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# Relation between low take-off of the left atrial appendage and thromboembolic events in patients with atrial fibrillation : evaluation with multi-detector CT

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## Abstract

**Background : The left atrial appendage (LA-Ap) is one of the major sources of cardiac thrombus formation responsible for thromboembolism in patients with atrial fibrillation (AF). We hypothesized that the particular anatomical characteristics of the LA-Ap may facilitate thrombus formation. Methods : Seventy-four AF patients underwent transesophageal echocardiography (TEE) and multi-detector CT (MDCT) examinations. These patients were divided into two groups, with and without systemic embolism (Emb) [Emb (+) group, 10 patients, male/female=7/3 ; Emb (−) group, 64 patients, male/female=51/13]. To evaluate the location of the LA-Ap in relation to the left atrium (LA), we determined four distinctive points on MDCT images using two carefully defined orthogonal sections : the superior summit of the mitral annulus (point-A), the anterior and posterior sites of the LA-Ap orifice (point-B and C), and the posterior LA (point-D). Next, we evaluated the relation of the geometrical intervals (A-B, B-C, C-D) to the prior thromboembolism. Results : Using multivariate analysis, a shorter A-B interval was recognized as an independent factor positively associated with a history of thromboembolism. Conclusion : The position of the LA-Ap orifice may affect the hemodynamic state of the LA-Ap, and anterior deviation of the LA-Ap orifice (low take-off of the LA-Ap) may be a risk factor for thrombus formation in LA-Ap and systemic embolism.**

**Key words : atrial fibrillation, thromboembolism, left atrial appendage, multi-detector CT, transesophageal echocardiography**

## Introduction

Thromboembolism is the most serious clinical complication of atrial fibrillation (AF).[1–5] Antithrombotic therapy with warfarin or novel oral anticoagulants lowers the risk of clinical thromboembolism in AF patients with proper risk factors irrespective of the AF type (paroxysmal, persistent).[1] $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years old, diabetes mellitus, history of stroke (doubled)],[5] a scoring system widely used to evaluate the risk of thromboembolism, has been of considerable help in preventing systemic thromboembolism in patients with non-rheumatic AF. Yet even in patients classified as low risk by $CHADS_2$ (score ≤1), the annual event rates for systemic thromboembolism reach as high as 1.9% to 2.8%,[5] indicating that $CHADS_2$ has several limitations.

The left atrial appendage (LA-Ap) is one of the major sources of cardiac thrombus formation responsible for systemic thromboembolism in patients with AF.[6–8] Some studies using transesophageal echocardiography (TEE) have demonstrated a significant relationship between enlargement of the LA-Ap and thrombus forma-

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tion.[9–11] It remains uncertain, however, whether thromboembolic risk can be reliably determined by assessment of the size or morphology of the LA-Ap using TEE,[11–13] multi-detector CT (MDCT) or magnetic resonance imaging (MRI).[14–16] The aim of this study was to test the hypothesis that particular, but unknown anatomical characteristics of the LA-Ap may facilitate thrombus formation.

## Methods

### Patients

We retrospectively investigated 94 consecutive patients in whom both MDCT and TEE were performed more or less at the same time (within one month) in our hospital from April 2012 to June 2013. The main aim of these examinations was to rule out the presence of thrombus in LA-Ap before catheter ablation (ablation). Twenty patients were excluded from the study because 18 patients had undergone a previous session of ablation before the corresponding period and 2 patients had suffered thromboembolism more than three years earlier. Finally, 74 patients were enrolled in the study and divided into two groups, i.e., subjects with and without systemic embolism (Emb) before ablation [Emb (+) group; 10 patients, Emb (−) group; 64 patients] (Table 1).

All patients underwent appropriate anticoagulant therapy at the time of MDCT and TEE imaging. Warfarin was prescribed to 25 patients, and the target range of the PT-INR level was between 2.0 and 3.0 (1.6-2.6 in elderly patients, age ≥70).

### Clinical variables

The $CHADS_2$ score, $CHA_2DS_2$-VASc score[17], and parameters listed in the scoring systems (chronic heart failure, hypertension, age, diabetes mellitus, stroke, vascular diseases, female gender) were evaluated to determine whether they were relevant factors for prior embolic events. The $CHADS_2$ score in Emb (+) group was evaluated before the thromboembolic episode to clarify predictive factors of the first episode of thromboembolism, which indicates that double points of "stroke" in the $CHADS_2$ score were not counted in the Emb (+) group. Brain natriuretic peptide (BNP) and body mass index (BMI) were also assessed. The presence of malignant cancer or inflammatory disease known to facilitate coagulability was also investigated.

**Table 1** Clinical variables

| | Emb (−) n=64 | Emb (+) n=10 | p Value |
|---|---|---|---|
| Age (years) | 63.9±10.3 | 61.5±7.9 | 0.4791 |
| Gender | | | 0.4427 |
| Male | 51 (79.7) | 7 (70.0) | |
| Female | 13 (20.3) | 3 (30.0) | |
| BMI (kg/m$^2$) | 24.2±4.8 | 25.1±5.1 | 0.5830 |
| Heart failure | 8 (12.5) | 2 (20.0) | 0.6166 |
| Hypertension | 31 (48.4) | 5 (50.0) | 1.0000 |
| Diabetes mellitus | 11 (17.2) | 2 (20.0) | 1.0000 |
| AF type | | | 1.0000 |
| Paroxysmal | 37 (57.8) | 6 (60.0) | |
| Persistent | 27 (42.2) | 4 (40.0) | |
| $CHADS_2$ | 0.9±0.9 | 0.9±0.6 | 0.9750 |
| 0 | 25 (39.1) | 2 (20.0) | |
| 1 | 26 (40.6) | 7 (70.0) | |
| 2 | 8 (12.5) | 1 (10.0) | |
| 3 | 5 (7.8) | 0 (0.0) | |
| 4-6 | 0 (0.0) | 0 (0.0) | |
| $CHA_2DS_2$-VASc | 1.7±1.3 | 1.7±0.9 | 0.9659 |
| 0 | 12 (18.8) | 1 (10.0) | |
| 1 | 20 (31.3) | 3 (30.0) | |
| 2 | 15 (23.4) | 4 (40.0) | |
| 3 | 10 (15.6) | 2 (20.0) | |
| 4 | 5 (7.8) | 0 (0.0) | |
| 5 | 2 (3.1) | 0 (0.0) | |
| 6-10 | 0 (0.0) | 0 (0.0) | |

Data are presented as the mean ±SD or n (%),
Emb (−): group without a history of systemic embolism,
Emb (+): group with a history of systemic embolism,
AF: atrial fibrillation, BMI: body mass index,
The reported $CHADS_2$ and $CHA_2DS_2$-VASc scores were calculated before any thromboembolic event.

### Transthoracic echocardiography (TTE)

Patients were imaged in the left lateral decubitus position with a commercially available system. Images were obtained in the parasternal and apical views (standard long-axis and 2- and 4-chamber images). Standard 2-D and color Doppler data triggered by the QRS complex were saved in cine-loop format. The LA dimension (LAD) was measured using a conventional long-axis view. The left ventricular (LV) end-diastolic dimension (LVDd) and LV ejection fraction (LVEF) were calculated from the conventional apical 2- and 4-chamber images with the biplane Simpson technique.[18] The

following TTE parameters were compared between the two groups: LAD, LVDd, LVEF.

**Transesophageal echocardiography (TEE)**

TEE was performed using Philips Sonos 5500 with a single-plane probe equipped with a 5-MHz transducer.[19–21] Sedation with 5-10 mg i.v. midazolam was used if necessary. The pharynx was anesthetized with topical lidocaine spray, and the probe was introduced into the esophagus with the patient lying on the left side. The LA-Ap was viewed from the basal short axis, with the tip of the probe slightly flexed to observe the whole LA-Ap. Three parameters were evaluated using TEE: the presence of thrombus in the LA-Ap, spontaneous echo contrast,[20,21] and emptying and filling flow velocities in the LA-Ap. The emptying and filling flow velocities of LA-Ap were measured by placing pulsed wave Doppler sample volume inside the base of the appendage.[20] For patients in a state of AF during the procedure, the maximum emptying and filling flow velocities were measured in each of five subsequent cardiac cycles, and the values were averaged.[20–22]

**MDCT**

Electrocardiographic-gated 64-slice MDCT (GE Healthcare) was performed by the test bolus tracking method.[23] The scan parameters were as follows: 120 kV, 500-700 mA, 0.16 helical pitches, 350 msec gantry rotation time, 0.625×0.625 mm slice thickness by interval. The slice thickness of the reconstruction was 0.625 mm, and reconstruction method was selected segment reconstruction or half reconstruction according to heart rate. The contrast agent (Iopamiron 370, 0.8 ml/kg) was injected into the antecubital vein within 12 seconds using a power injector. In order to reduce the influence of geometrical movement of the mitral valve annulus through the cardiac cycle, we constructed a CT image at 75% of RR intervals. The data in the patients with atrial fibrillation during CT examination might be influenced by a variation of R-R intervals.

The morphology and location of the LA-Ap in relation to the LA were evaluated using Aze Virtual Place Fujin (Aze Ltd., Tokyo, Japan),[24] a commercially available software application designed to make exact geometrical measurements of MDCT images. Because the 3-D structure of LA-Ap is so complicated, exact determination of the volume of LA-Ap is difficult, and challenges to classify a LA-Ap configuration is much subjective. In order to perform highly quantitative evaluation, we have created new methods on MDCT images as shown in Figure 1 and 2. To begin, a distinctive "standard line" was defined for the left cardiac chambers from the LV apex to the middle of the mitral annulus (MA middle). The LV apex was easily identified using three different orthogonal sections of CT images. Several sagittal sections containing the point of the LV apex were then constructed, and the slice with the maximum MA diameter was selected. The MA middle in the selected slice was set as the central point of the MA, and the "standard line" between the LV apex and MA middle (Figure 1) was created. Frontal sections were constructed at the orthogonal axis with the standard line to demonstrate the proximal (anterior) and distal (posterior) sites of the LA-Ap orifice and posterior LA wall (Figure 2).

Finally, four distinct points, namely, the summit (most superior site) of the mitral annulus (point A), the anterior and posterior sites of the LA-Ap orifice (points B and C), and the poste-

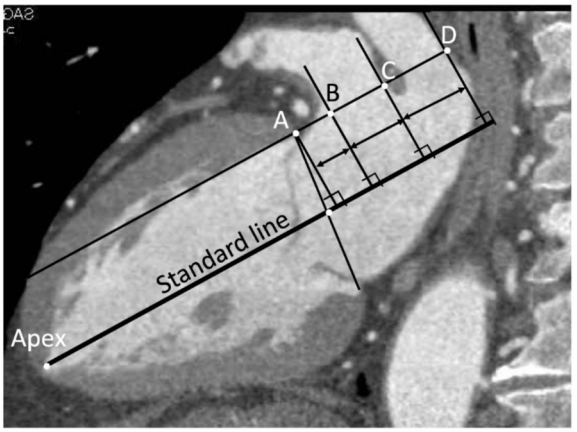


**Fig. 1** Definition of four distinct points (A to D) on sagittal section of multi-detector CT

Representative sagittal section of multi-detector CT image in which we defined four distinct points (A to D). Several sagittal sections containing the point of the LV apex were constructed, and the slice with the maximum diameter of mitral annulus (MA) was selected. On this image, the MA middle in the selected slice was set as the central point of the MA, and the "standard line" between the LV apex and MA middle was created. Each point indicates mitral annulus (point A), the anterior and posterior sites of LA-Ap orifice (point B and C), and the posterior site of LA (point D) respectively. The distance between each pair of points, (A-B, B-C, and C-D) was measured by projecting to the standard line (arrows). The detailed methods to identify the points B and C are described in Figure 2.

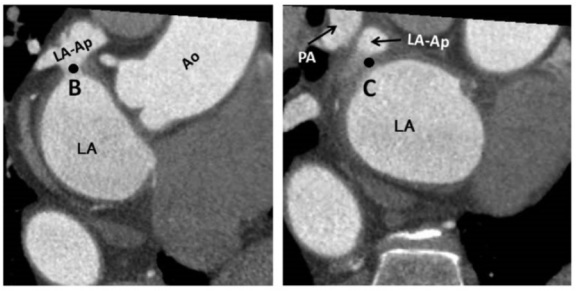


**Fig. 2** Determination of points B and C on frontal section of multi-detector CT
Frontal sections of multi-detector CT image were constructed at the orthogonal axis with "standard line" (shown in Figure 1) to detect the proximal (anterior) and distal (posterior) sites of the LA-Ap orifice (points B and C). We determined point B where LA-Ap and left atrium merged (left panel), and determined point C where LA-Ap and the left atrium become separated (right panel).
LA-Ap : left atrial appendage, LA : left atrium, Ao : aorta,
PA : pulmonary artery.

rior site of the LA (point D), were constructed. The distance between each pair of points, (A-B, B-C, and C-D) was measured by projecting to the standard line (Figure 1), and these intervals were evaluated as the corresponding factor for previous episodes of thromboembolism.

**LA-Ap position and blood flow in LA-Ap**

To confirm the relationship between the LA-Ap position and blood flow within the LA-Ap, three geometrical intervals (A-B, B-C, C-D in Figure 1) with the LA-Ap flow velocity were evaluated by TEE in 23 patients during AF [19 in the Emb (−) group and 4 in the Emb (+) group ; heart rate <120 beats/min, normal LV function]. The relationship between the average emptying or filling flow velocities of LA-Ap and three geometrical parameters was investigated. Patients with heart rate >120 beats/min and LVEF <50% were excluded from this evaluation because increased heart rate[25,26] and LV dysfunction[27–31] are well known to decrease the blood flow of the LA-Ap during AF.

**Diagnosis of stroke and thromboembolism**

Based on the MONICA project,[32] stroke was defined as rapidly developed signs of focal (or global) disturbance of cerebral function lasting >24 hours (unless interrupted by surgery or death), with no apparent nonvascular cause. The diagnosis of embolic cerebral infarction is based on the symptoms [abrupt onset, completion of the neurologic deficits within a few minutes, and little to no disturbance of consciousness at the onset] and findings [brain infarction in the CT or MRI examination, together with a detectable source of the embolus (e.g., AF)]. Systemic thromboembolism is defined as acute ischemic symptoms in any of the general organs, together with a definite infarcted region and a particular vascular supply on CT or MRI imaging.

**Measurements and Statistical analysis**

All data in MDCT, TTE, and TEE were measured and analyzed without knowledge of the patient grouping.

First, using univariate logistic regression analysis, we searched for factors associated with the occurrence of thromboembolism. Next, we performed multivariate logistic regression analysis using variables with $p<0.05$ in the first univariate analysis and other several parameters which may relate to anatomical characteristics of LA-Ap, and $CHADS_2$ score were included as independent factors. The ability of the independent factor to discriminate patients with and without history of thromboembolism was assessed using the area under the receiver-operating characteristic (ROC) curve (AUC). An AUC equal to 1.0 indicates perfect discrimination. Third and finally, we examined the relationship between the independent factors and LA-Ap emptying and filling flow velocities by scatter and coefficients.

Differences between the two groups in categorical and continuous variables were detected with Fisher's exact test and Student's t-test, respectively.

## Results

**Clinical variables**

Clinical variables are shown in Table 1. The two groups were similar with respect to age, gender, BMI, heart failure, hypertension, diabetes mellitus, AF type (paroxysmal or persistent), $CHADS_2$, $CHA_2DS_2$-VASc, and BNP. These variables were also not found to be related to thromboembolism including even the $CHADS_2$ score in univariate analysis. In the Emb (+) group, 8 patients had brain infarction (stroke), 1 had renal infarction, and 1 had myocardial infarction. No malignant cancer or inflammatory disease known to facilitate coagulability was observed in either group.

**TTE, TEE and MDCT data**

The parameters of TTE and TEE examina-

tions are presented in Table 2. The two groups were similar with respect to LAD, LVDd, LVEF, presence of thrombus and spontaneous echo contrast in LA-Ap. No variables in univariate analysis were found to be related to thromboembolism.

Among three measured MDCT indices in the LA, univariate analysis showed that the A-B interval (from the MA summit to the anterior site of the LA-Ap orifice) was significantly related to a history of thromboembolism [odds ratio (OR) 0.65, 95% confidence interval (CI) 0.43 to 0.90, p=0.0081]. This suggests that the location of the anterior site of the LA-Ap orifice deviates more anteriorly (defined as a "low take-off" of the LA-Ap). The sagittal diameter between the anterior and posterior sites of the LA-Ap orifice (B-C) and between the posterior orifice of the LA-Ap and posterior wall of the left superior pulmonary vein (C-D interval) did not relate to a history of thromboembolism. In comparison of the A-B, B-C, and C-D intervals between Emb (+) and Emb (−) groups, only the A-B interval in Emb (+) group was significantly shorter than that in Emb (−) group (8.7±1.6 mm vs 10.7±2.5 mm; p=0.0127, 18.7±4.6 mm vs 16.2±3.8 mm; ns, 27.2±9.2 mm vs 24.0±6.2 mm; ns,

**Table 2** Echocardiography data

| | Emb (−) n=64 | Emb (+) n=10 | p Value |
|---|---|---|---|
| Transthoracic echocardiography | | | |
| LAD (mm) | 40.7±6.1 | 41.9±5.3 | 0.5649 |
| LVDd (mm) | 48.5±4.1 | 51.0±5.1 | 0.0898 |
| LVEF (%) | 65.0±7.9 | 67.8±6.7 | 0.2904 |
| Transesophageal echocardiography | | | |
| Spontaneous echo contrast | 10 (15.6) | 1 (10.0) | 1.0000 |

Data are presented as the mean ±SD or n (%),
Emb (−): group without a history of systemic embolism,
Emb (+): group with a history of systemic embolism,
LAD: left atrial dimension, LVDd: left ventricular end-diastolic dimension,
LVEF: left ventricular ejection fraction

**Table 3** Multivariate logistic regression analysis

| | OR (95% CI) | p Value |
|---|---|---|
| A-B interval | 0.66 (0.40-0.97) | 0.0361 |
| B-C interval | 1.14 (0.92-1.45) | 0.2301 |
| C-D interval | 1.07 (0.97-1.19) | 0.1864 |
| LAD | 1.01 (0.87-1.18) | 0.9246 |
| $CHADS_2$ | 0.74 (0.26-1.79) | 0.5221 |

OR: odds ratio, CI: confidence interval, LAD: left atrial dimension

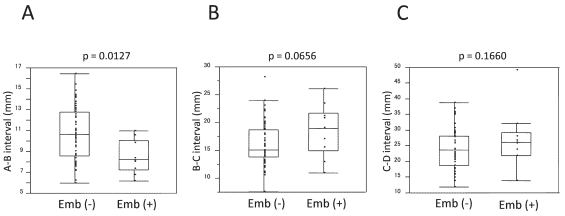


**Fig. 3** Comparison of the A-B, B-C, C-D intervals between the two groups
Comparison of the A-B, B-C, and C-D intervals between the two groups. The A-B interval in Emb (+) group was significantly shorter than that in Emb (−) group (panel A), but B-C and C-D intervals were not significantly different between the two groups (panel B and C, respectively).
Emb (+): group with a history of systemic embolism,
Emb (−): group without a history of systemic embolism

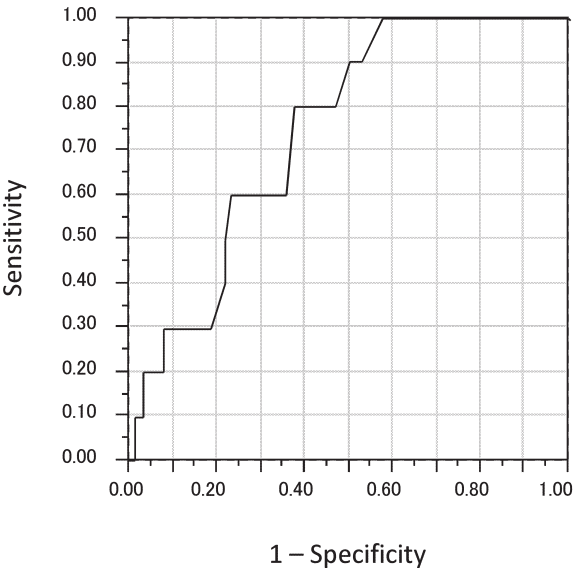


**Fig. 4** Area under the receiver operating characteristic (ROC) curve (AUC) to determinate patients with and without history of thromboembolism
AUC was calculated to assess the capability of A-B interval to discriminate patients with and without history of thromboembolism. AUC of A-B interval was 0.75 which indicates that A-B interval has moderate accuracy for the history of thromboembolism. Using a cutoff level of 9.9 mm, A-B interval predicted systemic thromboembolism with a sensitivity of 80% and specificity of 62.5%.

respectively, Figure 3). AUC was calculated to assess the capability of A-B interval to discriminate patients with and without history of thromboembolism. As shown in Figure 4, AUC of A-B interval was 0.75 which indicates that A-B interval has moderate accuracy for the history of thromboembolism.

**Relationship between the A-B interval and flow velocity in the LA-Ap**

Figure 5 shows the relationship between the A-B interval and the averaged LA-Ap flow velocities during AF (emptying and filling) in 23 patients with or without a history of thromboembolism. The A-B interval significantly correlates to both the averaged emptying and filling flow velocities in the LA-Ap during AF ($R=0.5700$, $p=0.0045$, and $R=0.4781$, $p=0.0210$, respectively). This demonstrates that a low take-off of the LA-Ap orifice may result in decreased blood flow within the LA-Ap during AF.

**Multivariate analysis**

As the A-B interval was the only parameter in univariate analysis significantly related to a history of thromboembolism, we performed multivariate analysis using the A-B interval, other several parameters which may relate to anatomical characteristics of LA-Ap (B-C and C-D intervals and LAD), and $CHADS_2$ score. In this latter analysis, the A-B interval was recognized as an independent factor related to a history of thromboembolism [OR 0.66, 95% CI 0. 40 to 0.97, $p=0.0361$].

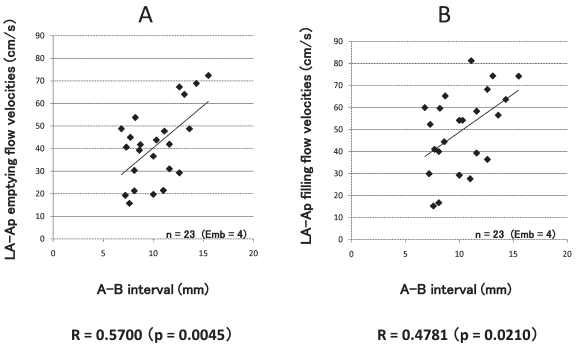


**Fig. 5** The relationship between the A-B interval and averaged LA-Ap flow velocities during AF
Figure 5 shows the relationship between the A-B interval and averaged LA-Ap flow velocities during AF (emptying in panel A and filling in panel B) in 23 patients irrespective of a history of thromboembolism. The A-B interval significantly correlates to both the averaged emptying and filling flow velocities in LA-Ap during AF ($R=0.5700$, $p=0.0045$, and $R=0.4781$, $p=0.0210$, respectively).
AF: atrial fibrillation, LA-Ap: left atrial appendage,
Emb: group with a history of systemic embolism, R: correlation coefficient

## Discussion

This study demonstrated one major finding: the position of the LA-Ap orifice may affect the hemodynamic state of the LA, in particular, anterior deviation of the LA-Ap orifice (low take-off of the LA-Ap) is a risk factor for thrombus formation in the LA-Ap and thromboembolism. We also confirmed that the distance from the summit of the MA to the anterior orifice of the LA-Ap (the A-B interval) was positively related to the flow velocity in the LA-Ap during AF rhythm.

**Anatomical characteristics of the LA-Ap in patients with AF and thromboembolism**

The first detailed description of the varied morphology of the LA-Ap in AF patients was provided by Ernst et al.,[33] who studied the morphology of the LA-Ap in 220 cases using synthetic resin casts made at necropsy. Compared with the casts from patients who had been in sinus rhythm, the casts from the patients who had been in AF were larger and had larger orifices and fewer branches. While they found the LA-Ap to be significantly larger in the patients with thrombus, they were unable to demonstrate a clear relationship between the size of the LA-Ap and a history of thromboembolism. The characteristics of their patients were different from those of ours, and many of their patients had heart failure or mitral stenosis.

The advance of imaging technologies such as TEE, MDCT and MRI allows noninvasive methods to perform more precise quantitative analysis of the LA-Ap size in relation to thromboembolism. Several clinical studies have reported that LA-Ap dilatation from two-dimensional (2-D) images in TEE relates to thrombus formation,[9–11] yet no other studies using 2-D imaging by TEE have found a significant role of LA-Ap enlargement in the subsequent occurrence of thromboembolism[12,13] or the presence of LA-Ap thrombus.[12] We know from these discordant results that 2-D images by TEE for highly complicated configurations of LA-Ap provide no promising hints about the particular morphology of LA-Ap suggestive of thromboembolic risk.[16]

Beinart et al.[17] investigated the features of LA-

Ap using MRI, and they reported that the LA-Ap volume, LA-Ap depth and long and short axes of the LA-Ap neck were larger in patients with prior embolic events. In contrast, Di Biase et al.[14] found no significant relationship between the LA-Ap size and the risk of thromboembolism by measuring the volume of the LA-Ap using MDCT and MRI. This discrepancy in results may be due to methodological differences or the non-standardized definition of the boundary between the LA-Ap and LA. Di Biase et al.[14] meanwhile used MDCT/MRI images to classify the morphologies of the LA-Ap in patients with AF into four different types. Based on their classification, they proposed that patients with a particular LA-Ap morphology were significantly more likely to suffer an embolic event. While their method for determining the specific LA-Ap shape indicative of risk of embolic events was intriguing and unique, it failed to provide a quantitative evaluation of the LA-Ap.

In this study we established a novel method to evaluate the particular anatomical characteristics of the LA-Ap and demonstrated that low take-off of the LA-Ap may be a risk factor for thromboembolism. Our method can clearly determine the landmarks of LA-Ap and LA and provide more quantitative analysis.

**A-B interval and flow velocity of the LA-Ap.**

In our study we found that low take-off of the LA-Ap may cause thromboembolic episodes in patients with AF, possibly in relation to decreased blood flow of the LA-Ap during AF. Clinical studies using TEE revealed a significant positive relationship between flow velocity in the LA-Ap and thromboembolic events.[11,13] Low take-off of the LA-Ap may prolong the current pathway between the left superior pulmonary vein and LA-Ap, and thereby reduce blood flow within the LA-Ap during AF.

Fyrenius et. al.[34] reported that vortex blood formation, which is mainly created by blood flow from the left pulmonary veins into the left atrium, has beneficial effects in avoiding left atrial blood stasis. In the situation of AF, the absence of contraction of atrium and LA-Ap may result in a significant blood stasis in LA-Ap, especially in patients with longer distance between LA-Ap and left superior pulmonary vein.

Additional findings in our study, e.g., the significant relationship between the A-B interval (MA to the anterior orifice of the LA-Ap) and the flow velocities in LA-Ap during AF, support our main results.

## Clinical implications

The indication of anticoagulant therapy for AF patients with $CHADS_2$ score $\leq 1$ is still controversial.[35] The "low take-off" feature of the LA-Ap can be used as a novel independent index to predict the risk of thromboembolism and provide better informed choices for anticoagulant therapy, especially in patients with non-valvular AF and a low $CHADS_2$ or $CHA_2DS_2$-VASc score.

## Limitations of this study

There were two major limitations of this study. First, the retrospective study design may have created bias, as we only enrolled patients for whom ablation had been scheduled. Compared to general patient's background of AF, our study includes younger and/or healthier patients, less female gender, and more paroxysmal type of AF.

Second, there was a certain amount of periodical discrepancy between the time of $CHADS_2$ evaluation and the imaging examinations in Emb (+) group. To minimize this gap, we exclude two patients in whom thromboembolism had occurred more than three years before the image diagnosis. Although a shorter interval would have been preferred, several studies have shown that an increase in LA size in patients with AF tends to be insignificant during several years follow up.[36–38]

### Acknowledgments

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