Estimation of left atrial blood stasis using diastolic late mitral annular velocity

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Aims
Diastolic late mitral annular velocity (a’) measured by transthoracic echocardiography (TTE) is reported to represent left atrial (LA) pump function and the severity of LA remodelling. The purpose of this study is to investigate the association between a’ and LA blood stasis in patients with non-valvular paroxysmal atrial fibrillation.

Methods and results
We enrolled 138 consecutive patients with non-valvular paroxysmal atrial fibrillation who had spontaneous sinus rhythm at the time of echocardiography. Using TTE, a’ was determined as an average of tissue Doppler velocities measured at septal and lateral mitral annuli. Transoesophageal echocardiography was also performed on the same day as TTE, and spontaneous echo contrast (SEC) and LA appendage flow velocity were examined. Spontaneous echo contrast was observed in 21 (15%) patients. Patients in the lowest quartile of a’ (≤6.4 cm/s) demonstrated SEC more frequently (44 vs. 6%, P<0.0001) and had lower LA appendage flow velocity (39±13 vs. 53±16 cm/s, P<0.0001) than those in the other quartiles. Receiver-operating characteristic curve analysis showed that the best cut-off value of a’ was 7.0 cm/s for the prediction of SEC with a sensitivity of 80%, specificity of 81%, and predictive accuracy of 80%. Multivariate analysis revealed that decreased a’ (OR = 0.61, P = 0.0026) was independently associated with SEC.

Conclusion
Decreased a’ may be a useful parameter for the estimation of LA blood stasis in patients with paroxysmal atrial fibrillation.

Keywords
Left atrium • Thrombus • Blood stasis • Mitral annular velocity • Spontaneous echo contrast

Introduction
In patients with atrial fibrillation, left atrial (LA) thrombus sometimes causes a systemic thromboembolism including stroke, and estimation of the risk for thromboembolism is essential in clinical practice. The risk of a thromboembolic event is often assessed using the CHA2DS2-VASc score.1 Furthermore, transoesophageal echocardiographic parameters, spontaneous echo contrast (SEC), and LA appendage flow velocity are also thought to provide important information about the risk of LA thrombus formation and thromboembolic event.2–5 However, transoesophageal echocardiography is semi-invasive and not easily performed. A transthoracic echocardiographic method to reliably predict the risk of LA thrombus formation would be useful in the management of patients with atrial fibrillation.

Previous studies reported that advanced atrial remodelling increases the risk of SEC and thromboembolic events.6,7 In addition, tissue Doppler diastolic late mitral annular velocity (a’) measured by transthoracic echocardiography is thought to represent LA pump function, and depressed a’ has been reported to be associated with advanced LA remodelling in patients with paroxysmal atrial fibrillation.8–11 Therefore, we hypothesized that decreased a’ during sinus rhythm can be used as an estimation of SEC and LA blood stasis in patients with paroxysmal atrial fibrillation.

In order to investigate this hypothesis, we performed both transthoracic and transoesophageal echocardiography during

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sinus rhythm in patients with non-valvular paroxysmal atrial fibrillation.

Methods

Study patients

From April 2009 to October 2010, we enrolled consecutive patients with symptomatic drug-refractory paroxysmal atrial fibrillation scheduled for catheter ablation. We excluded patients without spontaneous sinus rhythm at the time of transoesophageal and transthoracic echocardiography. We also excluded patients who had symptomatic atrial fibrillation episodes within 2 days prior to echocardiography to avoid the influence of atrial stunning after conversion of atrial fibrillation to sinus rhythm. Other exclusion criteria were significant mitral stenosis, mitral regurgitation, prior catheter ablation, prior cardiac surgery, and poor echocardiographic images. The study protocol was approved by the hospital’s Ethics Committee and informed consent for the participation in this study was obtained from all patients.

Anti-arrhythmic drugs were discontinued five half-lives before echocardiography. Anticoagulation therapy was initiated based on the discretion of the attending physician according to international guidelines. We calculated the CHA2DS2-VASc score to evaluate the clinical background associated with the risk of thromboembolism. About 1 week before echocardiographic study, 64-detector contrast-enhanced computed tomography was performed. Pre-atrial contraction LA volume was calculated at the onset of P-wave on electrocardiogram excluding the pulmonary veins and appendage, and was indexed to body surface area.

Transoesophageal echocardiography

We performed transoesophageal echocardiography 1 or 2 days prior to catheter ablation, using an SSD-6500 system (Aloka, Tokyo, Japan) equipped with a 5.0 MHz multiplane transoesophageal probe. Left atrial appendage images were obtained both in the basal short-axis view with a transverse scan and in LV-LA two chamber view with a vertical scan. Left atrial thrombus was defined as a well-circumscribed, echogenic mass that was of different texture than the LA wall and had a uniform consistency. Spontaneous echo contrast was defined as a dynamic smoke-like signal that swirled slowly in a circular pattern within the LA and appendage, with appropriate gain settings to distinguish SEC from echoes due to excessive gain. Left atrial appendage flow velocity was measured by placing the pulsed Doppler sample volume at the tip of the mitral leaflets. Tissue Doppler flow were measured by apical four-chamber view using Simpson’s method. Left ventricular mass (grams) was calculated as 0.80 × (1.04 × ([septal wall thickness in diastole + left ventricular end-diastolic dimension + left ventricular posterior wall thickness in diastole]) − left ventricular end-diastolic dimension2) + 0.6 and was indexed to body surface area.

Transthoracic echocardiography

Transthoracic echocardiography was performed on the same day as transoesophageal echocardiography, using a Sonus iE33 system (Philips, Andover, MA, USA). Left ventricular ejection fraction was assessed from the apical four-chamber view using Simpson’s method. Left ventricular mass (grams) was calculated as 0.80 × (1.04 × ([septal wall thickness in diastole + left ventricular end-diastolic dimension + left ventricular posterior wall thickness in diastole]) − left ventricular end-diastolic dimension2) + 0.6 and was indexed to height2,7,15,16. Peak velocities of diastolic early (E) and late (A) transmural Doppler flow were measured by apical four-chamber view with the sample volume placed at the tip of the mitral leaflets. Tissue Doppler velocities during early (e’) and late (a’) diastole were measured with a colour tissue Doppler technique at the basal septal and lateral mitral annuli on the apical four-chamber image. Diastolic function was graded according to the recommendation by the American Society of Echocardiography and the European Association of Echocardiography. The mean values of five consecutive heart beats from septal and lateral measures were used. Interobserver variability of a (6%) was calculated in 12 randomly selected patients as the difference in two measurements in the same patients by two different observers divided by the mean value.

Statistics

Continuous values were expressed as the mean ± SD unless otherwise indicated. Categorical data were presented as absolute values and percentages. Tests for significance were conducted using a t-test or repeated measures analysis of variance to compare continuous variables, and a χ² test or Fisher’s exact test for categorical variables. Univariate and multivariate logistic regression analyses were used to determine the factors that were associated with the presence of SEC. Variables with a P value ≤ 0.05 in the univariate model were included in the multivariate analysis. For the prediction of SEC, receiver-operating characteristic curves were constructed for different cut-off values of a. The area under each curve was determined along with the 95% CI using the bootstrap method. All analyses were conducted using SPSS for Windows, version 15.0.

Results

Patient characteristics

Of the 180 patients with paroxysmal atrial fibrillation scheduled for ablation during the study period, 138 patients were included in this study. Reasons for exclusion were as follows: atrial fibrillation at the time of echocardiography (four patients), symptomatic atrial fibrillation episodes within 2 days prior to echocardiography (nine patients), prior history of ablation (23 patients), or cardiac surgery (two patients), severe mitral valve disease (three patients) and poor echocardiographic image (one patient). Left atrial thrombus was observed in two of 138 (1%) patients, and SEC was detected in 21 (15%) patients on transoesophageal echocardiography. Clinical characteristics stratified according to the presence or absence of SEC are shown in Table 1. Heart failure was more often present in patients with than without SEC, and other clinical risk factors for thromboembolism, such as high age, hypertension, diabetes mellitus, and previous history of thromboembolism, tended to be more frequent in patients with SEC. Therefore, the CHA2DS2-VASc score was significantly higher in patients with SEC. In addition, LA volume and its index measured by computed tomography were significantly larger in patients with SEC. In contrast, there was no difference between patients with and without SEC in the frequency of anticoagulation therapy, haemocrit level, and international normalized ratio of prothrombin time.

Echocardiography

The echocardiographic parameters are listed in Table 2. Patients with SEC had higher left ventricular mass index, lower e’ and a’, and higher E/e’ index. In addition, LA appendage flow velocity was significantly lower in patients with SEC.

There were two patients with LA thrombus and both were on anticoagulation therapy (international normalized ratio of prothrombin time was 2.3 ± 0.1). Spontaneous echo contrast was observed in 2/2 (100%) patients with LA thrombus.
Association with a′ and surrogate makers for LA thrombus

We divided the study patients into four groups based on the quartile of a′, and compared the incidence of SEC and LA appendage flow velocity among the quartiles. As demonstrated in Figure 1, more patients in the lowest quartile of a′ (≤6.4 cm/s) had SEC than those in the other quartiles (44 vs. 6%, P < 0.0001). Figure 2 shows that patients in the lowest quartile of a′ had significantly lower LA appendage flow velocity than those in the other quartiles (39 ± 13 vs. 53 ± 16 cm/s, P < 0.0001). Furthermore,
Increased quartile of a’ was significantly associated with higher LA appendage flow velocity (P < 0.0001 by analysis of variance).

Receiver-operating characteristic curve analysis was performed to determine the best cut-off value of a’ for the prediction of SEC (area under the curve = 0.82, 95% CI = 0.74–0.91) as shown in Figure 3. The best cut-off value of a’ was 7.0 cm/s with a sensitivity of 80%, specificity of 81%, and predictive accuracy of 80%.

**Transthoracic echocardiographic factors associated with SEC**

In order to determine the echocardiographic factors associated with SEC, we performed univariate and multivariate logistic regression analyses (Table 3). In the univariate analysis, high CHA2DS2-VASc score, large LA volume index by computed tomography, increased LV mass index, increased E/e’, decreased a’ were the associated factors. As a result of multivariate analysis, increased CHA2DS2-VASc score and decreased a’ were independently associated with SEC.

**The value of a’ and history of thromboembolism**

Of the 138 patients, eight (6%) patients had a history of thromboembolism. The value of a’ was significantly lower in patients with than without a history of thromboembolism (6.3 ± 2.9 vs. 8.2 ± 2.3 cm/s, P = 0.03). In addition, the frequency of patients with a history of thromboembolism tended to be higher in the lowest quartile of a’ compared with the other quartiles (12 vs. 4%, P = 0.10).

**LA pump function and left ventricular filling pressure: association with LA volume**

We investigated the relationship between a’ and E/e’ which represents left ventricular filling pressure. Seventeen of 138 (12%) patients in our study had E/e’ > 15, which is thought to be associated with elevated left ventricular filling pressure.18 E/e’ showed a significant inverse correlation with a’ (r = −0.43, P < 0.0001). Furthermore, patients with E/e’ > 15 had significantly
vascular events. The advantage of our method is that a decreased LA appendage wall velocity measured by transthoracic echocardiographic method to estimate the risk of ischaemic fibrillation, irrespective of cardiac rhythm during transoesophageal echocardiography was associated with increased risk of cerebrovascular events. In addition, patients with low LA appendage flow during atrial fibrillation were shown to have increased risk of thrombus formation. Handke et al. demonstrated that, independent of cardiac rhythm, low LA appendage flow was closely related to SEC and thrombus formation.

A possible explanation for the relationship between decreased a’ and LA blood stasis is as follows. The impairment of LA contractile function during atrial fibrillation and atrial stunning would be more severe in patients with advanced atrial remodelling. Decreased a’ was also reported to reflect advanced atrial remodelling in patients with paroxysmal atrial fibrillation. Therefore, decreased a’ could indicate LA low blood flow.

The contraction of atrial myocardium is proportional to its initial length, according to the Frank–Starling mechanism. Therefore, LA pump function should be enhanced in response to larger pre-atrial contraction LA volume (preload) to some extent. However, there was an inverse correlation between LA pump function (a’) and pre-atrial contraction LA volume in the present study. The Frank–Starling curve has been shown to have a descending limb at very large atrial volumes, as demonstrated by Anwar et al. It is possible that patients in this study were operating on the descending limb of the Frank–Starling curve, and this may explain the inverse correlation between LA pump function and pre-atrial contraction LA volume. In addition, depressed LA myocardial contractility due to further progression of LA structural remodelling beyond the range of compensation could explain this inverse correlation. A previous study showed that LA pump function was inversely correlated with LA volume (preload) in patients with paroxysmal atrial fibrillation.

Decreased a’ could be used as a substitute for SEC and reduced LA appendage flow velocity. Measurement of a’ using transthoracic echocardiography is easy and may provide additional information about the risk of LA thrombus formation. However, this study included a selected and limited number of patients, and an association between decreased a’ and thromboembolic events remains uncertain. Further studies are required before this method is used to manage patients in routine clinical practice.

This study has several limitations. First, we mainly investigated the relationship between a’ and surrogate makers for LA thrombus formation (SEC and appendage flow velocity), and could not directly assess the relationship between a’ and LA thrombus, because the number of patients with LA thrombus was too small for adequate statistical analysis. However, the relationship between SEC or LA appendage flow velocity during sinus rhythm and stroke risk in patients with paroxysmal atrial fibrillation has never been fully determined. Next, recent episodes of atrial fibrillation might cause subsequent atrial stunning, and was possible to influence echocardiographic data. To avoid this influence, we excluded patients that had symptomatic episodes of atrial

### Discussion

The major findings of this study are as follows. Decreased a’ was significantly associated with SEC and reduced LA appendage flow velocity. Furthermore, multivariate analysis revealed that decreased a’ was independently associated with SEC. The optimal cut-off value of a’ for predicting SEC was 7.0 cm/s.

Recently, Tamura et al. reported a different transthoracic echocardiographic method to estimate the risk of ischaemic stroke in patients with atrial fibrillation. They showed that decreased LA appendage wall velocity measured by transthoracic echocardiography was associated with increased risk of cerebrovascular events. The advantage of our method is that a’ would be more easily measured than LA appendage wall velocity in most cases. In 9.4% of patients, according to their report, LA appendage wall velocity could not be measured; while a’ could not be measured only in one of 180 (0.6%) patients in this study.

Previous studies reported that in patients with paroxysmal atrial fibrillation, irrespective of cardiac rhythm during transoesophageal echocardiography, SEC in the LA was significantly associated with an increased risk of thromboembolic events. In addition, patients with low LA appendage flow during atrial fibrillation were shown to have increased risk of thrombus formation. Handke et al. demonstrated that, independent of cardiac rhythm, low LA appendage flow was closely related to SEC and thrombus formation.

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The major findings of this study are as follows. Decreased a’ was significantly associated with SEC and reduced LA appendage flow velocity. Furthermore, multivariate analysis revealed that decreased a’ was independently associated with SEC. The optimal cut-off value of a’ for predicting SEC was 7.0 cm/s.

On the other hand, a’ negatively correlated with pre-atrial contraction LA volume and LA volume index (r = −0.41, P < 0.0001 and r = −0.37, P < 0.0001), and E/e’ positively correlated with LA volume and LA volume index (r = 0.41, P < 0.0001 and r = 0.41, P < 0.0001).
fibrillation within 2 days prior to echocardiography. However, atrial stunning could last longer than 2 days, and we might fail to recognize atrial fibrillation events without significant symptom. Additionally, the grade of SEC was not evaluated in this study, although the prevalence of LA thrombus in atrial fibrillation is associated with a higher grade of SEC. Furthermore, we used same patients to determine the best cut-off value of a′ for the prediction of SEC and to evaluate the diagnostic performance of the determined cut-off value, which is not necessarily a fair method to test diagnostic performance. Finally, there are some technical difficulties with Doppler echocardiography. The motion of the mitral annulus is not entirely due to myocardial contraction, but rather the summation of contraction, rotation, and translation of the heart. Furthermore, a′ is dependent on the Doppler angle and can change slightly from beat to beat.

In conclusion, decreased a′ during sinus rhythm may be a useful parameter for the prediction of LA blood stasis in patients with non-valvular paroxysmal atrial fibrillation.

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Conflict of interest: none declared.

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