poor image qualities.
5. All patients with severe LV dysfunction.

2.2 Echocardiographic Methods

Standard echocardiography was performed under ECG connection so timing of cardiac cycles determined different atrial phases. with Doppler studies by (PHILIPS CX50 ultrasound USA) machine with a 3.5-MHz multiphase array probe in subjects lying in a left lateral decubitus position.

LA dimension measured by 2-D method.Transmitral Doppler flow velocity was obtained from the apical four-chamber view, and peak early filling velocity (E) was recorded.Pulse tissue Doppler imaging was obtained from the medial and lateral annulus, and peak systolic annulus velocity (S) and early diastolic annulus velocity (E’) were measured.The E to E’ ratio (E/E’) was used as an index for LA pressure. Two-dimensional images were acquired from apical four- and two-chamber views for three- five cardiac cycles and digitally stored a frame rate of 50–90 frames per second.The images were analyzed off-line by PHILIPS CX50 ultasound USA software.

LA volume was measured by the biplane area-length method from two-dimensional echocardiography. LA size was represented by LA maximal LAVs and indexed by body surface area (LA volume index [LAVI]).

2.3 Measurement of LA strain by speckle tracking echocardiography

The endocardial border was manually defined using a point-and-click technique. An epicardial surface tracing was automatically generated by the system, creating a region of interest, which was manually adjusted to cover the full thickness of the myocardium in the systolic frame. The width of the smallest region of interest was 8 mm. Before processing, a cine loop preview was used to confirm if the internal line of the region of interest followed the LA endocardial border throughout the cardiac cycle.

2D Speckle Tracking Imaging was used to analyze LA strain values in six segments. For this purpose, a line was manually drawn along the LA endocardium at peak systole in an apical 4-chamber view and two chamber view. The software then automatically generated tracking of the LA endocardium, which was further adjusted by the operator. The six segments of the left atrium were analyzed and an average value of all segments was considered. LA function can be evaluated through 2D Speckle Tracking Imaging by analyzing its three curve strain components. In sinus rhythm, a QRS- timed analysis identifies: the reservoir phase by peak ventricular systolic value (εR), which corresponds to maximum atrium filling; the contractile phase by peak late diastole (εCT); and the conduit phase by peak early diastole (εCD), corresponding to the difference between peaks εR and εCT. In AF, it is believed that the reservoir and conduit function are impaired and pump function is lost. Thus, in these patients, only peak positive systolic strain (PPS) and peak negative diastolic strain (PNS) of the curves were analyzed, as there was no an accurate way of identifying the different stages of atrial function. An average of different measurements of LA strain curves was taken (in 5 consecutive cycles) in each case. The average result of GLS of LA calculated automatically by machine software.

2.4 Statistical analysis

Statistical analysis was done using computerized statistical software, statistical package for social science (SPSS ver.25). Differences between the groups were compared with the Student t test for continuous variables or the Chi-square test for categoric variables.

Multiple logistic regression analysis was used for independent factors. All data are presented as the mean. SD. A P- value of ≤ 0.05 was considered statistically significant.

3. Results

The three groups data were analyzed the mean age for all groups (57.4 ± 13.1) included in this study with 53(49.5%) females and 54 (50.5%) males with M:F ratio 1.01:1. Forty four patient normal control (41%), thirty five patients with AF (32.7% without stroke) and twenty eight AF with stroke (26%). Sixty eight (63.5%) with hypertension, thirty eight (35.5%) with diabetes, twenty three (21.4%) with ischaemic heart disease as shown in table 1.

Table 1: Distribution of standard groups according to their demographic characters

	Atrial Fibrillation		**Control No. (41%)**	**Total %**
	No stroke No. (32,7%)	**stroke No. (26%)**		
Female	16 (46%)	19 (68%)	18 (41%)	49.5%
male	19 (54%)	9 (32%)	26 (59%)	50.5%
HTN/YES	23 (66%)	24 (86%)	21 (48%)	63.5%
NO	12 (34%)	4 (14%)	23 (52%)	36.5%
DM YES	18 (51%)	12 (43%)	8 (18%)	35.5%
NO	17 (49%)	16 (57%)	36 (82%)	64.5%
IHD YES	9 (26%)	12 (43%)	2 (5%)	21.4%
NO	26 (74%)	16 (57%)	42 (95%)	78.6%
Total No.	35	28	44	107

Mean and standard deviation of normal control and AF and AF with stroke groups variances and their P-value is done for means and standard deviation of variances and demographic characters as shown in table 2.The mean age are 42.1 ±15. 5, 58.91±11.22and 67.53± 8.11 respectively. The mean BSA for control group and AF group and stroke group 1.78 ±0.24, 1.78±0.22 and 1.71±0.11 respectively. The mean BMI for control group and AF group and stroke group are 28.01±5.29, 27.8±4.47and 26.17±3.12 respectively. The mean body WT for control group and AF and stroke group are 74.63±17.13, 74.57±16.29 and72.00±11.45 respectively. The mean height for control group and AF group and stroke group are 164.68±10.34, 161.40±9.93and 164.10±9.25 respectively.

Table 2: Means and standard deviation of different groups variables

Mean and standard deviation of different groups with P-value correlation							
variables	Atrial fibrillation group		Control group		Stroke with AF group		P- value
	mean	SD	mean	SD	mean	SD	
AGE	58.91	11.22	42.15	15.56	67.53	8.11	0.834
BSA	1.78	0.22	1.70	0.24	1.76	0.16	0.629
BMI	27.81	4.47	28.01	5.29	26.17	3.12	0.972
WT	74.57	16.29	74.63	17.13	72.00	11.45	0.825
HEIGHT	161.40	9.93	164.68	10.34	164.10	9.25	0.802
STROKE (No.)	.00	.00	0.0	0.0	28.00	0.00	0.0001
CHADS-VASC SCORE	2.80	1.67	1.18	1.06	5.82	1.12	0.372
LA VOLUME	68.91	36.80	41.02	13.50	77.96	27.13	0.735
LA VOLUME INDEX	37.28	20.14	22.52	7.97	43.17	15.84	0.796
LA STRAIN	18.25	4.40	40.63	13.63	9.89	3.01	0.00
LA DIMENSION	36.71	6.41	31.63	4.53	39.71	6.32	0.563
LVIDd	50.60	8.41	48.75	6.54	51.28	10.12	0.119
LAIDs	34.51	8.28	31.43	6.58	37.21	11.65	0.111
LV EF	58.25	14.04	68.04	5.47	54.92	15.56	0.192
E/E~	10.22	3.894	6.36	1.61	13.10	3.95	0.352
S~	10.46	1.37	10.68	3.49	7.08	2.03	0.880
RV ANNULAR EX.	22.48	6.07	25.77	3.73	17.53	4.98	0.760
Total number	35		44		28		
*P- value of ≤ 0.05 was significant							

Independent t-test correlation of left atrial global strain variable with all variables of general groups show significant correlation with linear regression test of these significant variables show only significant linear relationship with stroke (P-value =0.001) and diabetes (P –value= 0.015). and there is no significant correlation with hypertension(P-value =0.909) or ischaemic heart disease (P-value 0.386). also there is no significant correlation between LA –strain and left atrial volume(P-value=0.735) or LAVI (p-value=0.996) and left atrial dimension(P-value= 0.563) and left atrial filling E/E`(P-value =0.352),(table 3).

Table 3: Linear regression test (independent variable LA strain) with other different variables.

model	t	P value
Age	0.210	0.834
AF	-0.545-	0.588
HTN	0.115	0.909
DM	2.517	0.015
IHD	0.874	0.386
Stroke	-3.530-	0.001
Chads-vasc score	-0.901-	0.372
La vol.	-0.340-	0.735
LAVI	-0.005-	0.996
La dimension	-0.583-	0.563
LVIDS	-1.626-	0.111
LV EF	-1.322-	0.192
E/e~	0.941	0.352
Tapse	0.307	0.760

*P- value of ≤ 0.05 was significant

Different types of atrial fibrillation shows different levels of atrial strain the more prolong AF duration show more reduction in strain level as shown in table 4 the permanent or prolong AF show the lowest level of strain (13.7 ±5.5).

Table 4: Strain level between different type of AF

Atrial Fibrillation	N	Mean ± SD
Paroxysmal	4	18.0 ±7.1
Persistent	13	16.1 ±5.5
Permanent	46	13.7 ±5.5
Total	63	14.5 ±5.6

Table 5 show different value of LA strain among different groups with reduced strain level in AF with stroke (9.8±3.0) from those with AF and no stroke18.2±4.4) (also in control group 40.6±13.6) and total AF group (14.5±5.6) with or without stroke.

Table 5: LA strain level in different groups with their significant values

LA strain	Mean ± SD	N	P-values
La Strain (control group)	40.6±13.6	44	0.570
La Strain (AF no stroke)	18.2±4.4	35	0.973
La Strain(total AF group)	14.5±5.6	63	0.067
La Strain (stroke group)	9.8±3.0	28	0.0001

There is no significant value for LA filling E/E` between different groups as shown in table 6 below the value plus their significant correlation.

Table 6: LA Filling value and significant values

variables		E/E` value	NO.	P value
E/E`	Control group	6.36± 1.61	44	0.336
E/E`	AF group no stroke	10.22±3.89	35	0.126
E/E`	AF Stroke group	13.10±3.95	28	0.233

Table 7 demonstrate different LA strain values in different co-morbidities groups which significant for DM only. Even there is reduction in all strain value but never below the level of 9.8 ±3.01 which significant in stroke patient only.

Table 7: LA strain in different co morbidities and their P-values

LA strain values indifferent co- morbidities groups			
Co-morbidities	MEAN+SD positive (no.)	MEAN+SD negative (no.)	NO. (%)
HTN	21.2±13.1 (68)	32.2±18.5 (39)	0.909
DM	20.6 ±10.9 (38)	27.8 ±17.9 (69)	0.015
IHD	15.2 ±7.4 (24)	28.1 ± 16.8 (83)	0.386
AF	14.5±5.6 (63)	40.6±13.6 (44)	0.588

Table 8 different LA strain values according to CHADS - VASC scores there no significant linear relationship to LA strain. There is more reduction in strain in score 5,6 than others. the level well correlated with CHA2DS2-VASC score but because of small sample which slightly elevated level at score 7,8.

Table 8: LA strain according to CHA_2DS_2-VASC score

LA strain according to CHA_2DS_2 –VASC score points			
	CHADS-VASC score NO.	No.	Mean ± SD LA- strain
LA strain	1.00	20	36.1 ± 18.3
	2.00	19	28.1 ± 9.4
	3.00	11	23.8 ± 6.9
	4.00	14	18.9 ± 11.8
	5.00	7	10.0 ± 2.8
	6.00	12	10.0 ± 3.5
	7.00	5	11.8 ± 3.2
	8.00	3	11.3 ± 5.0

The sensitivity and specificity of LA strain 9.8±3.01 are 78% and 88% respectively and positive predictive value of 84% and negative predictive value of 83% and accuracy of 87% which is significant in this study.

4. Discussion

This study conducted in Baghdad medical city, catheterization unit 8th floor, department of echocardiography demonstrate that among patients with AF, those with AFand stroke had significantly reduced LA strain than those without stroke, whereas LAVI and LA filling (E/E`ratio),S`did not show significant differences LA. Strain independently associated with stroke in patients with AF. Those with GLS <12.8 % had a significantly higher rates of stroke than those with LA GLS > 12.8 %.

Multivariate analysis show, global LA strain were correlate significantly with age, LA vol., LAVI, LAD, LV systolic dimension, LV EF,E/E` and TAPSE All these variables affect LA function and add risk for thromboembolism but there is no linear regression relationship with LA strain only for stroke and DM with P- value =0.0001and 0.015 respectively.

When we analyze all variable using stroke as fixed variable multivariant significantly correlated with stroke as many disease condition play as risk factor for stroke but significant linear relationship goes only with age, CHADS-VASC score and LA strain with P-value = 0.024, 0.0001, and 0.005 respectively.

Age, CHADS-VASC score and diabetes associated with high morbidity and mortality and can be involved in many diseases as risk factors in this study we concentrate on echocardiographic data of LA deformation only.

LA strain was reduced in all type of AF with more reduction in permanent type AF which directly related to long duration of AF and much time for left atrial wall deformation.

There is significant reduction in left atrial strain with increment scores of CHA_2DS_2-VASC score (scores >3) but no linear regression relationship is shown during study.

The mechanism is that decreased strain during the reservoir phase has been closely correlated to LA fibrosis, as documented by magnetic resonance imaging.[25]Fibrosis of LA wall decreases compliance of LA cavity during the reservoir phase. We propose that decreased LA deformation, representing decreased LA compliance in the reservoir phase, might lead to more stasis of blood flow in LA during AF and therefore be associated with an increased risk for thromboembolism.

Many recent studies mention similar result of reduction of left atrial strain using different parameters in patient with AF and stroke.Several traditional echocardiographic parameters including increased LA dimension, decreased LA appendage flow velocity, and proof of thrombi or spontaneous echo contrast were associated with an increased risk of stroke. Recently, LA strain was reported to decrease proportionately with increasing $CHADS_2$-vasc score and was an independent predictor of prior stroke [26, 28].

Shih *et al.* found decreased LA strain and strain rate were independently associated with prior stroke, but E and E/E' were not [26]. The finding might indicate that stroke event was correlated better with LA-related parameters. LA strain provided incremental value for embolism risk stratification over CHA_2DS_2-VASc score in patients with AF [27]. In the present study, we similarly found decreased LA strain was correlated with increased CHA_2DS_2-VASc score in the univariate analysis and further found decreased LA strain was significantly associated with subsequent stroke event even after adjustment for many important echocardiographic parameters. In addition, the addition of LA strain to a Cox model consisting of conventional clinical and echocardiographic parameters could cause an improvement in prediction of subsequent stroke event. Hence, impaired LA strain may be useful in predicting subsequent stroke event in AF patients.

Inaba *et al*. [17] showed that the LASRr correlates inversely with age, and that LASRc correlates positively with age and lost during AF. In their study, the mean LASRr was significantly lower in patients with persistent AF than in age-matched controls. The decreased strain and strain rate in patients with AF may be related to the remodeling of the LA, including LA dilatation and increased interstitial fibrosis. These structural changes in LA remodeling lead to stiffness of the LA and impairment of the reservoir function [18, 19].

Tamura *et al*. [15] reported that Doppler tissue velocity of the LAA tip can be measured from the transthoracic parasternal view and that it has a good correlation with LAA emptying flow velocity measured by transesophageal echocardiography [15].

The decreased Doppler tissue velocity of the LAA tip was shown to be an independent predictor of LAA thrombus formation. Another study demonstrated that Doppler tissue velocity of mitral annulus could be useful in risk stratification for cardiovascular events in heart failure in patients with preserved ejection fraction and AF [16]. Decreased LA deformation during the cardiac cycle can be used for risk stratification for stroke in patients with AF.

4.1 Study Limitations

1. One of the most significant limitations was the small sample patient population, since small samples may lack statistical power to demonstrate the presence of significant statistical differences.
2. LA strain analysis has not yet been released, we used the current software for LV analysis to study the LA pattern strain. Future evolutions in this regard may be useful to improve tracking quality of LA myocardial deformation, and to provide a better instrument for the study of LA function.
3. The speckle analysis of LA motion can be influenced by heart rate, especially in the patients with AF. However, ventricular rate was similar between patients with or without stroke in our study.
4. We did not know the exact duration of AF in our study patients, and it is possible that atrial remodeling over time might affect the strain and strain rate measurements.

5. Conclusion

1. This study demonstrated that LA deformation reduced in patients with AF and stroke. Global LA strain measured by speckle tracking.
2. Echocardiography can be used for risk stratification for stroke in patients with AF and has incremental diagnostic values in addition to clinical risk stratification.

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