Predictive Value of Left Atrial Appendage Functional Parameters on Left Atrial Thrombus or Spontaneous Echo Contrast in Patients with Nonvalvular Atrial Fibrillation

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Abstract

Background: Left atrial appendage (LAA) spontaneous echocardiographic contrast (SEC), sludge and thrombus were associated with a high incidence of thrombus formation and thromboembolic events in patients with non-valvular atrial fibrillation (AF). We aim to identify the main echocardiographic parameters associated with LAA SEC or LAA sludge/thrombus in nonvalvular AF patients.

Methods and results: 298 patients with nonvalvular atrial fibrillation were included in the current study between September 2019 and January 2021. Transthoracic echocardiography and transesophageal echocardiography were performed before scheduled electrical cardioversion. LA diameter and maximum left atrial appendage area were increased in the LAA SEC group than control group, and were further increased in patients with LAA sludge or thrombus. LAA-EV, LAA-FV, anterior mitral annular plane systolic excursion (MAPSE) and LAA FAC were lower in the group with LAA SEC than control group, and were further reduced in LAA sludge or thrombus group. Lower LAA FAC and anterior MAPSE were associated with an increased risk of LAA SEC or LAA sludge/thrombus, and LAA FAC and anterior MAPSE showed high accuracy on predicting LAA SEC or LAA sludge/thrombus.

Conclusion: Left atrial appendage FAC and anterior MAPSE improves left atrial appendage stasis in patients with nonvalvular atrial fibrillation.

Introduction

Among the clinical and echocardiographic indices used to stratify thromboembolic risk to patients with nonvalvular atrial fibrillation (AF), left atrial appendage (LAA) thrombus is a powerful predictor of increased risk¹. Spontaneous echocardiographic contrast (SEC) and LAA sludge have also been proposed as predictors of high incidence of thrombus formation and thromboembolic events in patients with nonvalvular atrial fibrillation¹⁻⁴.

The LAA often extends between the anterior and the lateral walls of the LA, and its tip is directed anterosuperiorly, overlapping the left border of the right ventricular outflow tract or the pulmonary trunk and the main stem of the left coronary or the circumflex artery. Because of its slightly flattened shape, the lower surface usually overlies the anterior and lateral wall of left ventricle and the upper surface is beneath the fibrous pericardium. In the LAA vision of TEE, anterior wall of LV and AV groove was adjacent to LAA (Fig. 1). We speculated that the structure and function of LV anterior wall was associated with LAA SEC or LAA sludge/thrombus.

The aim of this study was to identify the main echocardiographic parameters associated with LAA SEC or LAA thrombus, and investigate the correlation between the structure and function of basal anterior left ventricular wall and the adjacent structure with LAA stasis in nonvalvular AF patients.

Methods

Study population

The study was approved by the institutional review board. Between September 2019 and January 2021, we prospectively studied 298 patients with nonvalvular atrial fibrillation were involved in our study prospectively after providing informed written and verbal consent form a local ethics committee at the first affiliated hospital of Soochow university, 2D-TEE examination was performed for them to exclude the presence of spontaneous echo contrast (SEC) and or thrombus before radiofrequency ablation. Patients exhibiting the following criteria were excluded from this study: moderate to severe valvular dysfunction, hypertrophic cardiomyopathy, failed TEE, and cases containing unqualified images. Clinical information was demographic data, current medications, and past medical history. The CHA₂DS₂-VASc score was calculated for each patient ⁵.

Transthoracic echocardiography

TTE was performed using General Electric Vivid E95 device and a sector array M5Sc (2.5-3.5 MHz) transducer. Images were acquired to measure left atrial diameter, left atrial volume index, left ventricular end-diastolic diameter, left ventricular ejection fraction, E/e' and TR peak velocity. The LA diameter was measured in the parasternal long-axis view at the ventricular end-systole. LVEF was measured using Simpson's method, which was used as a standard index of global LV systolic function. In addition, the septal mitral annulus early (E') velocity was measured by tissue Doppler imaging, and the E/e' ratio was calculated using a cutoff value >14. All echocardiographic measurements used in the analysis were averaged from 3 heart beats.

Transesophageal echocardiography

All transesophageal exams were performed by the same operator using GE Vivid E95 device with a 5 MHz multiplane transducer. The LAA was visualized from the mid-esophageal position at an angle (typically 45°–90°) providing the longest apex to the orifice length. The grayscale frame rate was set to 60 to 90 frames/second. On average, five cardiac cycles were performed for both 2D and pulsed-wave (PW) Doppler recordings. LAA flow measurements were obtained approximately 1 cm below the outlet of the LAA cavity using PW-Doppler with suitable gain and filter adjustments. The LAA emptying (LAA-EV) and the LAA filling velocities (LAA-FV) were recorded. LAA fractional area change (LAA FAC) was calculated by (maximum LAA area - minimum LAA area) / maximum LAA area. LAA ostium is measured from the circumflex artery to a superior point 1 to 2 cm inside the left lateral ridge, and the LAA depth is measured from this line to the tip of the LAA ⁶. Mitral anterior annular plane systolic excursion was measured between end-diastole and peak systole by M-mode in the direction of LV longitudinal extension which is achieved from the apical approach (Fig. 2). Conjunction thickness was measured from 0-3mm beneath LCX and perpendicular to anterior wall of left ventricle, and it was defined as thickening gradient divided by maximum thickness of LAA conjunction.

SEC was recognized as dynamic, swirling, smokelike echoes within the LAA cavity⁷. LAA sludge was defined as an intracavitary echodensity with viscid gelatinous qualities giving the impression of

impending precipitation, but without a discrete organized mass, continuously seen throughout the cardiac cycle⁸. Sludge appears denser and more layered than severe SEC. LAA thrombus was defined from multiple imaging planes as a well-circumscribed, solid echodensity acoustically distinct from the underlying endocardium and pectinate muscles that was less heterogenous and dynamic than sludge^{9, 10}.

Statistical analysis

Patients enrolled in the present study were categorized in three groups, i.e. patients with SEC, those with sludge/thrombus, and controls. Analyses were performed using the SPSS 25.0. Continuous variables which are normally distributed are presented as mean ± SD. Variables that are not normally distributed will be presented as median with inter-quartile ranges (IQR = 25th–75th percentile). Categorical variables are expressed as absolute numbers and respective percentages. ANOVA test was used for group comparison. We applied univariable and multivariable logistic regression models to evaluate the relation between echocardiographic parameters and LAA SEC or thrombus. In multivariable model, we adjusted for a broad range of potential confounders presented in Table 3. To avoid data overfitting and collinearity, variables with P<0.05 and VIF < 5 in the univariate models were included in the multivariate model. The optimal cutoff values for determination of sensitivity and specificity of echocardiographic parameters to determine LAA SEC and thrombus were obtained from receiver operating characteristic (ROC) curve analysis.

Results

Characteristics of the population

Among the 298 study subjects, LAA SEC was identified by TEE in 152 (51.0%), and 13 patients (4.4%) had sludge or thrombus within LAA. Previous embolic events, TIA, or ischemic stroke and persistent AF were more prevalent in group with LAA sludge or thrombus than in other groups. Patients with LAA sludge or thrombus had a higher CHA₂DS₂-VASc score and lower BSA than LAA SEC group and control group (Table 1).

Table 1: Demographic and clinical characteristics of the study population

Variable	Control (n=133)	SEC (n=152)	Sludge/ Thrombus (n=13)	P
Age (y)	65.0 (57.0, 69.0)	65.0 (60.0, 70.0)	69.0 (66.0, 70.0)	0.11
Gender (male)	83 (62.4%)	91 (59.9%)	5 (38.5%)	0.24
BSA (m ²)	1.88±0.18	1.86±0.18	1.70±0.11	<0.01
Persistent AF	38 (28.6%)	108 (71.1%)	11 (84.6%)	<0.01
Previous embolic events, TIA, or ischemic stroke	5 (3.76%)	8 (5.26%)	3 (23.08%)	0.01
Hypertension	72 (54.14%)	84 (55.26%)	8 (61.54%)	0.87
Diabetes	9 (6.8%)	18 (11.8%)	3 (23.1%)	0.10
CHA ₂ DS ₂ -Vasc score	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (3.0, 4.0)	<0.01
Warfarin	8 (6.02%)	9 (5.92%)	1 (7.69%)	0.97
Dabigatran	70 (53.9%)	65 (47.5%)	3 (27.3%)	0.18
Rivaroxaban	52 (40.00%)	61 (44.53%)	7 (63.64%)	0.28
amiodarone	90 (67.7%)	91 (59.9%)	6 (46.2%)	0.18

SEC: spontaneous echo contrast; AF: atrial fibrillation, BSA: body surface area; TIA: transient ischemic attack.

CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age at least 75 years (doubled), Diabetes, Stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65–74 years, Sex category (female)

Baseline echocardiographic characteristics

Patients with LAA sludge or thrombus had lower left ventricular ejection fraction and higher tricuspid regurgitation peak velocity, LAA ostium and LAA depth than other groups. LA diameter and maximum left atrial appendage area were elevated in the LAA SEC group than control group, and were further increased in patients with sludge or thrombus. LAA-EV, LAA-FV, anterior MAPSE and LAA FAC were lower in the group with LAA SEC than control group, and were further reduced in patients with LAA sludge or thrombus (Table 2). Figure 3 shows the distribution of echocardiographic parameters in three groups (Fig. 3).

Table 2: Echocardiographic parameters of the study population

Variable	Control (n=133)	SEC (n=152)	Sludge/ Thrombus (n=13)	P
LA diameter (mm)	43.0 (39.0, 45.0)	46.0 (43.0, 50.5)	48.0 (44.0, 56.0)	<0.01
LVEDd (mm)	50.0 (46.0, 52.0)	49.0 (46.0, 52.0)	52.0 (49.0, 56.0)	0.14
LVEF (%)	62.0 (59.0, 66.0)	60.0 (56.0, 63.0)	58.0 (47.0, 60.0)	<0.01
E/e'	9.2 (7.5, 11.0)	9.2 (7.7, 12.2)	9.20(7.5, 9.9)	0.75
TR peak velocity (m/s)	2.4 (2.2, 2.6)	2.45 (2.3, 2.7)	2.7(2.5, 2.9)	<0.01
Number of LAA lobes	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)	4.0 (4.0, 5.0)	0.08
LAA-EV (m/s)	51.0 (37.0, 68.0)	30.0 (22.0, 42.0)	18.0 (16.0, 22.0)	<0.01
LAA-FV (m/s)	48.0 (37.0, 64.0)	37.0 (27.0, 51.0)	20.0 (17.0, 28.0)	<0.01
LAA ostial diameter (mm)	18.2±3.4	19.8±3.8	22.7±3.3	<0.01
LAA depth (mm)	27.6±5.3	29.7±6.5	35.7±5.9	<0.01
Conjunction thickening ratio (%)	25.5 (21.0, 30.8)	15.9 (11.7, 21.2)	6.6(5.7, 9.7)	<0.01
LAAmax (cm ²)	2.5 (2.0, 3.2)	3.1 (2.4, 3.7)	4.1 (3.2, 4.7)	<0.01
LAAmin (cm ²)	0.5 (0.2, 1.1)	2.0 (1.1, 2.7)	3.4 (2.7, 4.2)	<0.01
Anterior MAPSE (mm)	11.3 (9.6, 12.8)	7.4 (6.2, 9.2)	5.0 (4.6, 6.5)	<0.01
LAA FAC (%)	79.7 (58.0, 92.9)	32.2 (20.7, 51.6)	16.3(9.9, 22.3)	<0.001

SEC: spontaneous echo contrast; LA: left atrial; LVEDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation; LAA: left atrial appendage; EV: emptying velocity; FV: filling velocity; LAAmax: maximum left atrial appendage area; LAAmin: minimum left atrial appendage area, Anterior MAPSE: anterior mitral annular plane systolic excursion; LAA FAC: left atrial appendage fraction area change.

Correlation between echocardiographic parameters and LAA SEC or LAA sludge/thrombus

LAA FAC and anterior MAPSE were independent predictors for LAA SEC or LAA sludge/thrombus in patients with AF, and they all have good diagnostic accuracy for predicting LAA SEC or LAA sludge/thrombus. The area under the curve (AUC) for LAA FAC is 0.864 (cutoff value is 51.8.0%,

sensitivity is 82.0%, specificity is 77.6%). for anterior MAPSE, the AUC is 0.834 (cutoff value is 9.4, sensitivity is 76.7%, specificity is 79.4%) (Table 3, Fig. 4).

Table 3: The factors associated with LAA SEC and sludge/thrombus in univariate and multivariate logistic regression analysis

variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Gender	0.84 (0.53-1.34)	0.46	0.73 (0.34-1.56)	0.42
Age	1.02 (1.00-1.05)	0.06	0.98 (0.94-1.02)	0.36
Persistent AF	0.47 (3.89-10.74)	<0.01	1.47 (0.67-3.24)	0.34
LA diameter	1.13 (1.08-1.19)	<0.01	1.03 (0.34-1.56)	0.44
CHA ₂ DS ₂ -VASC	1.19 (1.01-1.39)	0.03	0.92 (0.69-1.23)	0.57
LVEF	0.94 (0.91-0.97)	<0.01	1.03 (0.98-1.07)	0.23
TR peak velocity	2.80 (1.42-5.53)	<0.01	0.88 (0.32-2.39)	0.80
LAA-EV (m/s)	0.96 (0.95-0.97)	<0.01	1.00 (0.99-1.02)	0.63
LAAmax	1.01 (1.00-1.01)	<0.01	1.00 (1.00-1.01)	0.11
LAA ostium	1.15 (1.07-1.23)	<0.01	0.94 (0.83-1.06)	0.33
LAA depth	1.07 (1.03-1.12)	<0.01	1.00 (0.94-1.08)	0.86
Anterior MAPSE	0.60 (0.54-0.68)	<0.01	0.80 (0.67-0.96)	0.02
LAA FAC	0.94 (0.93-0.96)	<0.01	0.96 (0.94-0.98)	<0.01
Conjunction thickening ratio	0.88 (0.85-0.91)	<0.01	0.97 (0.93-1.02)	0.27

AF: atrial fibrillation; LA: left atrium; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation; LAA-EV: left atrial appendage emptying velocity; LAAmax: maximum left atrial appendage area; anterior MAPSE: mitral anterior annular plane systolic excursion; LAA FAC: left atrial appendage fraction area change.

Discussion

Recent studies shows that spontaneous echocardiographic contrast (SEC) is associated with a high incidence of thrombus formation and thromboembolic events (1-3), and sludge within LAA is also associated with subsequent thromboembolic events and all-cause mortality in patients with AF (4). We aim to explore the correlation between echocardiographic assessments and LAA SEC or LAA sludge/thrombus. The current study shows that LAA sludge or thrombus group had lower Left ventricular

ejection fraction and higher tricuspid regurgitation peak velocity, LAA ostium and LAA depth than other groups. LA diameter and maximum left atrial appendage area were elevated in the LAA SEC group than control group, and were further increased in patients with sludge or thrombus. LAA-EV, LAA-FV, anterior MAPSE and LAA FAC were lower in the group with LAA SEC than control group, and were further reduced in LAA sludge or thrombus group. Lower LAA FAC and anterior MAPSE were associated with an increased risk of LAA SEC or LAA sludge/thrombus, and LAA FAC and anterior MAPSE showed high diagnostic performance on LAA SEC or LAA sludge/thrombus.

Prethrombotic phenomena such as LAA SEC or LAA sludge/thrombus may occurred because of LAA dysfunction due to reduced blood flow and stasis¹¹. Previous studies demonstrated that lower LAA-EV, LAA-FV measured by TEE were significant predictors of LAA thrombus¹², and can increased the risk of developing blood clots^{8,13}. Our study demonstrates that LAA flow velocity was lower in patients with LAA SEC, and further reduced in the LAA sludge/thrombus group, which is consistent with prior studies.

The current study showed that an increased LAA area correlated with LAA SEC or LAA sludge/thrombus, which is consistent with previous studies^{14,15}. What's more, in the current study, LAA FAC was decreased by degree in the three groups, and correlated with LAA SEC or LAA sludge/thrombus well. LAA FAC is easy to be assessed and has good re-productivity, and it showed high accuracy in predicting LAA SEC or LAA sludge/thrombus in the current study, so it should be considered in the evaluation of LAA function, which will provide incremental information for the risk stratification of AF patients.

LAA extends between the anterior and the lateral walls of the LA^{16,17}, so left atrial dysfunction is also correlated with LAA SEC or LAA sludge/thrombus. The current study demonstrated that left atrial diameter was decreased in the group with LAA SEC, and further reduced in patients with LAA sludge/thrombus, which is consistent with previous studies⁴.

The lower surface of LAA usually overlies the anterior and lateral wall of left ventricle and the upper surface is beneath the fibrous of AV groove. LAA was squeezed by part of anterior and lateral LV wall when ventricle diastole, which may contribute to outflow of LAA. Conjunction between LAA and basal LV anterior wall included anterior left ventricular myocardium, AV groove and left atrial appendage myocardium, and we assume that this structure may correlated to LAA prethrombotic phenomena. In our study, mitral anterior annular plane systolic excursion and conjunction thickening ratio were reduced in patients with LAA SEC, and further decreased in the group of LAA sludge/thrombus, and anterior MAPSE correlated with LAA SEC or LAA sludge/thrombus well and performed high diagnostic accuracy. Parameters about this structure should be paid more attention in clinical practice.

Conclusion

Our study suggested that left atrial appendage FAC and anterior MAPSE were congenital risk factor for LAA SEC, sludge and thrombus in patients with nonvalvular atrial fibrillation, and it may provide

additional information in the diagnosis of LAA stasis and in decision making and formulation of medical strategies.

Declarations

Competing interests

The authors declare that they have no conflict of interests.

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Figures

Figure 1

(A) Cardiac anatomy of pig; (B) Left atrial appendage in transesophageal echocardiography

A

B

C

Figure 2

Echocardiographic parameters. (A) LAA conjunction thickening ration (maximum LAA conjunction thickness and minimum LAA conjunction thickness); (B) LAA fraction area change (maximum LAA area and minimum LAA area); (C) Anterior mitral annular plane systolic excursion.

Figure 3

Echocardiographic parameters in three groups.

LA: left atrium, LAA: left atrial appendage; LAA-EV: left atrial appendage emptying velocity; LAA FAC: left atrial appendage fraction area change; anterior MAPSE: anterior mitral annular plane systolic excursion.

Figure 4

Diagnostic accuracy of LAA fraction area change and anterior MAPSE for LAA SEC or thrombus.

LAA FAC: left atrial appendage fraction area change, anterior MAPSE: mitral anterior annular plane systolic excursion.