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Original article

Evaluating the novel parameters for assessing the LAA function and thrombus formation with nonvalvular atrial fibrillation

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ABSTRACT

The dysfunction of left atrial appendage (LAA) is prone to form thrombus when atrial fibrillation (AF) sustained more than 48 h. Traditional 2D-TEE (transesophageal echocardiography) can not accurate evaluate the function of LAA. The purpose of this study is to analyze the relationship of LAA function parameters and thrombus formation in patients with non-valvular atrial fibrillation (NVAF) by real-time three-dimensional transesophageal echocardiography (RT-3D-TEE). High risk patients can be identified according to the characteristics of ultrasonic index in patients with left atrial appendage thrombosis, which has important clinical value and significance in the risk assessment, guiding treatment and judging prognosis. We examined the relationship between the echocardiographic parameters of LAA function and the incidence of thrombus in 102 NVAF patients. They underwent RT-3D-TEE and left atrial appendage thrombus (LAAT)/severe spontaneous echocardiographic contrast (SSEC) was found in 67 patients (thrombus group) but absent in the remaining 35 patients (non-thrombus group). After measured by QLAB software, the LAA functional parameters were significantly associated with LAAT/SEC formation. Univariate analysis indicated that AF time, LAD, LVEF, LAA-OAmax, LAAVmax, LAAVI and LAAEF demonstrated a positive association ($P < 0.05$). However, logistic regression analysis identified that AF time (OR:1.73, $P < 0.05$)、LAAEF (OR:4.09, $P < 0.01$)and LAAVI (OR:3.28, $P < 0.01$) were independent predictors of LAAT/SSEC. In patients with nonvalvular atrial fibrillation, echocardiographic parameters of LAA function are significantly associated with LAAT/SSEC.

1. Introduction

For all the cardiogenic stroke, 50%-67% were caused by NVAF. Left atrial appendage (LAA) is the most common region where cardiogenic thrombus comes from (Wolf et al., 1991). Once AF occurs, left atrial thrombus fell off and induced cerebral-embolism whose 90% originated from LAA (Donal et al., 2005; Negishi, 2019; Garshick et al., 2018; Wang et al., 2018). TEE is the golden standard for detecting LAA thrombus with 100% sensitivity and 99% specificity, which has higher resolution than multislice computerized tomography (Sallach et al., 2009). It has been demonstrated that decrease of LAA function was associated with formation of thrombus and SEC (Waldemar and Naser,2010) including reduced LAAEF, enlarged LAA area, dilated LAAV and increased LAD. But LAA couldn't be accurately measured by 2D TEE because of the complex structure. For instance, LAAEF is recognized as a well-known factor for reflecting LAA function, LAAEF was measured by LAA area variation (Porte et al., 1996). However, there is a diversity of LAA shape and size through 2D-TEE (Al-Saddy et al., 1999).

RT-3D-TEE does better in displaying cardiac structure and spatial image during cardiac cycle. RT-3D-TEE combined advantages of TEE and RT-3D technique, and obtained clear 3D image with higher resolution. The shape, size, area, and echo of thrombus can be

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detected easily through RT-3D-TEE. Multicenter research shows that 3D TEE offers better imaging resolution of the left atrium and its appendage, provides more diagnosis messages than 2D TEE, and significantly reduces the false positive rate (Decebal et al., 2009). Thus, RT-3D-TEE has been extensively used as a tool to detect the potentials of embolism in NVAF patients.

The purpose of this study is to analyze the relationship of LAA function parameters and thrombus formation in patients with non-valvular atrial fibrillation (NVAF) by real-time three-dimensional transesophageal echocardiography (RT-3D-TEE). According to the characteristics of echocardiography in patients with left atrial appendage thrombosis, we hypothesis the new echo index has important clinical value and significance in the risk assessment, guiding treatment and judging prognosis.

2. Materials and methods

2.1. Study Subjects:

One hundred and two patients (71males, 59.99 ± 11.01) were recruited from December 2009 and September 2019, where they were evaluated for AF. The patients met the following inclusion criteria: NVAF patients with clear echocardiography and complete clinical data; AF duration $\geq$ 48 h; and not on anticoagulation therapy. Each participant gave informed consent.

The basic information included age, height, weight, type of AF (proximal or persistent) and duration of AF. A variety of risk factors was reviewed respectively, including smoking, history of hypertension, diabetes, coronary heart disease and congenital heart disease. Patients were excluded on the basis of rheumatic heart disease, valvular heart disease, thrombocytopenic purpura and severe mitral regurgitation.

2.2. Transthoracic and transesophageal echocardiography

Transthoracic echocardiogram (TTE) and TEE was sequentially performed with no relevant time difference (< 5min) between them. Quality assessment includes standardized training of sonographers, and interobserver and intraobserver variabilities should be established by blind duplicate readings (Gottdiener et al., 2004), the echocardiographic parameters contain left atrial dimension (LAD) and left ventricular ejection fraction (LVEF).

The TEE examination was performed according to standard practice guidelines (Shanewise et al., 1999). All patients had fastened for 4–6 h before the TEE procedure. Thrombus and spontaneous echo contrast (SEC) were recorded according to the standardized criteria of Fatkin et al. (1994) and Kronik et al. (1995).

2.3. Data analysis

The 3D images were transferred for off-line analysis using the commercially available software QLAB. LAA orifice area (LAA-OA) was obtained under the iSlice interface by putting the coronal line and sagittal line into the diameter of LAA orifice, where the line between the connection of left atrium and LAA inferior wall and the connection of left atrium and left superior pulmonary vein. Left atrial appendage maximal orifice area (LAA-OAmax) was measured at the end-LAA diastole according to the international recommendations, while left atrial appendage minimal orifice area (LAA-OAmin) was measured at the end-LAA systole. Turned long axis of LAA to 0°,45°,90°,135°, respectively, and delineated the LAA outline in coronal plane and sagittal plane for each axis degree (Chen et al., 2017). The left atrial appendage maximal volume (LAAV-max) and left atrial appendage minimal volume (LAAV-min) were obtained automatically by SIMPSON biplane method, which was an average result of four axis degrees (Fig. 1). Other ultrasound indexes like LAA-OA variation, LAAEF and Left atrial appendage volume index (LAAVI) were calculated based on the data mentioned above. The calculational methods were listed as follows:

$$\text{LAA-OA variation} = (\text{LAA-OAmax-LAA-OAmin})/\text{LAA-OAmax} \times 100\%$$

$$\text{LAAEF} = (\text{LAAVmax} - \text{LAAVmin})/\text{LAAVmax} \times 100\%$$

$$\text{Body surface area (BSA) (m2)} = 0.0061 \times \textit{height}(cm)\ 0.0128 \times \textit{weight}(kg) - 0.1529$$

$$\text{Left atrial appendage volume index (LAAVI)(ml/m2)} = \text{LAAV/BSA}$$

The correlation between the TEE characteristics and LAA thrombus was subsequently assessed.

2.4. Statistical analysis

Dependent parameters for prediction of LAAT/SSEC were indicated by Logistic Regression Analysis.

3. Results

3.1. Baseline characteristics

102 patients (71 males) with non-valvular atrial fibrillation took part in this study. The mean age of participants was 59.99 ± 11.01. 67 patients (43 males, 60.23 ± 11.31) were found thrombus/severe spontaneous echocardiographic contrast in LAA.

3.2. Clinical characteristics assessment

Clinical characteristics of the study population are presented in Table 1, including general conditions, past history, type of AF, etc. There was no significant difference between the two groups for clinical characteristics except CHA2DS2-VASC score ($P < 0.05$). CHA2DS2-VASC score were associated with LAAT/SSEC.

3.3. TEE imaging assessment

As indicated in Table 2, LAD was larger in groupⅠ, which indicates that LAD was associated with LAAT/SSEC, the result is consistent with that of the prior study of AF patients[31]. But it can't be an independent predictor by multiple logistic regression analysis. LVEF is lower in groupⅠthan in group Ⅱ ($P < 0.05$), which indicates that LVEF is associated with LAAT/SSEC. However, it still could not be an independent predictor when calculated by multiple logistic regression analysis. When compared with group Ⅱ, LAA-OAmax is larger when there was thrombus/SSEC in LAA ($P < 0.01$), in the same time, LAA-OA variation is smaller in groupⅠ($P < 0.01$). LAAV-max was significantly larger in thrombus group($P < 0.01$). LAAEF was declined in thrombus group ($P < 0.01$). LAAVI is larger in thrombus group ($P < 0.01$) (Fig. 2). It is found that LAA-OAmax, LAAVmax, LAAVI, LAAEF, and LAA-OA variation were the strongest predictors of LAAT/SSEC.

3.4. Multiple logistic regression analysis

As illustrated in Table 3, we choose some indexes for multiple logistic regression analysis. In the univariate analysis, LAD and LVEF can be independent predictors of LAAT/SSEC($P < 0.05$), and LAAVmax, LAAEF, LAAVI, LAA-OAmax, LAA-OA variation, and time of AF were significantly associated with LAAT/SSEC($P < 0.01$). Nonetheless, in the multivariate analysis, LAAVI and LAAEF are independent predictors of LAAT/SSEC($P < 0.05$). Moreover, time of

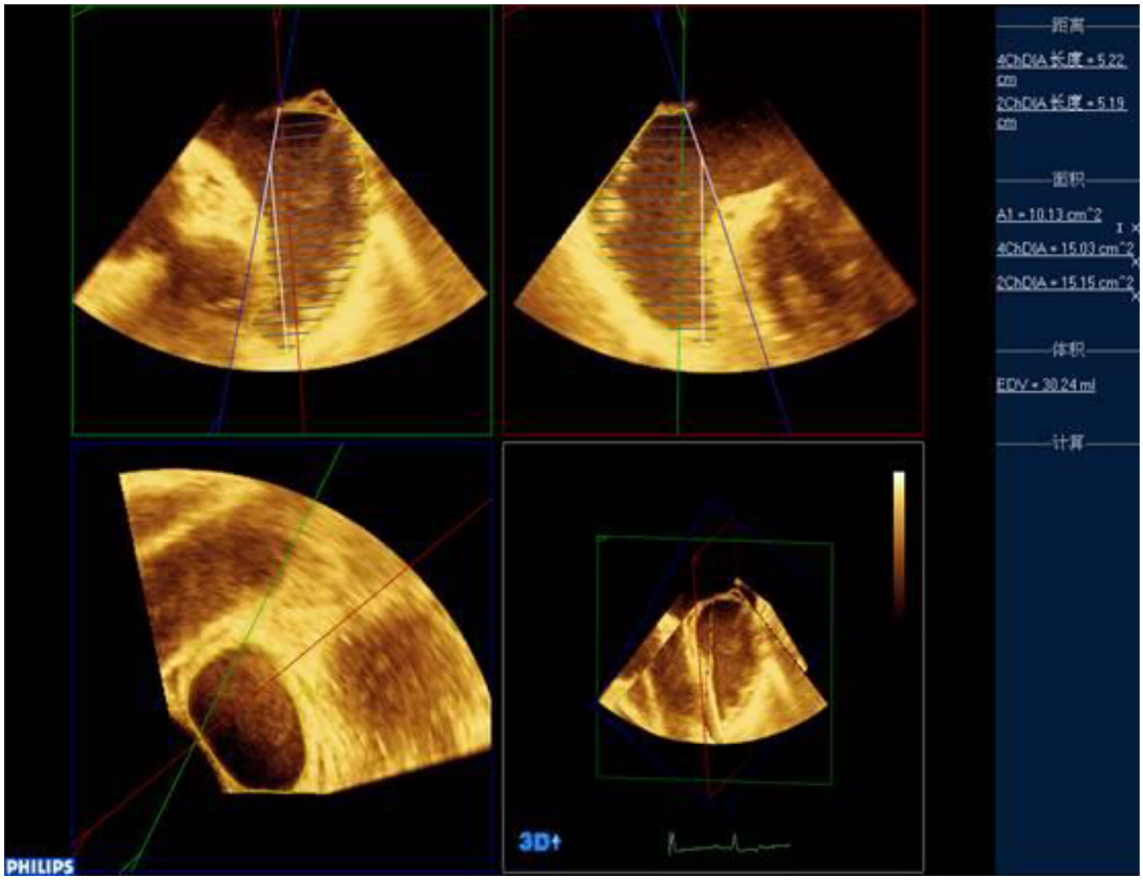

Fig. 1. Turned long axis of LAA to 0°,45°,90°,135°, respectively, and delineated the LAA outline in coronal plane and sagittal plane for each axis degree.

Table 1
Clinical Characteristics of patients with NVAF.

Clinical characteristics	Group I	Group II
P	(n = 67)	(n = 35)
Age	60.23 ± 11.31	59.51 ± 10.54 0.75
Male	43(64%)	28(80%)
0.10		
Hypertension	33(49%)	15(43%)
0.68		
Diabetes mellitus	3(5%)	1(3%)
0.69		
Coronary heart disease	32(48%)	19 (54%)
0.53		
Congenital heart disease	3(4%)	5(14%)
0.08		
Smoke	30(45%)	11(31%)
0.19		
Type of AF	60(90%)	35(100%)
0.09		

Table 2
The result of TEE imaging assessment.

TEE features	group I	group II
P	(n = 67)	(n = 35)
LAD(mm)	45.1 ± 7.31	42.25 ± 4.21
	0.014*	
LVEF (%)	0.57 ± 0.1	0.61 ± 0.08
	0.035*	
LAA-OAmax(cm^2)	6.19 ± 2.52	3.52 ± 1.41
	0.000**	
LAA-OA variation (%)	0.24 ± 0.13	0.49 ± 0.19
	0.000**	
LAAVmax (ml)	10.49 ± 5.68	5.73 ± 2.36
	0.000**	
LAAEF (%)	0.24 ± 0.11	0.52 ± 0.18
	0.000**	
LAAVI(ml/m^2)	6.05 ± 3.22	3.14 ± 1.15
	0.000**	

*:P < 0.05; **:P < 0.01.

AF is significantly independent predictor of LAAT/SSEC(P < 0.01). Gender, age and hypertension were not associated with LAAT neither in univariate analysis nor multivariate analysis.

4. Discussion

As the development of ultrasonographic technology, the structure and function of LAA are known by investigators gradually (Wolf et al., 1991). LAA is a myogenous residue of left atrial, which can diastole and systole initiatively. The LAA compliance and capability for blood storage is much stronger than other area of left atrial, thus LAA is an important part for releasing LA pressure and ensuring LV filling. Because of the complex structure and trabecular muscles, LAA is the most common place for LA thrombus. Once AF occurs, LA and LAA lost the capability of constriction, which leads to the failure of effective ejection and retention of the blood, and SSEC/LAAT is formed eventually. This study detailed the clinical features and TEE characteristics of non-valvular atrial fibrillation and concluded the risk factors of LAAT/SSEC. The data showed that the time of AF, LAAEF, LAAVmax, LAAVI, LVEF, LAD, LAA-OAmax, and LAA-OA variation are strong predictors of LAA thrombus formation ($P < 0.05$). In addition, time of AF, LAAEF, and LAAVI can be independent predictors of LAA thrombus.

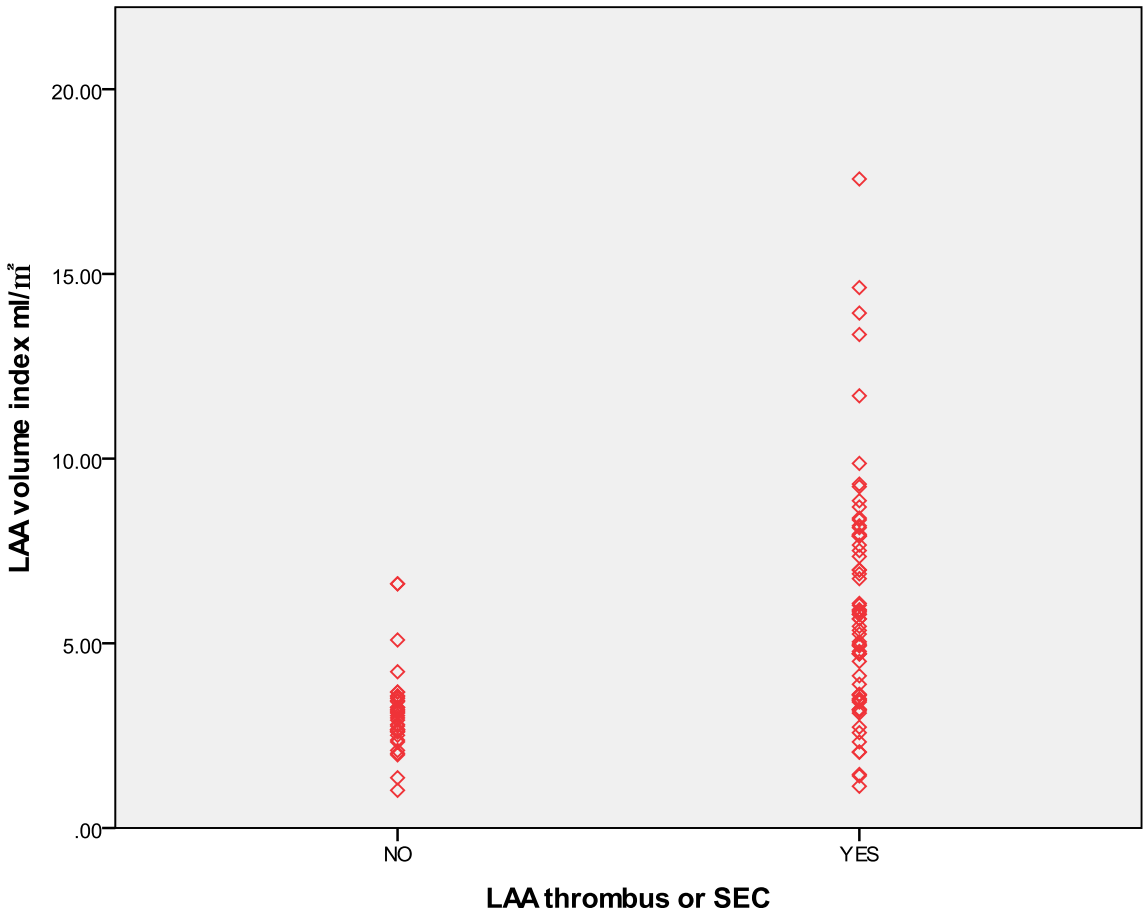

Fig. 2. The distribution of LAA volume index in patients with and without LAA thrombus or SEC. there was considerable overlap between the two groups.

Table 3
Multivariate Predictors of LAA Thrombusis.

Analysis (95%ROC)	Univariate analysis odd ratio(95%ROC)	Multivariate odd ratio
Gender	2.23(0.85–5.87)	
Age	1.49(0.80–2.79)	
LAD	1.69(1.05–2.74)*	
LVEF	5.00(1.10–22.69)*	
LAAVmax	2.66(1.69–4.18)**	
LAAEF	8.38(3.68–19.10)**	
4.09(1.61–10.37)**		
LAAVI	7.55(3.28–17.37)**	
3.28(1.43–7.52)**		
LAA-OAmax	4.89(2.29–10.41)**	
LAA-OA variation	5.77(2.85–11.70)**	
Hypertension	1.29(0.57–2.95)	
Time of AF	1.93(1.37–2.72)**	
1.73(1.01–2.98)*		

*:P < 0.05; **:P < 0.01.

4.1. Enlargement of left atrial

Our study shows that LAD of patients with thrombus is larger than those without thrombus (P < 0.05). However, multiple logistic regression analysis demonstrates that LAD could not be independent predictor of LAA thrombus. The prediction of LAA thrombus has been previously described by Ellis et al. (2006) using transthoracic echocardiogram. They demonstrated that the left atrial is enlarged in thrombus group by univariate analysis, which is consistent with our study. Furthermore, the enlargement of the left atrial could be an independent predictor of LAA thrombus with multivariate analysis, which is not coincidence with our study. The difference may be caused by sample capacity and grouping method, since we took severe SEC into thrombi group and our sample capacity is smaller than Keith's. In that case, the enlargement of left atrial is a strong risk factor of LAA thrombus. However, a prospective study with large sample should be proceeded to demonstrate whether it is an independent predictor.

4.2. Decrease of left ventricle ejection fraction

The LVEF of patients with thrombus is lower than those without thrombus (P < 0.05). Reduced LVEF leads to the enlargement of left ventricular end-diastolic volume, subsequently causes the increase of the pressure and volume of LA. LAA compliance is enlarged when LA filling pressure is increased, which caused LAA more prone to extend than LA. LAA's pressure burden and volume burden increased as Frank Starling mechanism, which changes the speed of blood flow and forms LAA thrombus. Studies have shown that LAA thrombus is related with the function of LA and LAA (Asha et al., 2004; Safavi-Naeini and Rasekh, 2020). Participants were divided into three groups according to LVEF (LVEF < 35%; 35%<LV EF < 45%; and 45%<LVEF). There is a significant difference for LAA function among three groups. What is more, LAAT/SSEC formations in the first and the second groups were higher than that in the third group. Another study by Lin et al (1996) demonstrated LV diastolic function could influence LAA function. In their study, the peak outflow speed of LAA in LV diastole was faster than that in LV systole [(0.23 ± 0.14)m/s vs (0.15 ± 0.13)m/s, P < 0.001], the peak inflow speed of LAA in LA diastole was faster than that in LV systole too [(0.22 ± 0.15)m/s vs (0.18 ± 0.11)m/s, P < 0.01].

In the persons with decreased LVEF, the peak outflow speed of LAA was lower, and demonstrated that LV diastolic function could influence LAA flow in AF patients. They presumed that LV function is a predictor of LAA thrombus. On the basis of the above studies, the decreased LVEF was represented as a favorable condition for thrombus formation.

4.3. LAA-OAmax and LAA-OA variation

When atrial fibrillation occurs, the LA volume enlarges and pressure increases. Qamruddin identified that LAA plays an important role in regulating LA hemodynamics when the LA volume and pressure increases (Qamruddin et al., 2010). Large volume and pressure of LA leads to an increased LAA compliance. In addition, the LAA opening area is broaded as sphericity or hemispheroid when SSEC/LAAT is formed. Our result showed that there is a difference between two groups in LAA-OAmax and LAA-OA variation ($P < 0.05$). But LAA-OAmax and LAA-OA variation still could not be independent predictors of LAA thrombus with multiple logistic regression analysis. Since LAA-OA variation mainly reflects the function of LAA basement. Among sinus rhythm persons, LAA apex was illegibility in the systole period because of utmost constriction, yet there is no obvious constriction from LAA basement to LAA cervix (30%-50% of LAA length) (Porte et al., 1996). As a result, the motion of LAA apex can reflect LAA filling and evacuating function better. In addition, we put SSEC into thrombus group, the LAA basement function is not significantly decreased while SSEC formations. In that case, LAA-OAmax and LAA-OA variation can predict thrombus, but cannot be the independent predictors.

4.4. Enlargement of LAA volume and decrease of LAAEF

LAA seldom forms thrombus in sinus rhythm because of well contractibility (Chan et al., 1995). Atrial fibrillation causes the function decrease and blood siltation of LAA. Besides, LAA volume significantly enlarges and LAAEF decreases, which lead to the tendency of LAA thrombus. The LAA function lost with different degree when AF was occurred. Nevertheless, LAA function significantly decreased when LAA thrombus was formed. Since LAA function was mainly reflected by the LAA systole and diastole capability, LAAV and LAAEF could be an objective and preferred selection for evaluating the LAA function.

LAA thrombus formation includes the spontaneous echocardiographic contrast phase (mild; midrange; severe) and thrombus formation phase. During the process of thrombus formation, LAA gradually enlarges, blood flow and heart movement decreases, especially, when SSEC/LAAT occurs. Post research found that structure of LAA is negatively correlated with its function. Change of LAA structure and function may predict LAA thrombus (Patti et al., 2017).

Thus, we choose LAAV and LAAEF for evaluating the formation of thrombus. There is a difference between two groups that we studied for LAAV and LAAEF ($P < 0.05$). Multiple logistic regression analysis shows that LAAVmax is different between two groups ($P < 0.01$); however, it cannot be an independent predictor of LAA thrombus by multiple logistic regression analysis. Nevertheless, LAAEF is an independent predictor (OR:4.09, $P < 0.01$). Based on the research above, we obtain a conclusion that LAAEF has great value in evaluating LAA function and predicting thrombus formation.

LAAEF was acquired by calculating LAA area variation in two dimension echocardiography for previous study. However, two dimension echocardiography is prone to cause diversity in LAA shape or size because of complexity of LAA structure. However, 3D-echocardiography is a better approach for observing the complex structure of LAA, which was highly coincided with anatomic structure (Roldán et al., 2001). Thus we chose RT-3D-TEE for detecting LAAV/LAAEF, and obtained more accurate results than previous researches and analyzed the relationship between LAA function and thrombus formation.

4.5. Enlargement of LAAVI

The relationship between LAA thrombus and LAAV has been demonstrated previously. However, because of the individual difference, LAAV is influenced by gender, height, weight, etc. In order to eliminate the influence of gender, height and weight, we standardized the body surface area (BSA) for evaluating LAAV, which could reflect LAA size accurately. Significant difference for LAAVI was found between two groups ($P < 0.05$). What is more, it can be an independent predictor of LAA thrombus by multiple logistic regression analysis(OR:3.28; $P < 0.01$). The result demonstrates that LAAVI reflects LAA size better than LAAV.

5. Conclusions

This retrospective, comparative study provides the evidence-based validation of the use of TEE for imaging the LAA thrombus. In the present data the relationship between LAA function and formation of thrombus using new parameters of TEE has been effectively studied. In patients with nonvalvular atrial fibrillation, AF time、LAAEF and LAAVI are significantly associated with LAAT/SSEC. New parameters of TEE can predict thromboembolic events and improve stroke prediction in NVAF patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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