Clinical Implications and Determinants of Left Atrial Mechanical Dysfunction in Patients With Stroke

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Background and Purpose—The evaluation of sources of cardioembolism with transesophageal echocardiography (TEE) in patients with stroke is crucial but semi-invasive. We hypothesized that the size and mechanical function of the left atrium (LA) assessed by transthoracic echocardiography (TTE) could provide useful information on high risk of cardioembolism on TEE in patients with stroke. Furthermore, we sought to define the determinants of LA mechanical dysfunction in these patients.

Methods—A total of 248 patients with acute ischemic stroke (147 men; 64±13 years) who underwent 2-dimensional and speckle tracking TTE followed by TEE were analyzed.

Results—LA appendage emptying velocity, prevalence of LA or LA appendage thrombus, prevalence of aortic plaques, and incidence of embolic stroke showed significant differences among the 4 groups classified according to the median values of the LA volume index and global LA longitudinal strain (LALS). Patients at high risk of cardioembolism evidenced by TEE revealed significantly larger LA volume index and lower global LALS than those without. Global LALS (cutoff, 11.5%; area under the curve, 0.947; sensitivity, 100%; specificity, 91%; P<0.001) revealed a significantly better diagnostic power (P=0.04) for LA or LA appendage thrombus than LA volume index (cutoff, 36.2 mL/m²; area under the curve, 0.823; sensitivity, 88%; specificity, 75%; P=0.002). Age, left ventricular systolic function, LA volume index, and pulse wave velocity were independent determinants for global LALS.

Conclusions—LA mechanical dysfunction is closely associated with high risks of cardioembolism. Global LALS assessed by speckle tracking TTE well discriminates the presence of LA or LA appendage thrombus on TEE in patients with acute ischemic stroke. (Stroke. 2016;47:1444-1451. DOI: 10.1161/STROKEAHA.115.011656.)

Key Words: atrial appendage • echocardiography, transesophageal • heart atria • pulse wave analysis • stroke • thrombosis

Cardiovascular evaluation in patients presenting with acute ischemic stroke is clinically important not only for the evaluation of potential sources of cardioembolism but also for the assessment of coexisting cardiovascular disease and risk of future events. During the past few decades, transesophageal echocardiography (TEE) has been the most sensitive technique for the detection of thrombi or flow stasis in the left atrium (LA) or LA appendage (LAA), as well as aortic athroma.1–3 TEE is widely available for patients with acute ischemic stroke; however, some patients, particularly those with neurological disabilities, cannot undergo TEE because of its semi-invasive nature.4 Therefore, dual-enhanced cardiac computed tomography with electrocardiographic gating has been suggested as an alternative imaging modality for detecting LA or LAA thrombi.5 However, it also has several issues, including radiation exposure, renal dysfunction, and allergic reaction to contrast media.

Recent studies suggest that enlargement of LA is associated with both first and recurrent episodes of stroke.6,7 Association of LA size and stroke is not well understood; however, compromised LA function would result in flow stasis and increase the risk of embolism. The global LA longitudinal strain (LALS) assessed by 2-dimensional (2D) speckle tracking TTE is a relatively simple and reproducible technique to assess LA function.8 We hypothesized that enlargement and impaired mechanical function of LA assessed by TTE with speckle tracking imaging could provide useful information for high risk of cardioembolism detected from TEE in patients...
with stroke. Furthermore, we sought to define the major determinants of LA mechanical dysfunction in these patients.

Methods

Study Subjects

The study population consisted of 316 acute patients with ischemic stroke who were referred to the cardiology division for both TTE and TEE based on part of the standard evaluation except in patients with decreased consciousness, impending brain herniation, poor systemic conditions, inability to accept an esophageal transducer because of swallowing difficulty or tracheal intubation, or lack of informed consent from April 2012 to June 2013. Exclusion criteria were significant valvular heart disease (n=28), previous history of valve repair or replacement (n=7), previous history of radiofrequency ablation (n=2), previous history of atrial fibrillation (AF; n=20), and newly documented AF (n=11) during TEE or TTE. Finally, a total of 248 patients were analyzed. All underwent TTE and TEE within 1 week of the initial stroke. Ischemic stroke was confirmed by a focal neurologic deficit of sudden onset and magnetic resonance imaging findings. Patients with a transient ischemic attack and negative imaging findings were not included. Clinical information of patients was determined at the time of examination. The subtypes of ischemic stroke were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria (TOAST criteria) by neurologists. Twelve-lead electrocardiography was done at admission, and continuous 12-lead electrocardiographic monitoring was performed on the stroke unit within the first 48 to 72 hours after admission to detect silent paroxysmal AF.

To assess the various parameters in relation to size and mechanical function of LA, patients were categorized into 4 groups according to their median LA volume index (28 mL/m²) and global LALS (23%): group 1 (n=81), small LA with preserved LALS; group 2 (n=43), large LA with preserved LALS; group 3 (n=43), small LA with impaired LALS; and group 4 (n=81), large LA with impaired LALS.

Conventional Transthoracic Echocardiography

Each patient underwent a comprehensive TTE study using a Vivid 7 or Vivid 9 cardiovascular ultrasound system (GE Medical Systems, Horten, Norway), equipped with 2.5- to 3.5-MHz phased-array sector probes. During TTE, 1-lead electrocardiographic was recorded continuously. Standard 2D and Doppler measurements were performed per the recommendations of the American Society of Echocardiography guidelines.

Speckle Tracking Echocardiography

Each patient underwent a 2D speckle tracking echocardiography of the LA. Three consecutive cardiac cycles were recorded and averaged, and the frame rates were set to 60 to 80 frames per second. The analysis was performed offline using customized software (EchoPAC PC; GE Medical Systems). The LA endocardial border was manually traced in both 4-chamber and 2-chamber views. Because 2 segments of the LA roof demonstrated a lower longitudinal strain curves than those of the other 4, they were excluded from both the 4-chamber and the 2-chamber views. Therefore, global peak LALS during the ventricular systole was then measured by averaging the values obtained in the 8 other LA segments. The time to peak LALS is also measured as the average of the 8 segments and by calculating the time delay from the QRS to the positive peak LALS. An experienced cardiologist unaware of the patients’ information analyzed all echocardiographic values.

Transesophageal Echocardiography

TEE was performed immediately after TTE using a 5- to 7-MHz multplane, and images were independently reviewed by 2 experienced cardiologists. Multiple standard tomographic planes were imaged, and LAA emptying velocity, the presence of LA or LAA thrombi, the presence of patent foramen ovale, and severity of spontaneous echo contrast in the LA or LAA were determined. Peak LAA emptying velocities were measured using pulsed Doppler by placing the sample volume ≈1 cm inside of the orifice of the LAA. The peak emptying wavelets were measured in 3 consecutive cycles, and the maximal velocities were then averaged. An LA or LAA thrombus was diagnosed by the presence of an echo-dense mass in the LA or LAA, distinct from the endocardium and the pectinate muscles of the LA.

The spontaneous echo contrast was diagnosed by the presence of characteristic dynamic smoke-like swirling echo in the LA or LAA, and the severity was classified into 1 of the 4 grades as previously described. A patent foramen ovale was considered to be present if any microbubble was seen in the left-sided cardiac chambers within 3 cardiac cycles using saline contrast injections.

Aortic assessment was performed in all patients. The proximal aorta (aortic arch and ascending aorta) was imaged in short and long axes. An aortic plaque was defined as a hyperechogenic thickened area causing protrusion in the arterial lumen with >2 mm. Aortic plaques were classified as simple or complex on the basis of morphology. A complex aortic plaque was defined as a plaque that protrudes at least 4 mm into the aortic lumen or that is associated with ulceration or mobile features. Maximal aortic wall thickness was measured in the descending aorta perpendicular to the aortic wall. After comprehensive assessments, high-risk findings of cardioembolism from TEE were defined by the presence of thrombi at LA or LAA, LAA emptying velocity <20 cm/s, or the presence of complex atheroma.

Pulse Wave Velocity

Brachial ankle pulse wave velocity (baPWV) was obtained by 1 measurement within 7 days of admission in the supine position using an automated device (VP-1000; Colin Co Ltd, Komaki, Japan) as described previously. For analysis, the averaged value of baPWV from both sides was calculated.

Statistical Analysis

Continuous variables were presented as mean±SD and categorical variables as absolute and relative frequencies (%) of the group total. Among the data, continuous variables were compared between the groups using the Student t test (for 2-group comparisons) and analysis of variance (for 4-group comparisons), whereas the categorical variables were compared by χ² test or analysis of variance. We constructed the receiver operating characteristic curves to determine the diagnostic ability of global LALS or LA volume index. The diagnostic performances of the global LALS and LA volume index were compared through the Delong tests. To find the independent determinants of global LALS, multiple linear regression analysis was performed.

Results

Clinical Characteristics

The mean age of patients was 64±13 years, and men made up 58.1% of the population. Table 1 shows baseline clinical characteristics of the 4 groups. Patients in group 4, who were characterized by large LA volume and decreased global LALS, were significantly older than those in the other groups. There was no statistically significant difference in the distribution of sex or comorbidities. In terms of type of stroke, embolic stroke was the most frequent in group 4 with statistical significance. Systolic blood pressure and pulse pressure in group 4 were significantly higher than those in group 1, and baPWV increased from group 1 to 4 in a stepwise manner.

Echocardiographic Characteristics

Echocardiographic parameters are described in Table 2. Because the patients were classified into 4 groups based on their LA volume index and global LALS, the LA volume index and global LALS were significantly different among the
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Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Group 1 (n=81)</th>
<th>Group 2 (n=43)</th>
<th>Group 3 (n=43)</th>
<th>Group 4 (n=81)</th>
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</thead>
<tbody>
<tr>
<td>57.9±12.2</td>
<td>59.6±11.9</td>
<td>64.1±11.2*</td>
<td>70.1±10.2†‡</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>52 (64)</td>
<td>25 (58)</td>
<td>26 (61)</td>
<td>44 (54)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>24.0±3.6</td>
<td>24.0±3.0</td>
<td>24.3±2.9</td>
<td>23.5±3.3</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>47 (58)</td>
<td>31 (72)</td>
<td>27 (63)</td>
<td>61 (76)*</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>24 (30)</td>
<td>14 (33)</td>
<td>18 (42)</td>
<td>27 (33)</td>
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<tr>
<td>Dyslipidemia, n (%)</td>
<td>22 (27)</td>
<td>8 (19)</td>
<td>10 (23)</td>
<td>12 (15)</td>
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<tr>
<td>Smoking, n (%)</td>
<td>26 (32)</td>
<td>15 (35)</td>
<td>15 (35)</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>15 (19)</td>
<td>9 (21)</td>
<td>8 (19)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

Type of stroke, n (%)

| Large artery atherosclerosis | 27 (33) | 12 (28) | 14 (32) | 25 (31) |
| Cardioembolism | 13 (16) | 8 (19) | 6 (14) | 29 (36)*†‡ |
| Lacunar | 23 (28) | 14 (33) | 11 (26) | 13 (16) |
| Cryptogenic | 19 (34) | 9 (21) | 12 (28) | 14 (19) |
| Systolic blood pressure, mm Hg | 136±19 | 143±20 | 137±17 | 142±19* |
| Diastolic blood pressure, mm Hg | 81±15 | 84±14 | 81±13 | 81±13 |
| Pulse pressure, mm Hg | 55±17 | 59±17 | 56±12 | 61±16* |
| Brachial ankle PWV, m/s | 1797±497 | 1802±361 | 2067±652† | 2111±425† |

Group 1, small LA with preserved LALS; group 2, large LA with preserved LALS; group 3, small LA with impaired LALS; and group 4, large LA with impaired LALS. LA indicates left atrium; LALS, left atrial longitudinal strain; MI, myocardial infarction; and PWV, pulse wave velocity.

*P<0.05, compared with group 1.
†P<0.05, compared with group 2.
‡P<0.05, compared with group 3.

Diagnostic Performance of LA Volume Index and Global LALS for High Risk of Cardioembolism

A global LALS <11.5% showed a significantly better diagnostic performance (P=0.04) for the presence of an LA or LAA thrombus (area under the curve [AUC], 0.95; sensitivity, 100%; specificity, 91%; P<0.001) than the LA volume index (cutoff, 36.2 mL/m²; AUC, 0.82; sensitivity, 88%; specificity, 75%; P=0.002; Figure 1A). All 8 patients who presented with thrombi at LA or LAA showed LALS <11.5%, whereas their LA volume index showed a wide range of distribution (Figure 1B). Patients with the global LALS <11.5% were significantly older than those with the global LALS >11.5% (71±10 versus 62±12 years; P<0.01).

For the decreased LAA emptying velocity <20 cm/s, which is prone to thrombus formation, both global LALS (cutoff, 10.8%; AUC, 0.91; sensitivity, 80%; specificity, 92%; P<0.01) and LA volume index (cutoff, 41.6 mL/m²; AUC, 0.91; sensitivity, 80%; specificity, 88%; P<0.001) showed good diagnostic values without significant difference between 2 parameters (P=0.95). On the other hand, the global LALS (cutoff, 24.2%; AUC, 0.74; sensitivity, 55%; specificity, 84%; P<0.001) showed better diagnostic performances of the preserved LAA emptying velocity ≥40 cm/s than LA volume index (cutoff, 29.5 mL/m²; AUC, 0.64; sensitivity, 57%; specificity, 73%; P=0.01) with a significant difference (P=0.03).

Both global LALS and LA volume index showed good diagnostic performances for the complex aortic plaque (AUC, 0.64; sensitivity, 72%; specificity, 51%; P<0.01 and AUC, 0.61; sensitivity, 61%; specificity, 55%; P=0.011,
groups. Time to peak LALS was significantly shorter in group 1 than in other groups, whereas A’ velocity was significantly lower in group 4 than other groups. The parameters representing LV structure, systolic function, and diastolic function were also different among the groups. The patients in groups 2 and 4, who had a large LA size, tended to have a larger LV dimension and higher LV mass index than those in groups 1 and 3. Patients in group 4 showed an impaired LV longitudinal systolic and diastolic function and higher estimated LV filling (E/e’) pressure than other groups. In terms of TEE parameters, LAA emptying velocities were significantly lower in group 4, and the incidences of thrombus or spontaneous echo contrast in LA or LAA also differed significantly. No patients in group 1 or 2 showed an LA or LAA thrombus. Aortic wall thickness increased gradually from group 1 to 4. The incidence of aortic arch plaque was significantly higher in group 4. Interestingly, the incidence of complex aortic plaques increased in a stepwise manner from group 1 to 4. Incidence of patent foramen ovale was significantly different among 4 groups and most frequently found in group 1.
respectively) without significant differences between 2 parameters ($P=0.44$).

Figure 2 describes different LA size and mechanical function in patients with or without high-risk findings of cardioembolism detected from TEE. Patients at high risks of cardioembolism revealed significantly larger LA volume index (36±14 versus 29±10 mL/m$^2$; $P<0.01$) and lower global LALS (19±9% versus 25±8%; $P<0.01$) than those without.

**Determinants of LA Mechanical Function**

Simple correlation analysis data are shown in Table I in the online-only Data Supplement. Global LALS revealed significant negative correlations with age, LV mass index, $E'/e'$, aortic wall thickness, and baPWV. Global LALS showed significant positive correlations with LV ejection fraction, $e'$ velocity, and $S'$ velocity. Global LALS showed a better correlation with $E'$ ($r=0.169$; $P=0.008$) and $S'$ ($r=0.445$; $P<0.001$) compared with the LA volume index. The global LALS also showed a better correlation with baPWV ($r=0.335$; $P<0.001$) and aortic wall thickness ($r=0.304$; $P<0.001$) compared with the LA volume index. Multiple linear regression analysis showed that age, LV ejection fraction, $S'$ velocity, LA volume index, and baPWV were independent determinants of global LALS (Table 3).

**Discussion**

The principal findings in the present study are that (1) LA enlargement and impaired mechanical function assessed comprehensively by 2D TTE with speckle tracking imaging reflect the presence of high-risk findings for cardioembolism on TEE in patients with acute ischemic stroke; (2) global LALS from
TTE speckle tracking showed good diagnostic values for the presence of flow stasis, thrombus in the LA and LAA, and complex aortic plaques in patients with ischemic stroke; and (3) LA mechanical function was independently correlated with age, LV function, LA volume index, and aortic stiffness.

Overall, the assessment of LA size and mechanical function with comprehensive TTE is useful for the risk assessment of cardioembolism in patients with ischemic stroke. The results of our study suggest clinical importance of LA mechanical function in patients with stroke and potential diagnostic usefulness of global LALS when patients with acute ischemic stroke cannot undergo a TEE.

**Clinical Effect of LA Mechanical Function in Stroke**

Previous studies showed a strong relationship between LA volume and disease prognosis in various cardiovascular diseases, such as heart failure, myocardial infarction, cardiomyopathy, and AF.20–22 Enlargement of LA is reported to be associated with both the initial ischemic stroke and recurrent cardioembolism or cryptogenic stroke.7 Although mechanism is still unclear, association of LA size with stroke incidence implicates clinical significance of LA function in patients with stroke. Two-dimensional speckle tracking is a new technique that allows a more direct measurement of LA contractility of endocardium and passive deformation.8 Global LALS more sensitively reflects the LA function than does LA volume as functional change precedes morphological changes.

Previous studies have consistently reported that global LALS predicts thromboembolic risks in AF population. Kuppahally et al23 described that LA fibrosis is inversely correlated with LALS in patients with AF, implying that fibrosis impairs LA compliance. Obokata et al reported that LALS provides incremental diagnostic information over the CHA2DS2-VASc score (a risk factor-based risk stratification schemes for embolisms in patients with AF) alone in patients with AF, emphasizing the role of LALS in risk stratification for stroke.12 A previous cross-sectional study by Saha et al24 demonstrated that global LALS was a predictor of stroke in patients with AF. In contrast to previous studies that were limited to patients with AF, the current study included acute ischemic stroke patients with normal sinus rhythm, which reflects real-world data.

Our results in this study confirm that impaired global LALS correlates with a decreased LAA emptying velocity, the presence of flow stasis, thrombus in LA or LAA, or complex aortic atheroma. Notably, the diagnostic performance of global LALS to detect thrombus in LA or LAA was significantly better than that of LA volume index. Eight patients from our cohort who presented with thrombus in LA or LAA showed relatively wide distribution of LA volume index, whereas all had decreased LALS <11.5%. Therefore, in real-world practice, when a patient with stroke cannot undergo TEE because of various reasons, such as contraindications for TEE, expense of medical cost, or neurological disabilities, the global LALS may be used as an alternative to rule out the likelihood of thrombus and to determine subsequent needs for other imaging assessments. The global LALS may give valuable additive information for the possible presence of thrombus in LA or LAA. Thus, if a patient shows low LALS <11.5%, TEE should be performed to verify thrombus to decide on the necessity of anticoagulant treatment. If TEE cannot be performed, alternative imaging modalities, such as cardiac computed tomography or magnetic resonance imaging, may be used cost effectively in patients with significant LA mechanical dysfunction.

From our results, both global LALS and LA volume index showed good diagnostic values for LAA emptying velocity <20 cm/s with no significant differences in diagnostic performance. However, when diagnosing thrombus in LA or LAA or LAA emptying velocity ≥40 cm/s, the diagnostic power of the global LALS was significantly better than that of the LA volume index. This discrepancy can be explained by different stages of diseased LA and higher sensitivity of the global LALS for detecting LA dysfunction. This indicates that the global LALS better reflects LA function than LA volume index even in subclinical stage when LAA emptying velocity ≥40 cm/s. When the function of the LA is impaired enough to decrease LAA emptying velocity <20 cm/s, it is most often accompanied by an enlargement of the LA. In such stages, the diagnostic power of the global LALS becomes similar to that of the LA volume index. Moreover, global LALS may also be

![Figure 1. Size and mechanical function of left atrium (LA) in relation to the presence of thrombus at LA or left atrial appendage (LAA). A. Receiver operating characteristic curve of presence of LA or LAA thrombus. B. Distribution of the global left atrial longitudinal strain (LALS) and LA volume index in patients with or without thrombus at LA or LAA.](http://stroke.ahajournals.org/figure.html)
informative even with a similar LA volume. In our study, we grouped patients into 4 groups according to the median values of global LALS and LA volume index to demonstrate different stages of LA dysfunction according to size and function. When comparing groups with an already large LA volume index (group 2 versus 4), the presence of LA or LAA thrombosis or overall spontaneous echo contrast was significantly different even with a similar LA volume. Overall, the clinical usefulness of global LALS may be appreciated more in patients with early- or advanced-stage LA dysfunction. Thus, LALS can provide additive information to LA volume index.

Mechanical Linkage Between Aortic Stiffness and LA Function

Previous studies have consistently revealed relationships between aortic stiffness and LV diastolic dysfunction in various populations. In our study, LALS was closely correlated with baPWV ($r=0.36$; $P<0.001$). This result provides an insight into atrial-ventricular–arterial coupling in concordance with previous studies. Impaired LA and LV relaxation in longitudinal directions has been demonstrated to be the early signs of abnormal LA–LV coupling related to the arterial stiffness in preclinical patients with cardiovascular risk factors, and only peak LA strain rate during ventricular systole was significantly related to carotid arterial stiffness. In our study, multivariate regression analysis revealed that baPWV showed an independent correlation with the global LALS even after controlling for age, sex, body mass index, comorbidities, and LV functional parameters.

Our study also showed a close correlation between the global LALS and the presence of aortic plaques. We cautiously interpreted that the linkage between the global LALS and aortic plaque can be explained by increased stroke burden. Aortic plaque is one of the parameters in CHA2DS2-VASc score and clearly is one of clinical risk factors for stroke. Recent studies have already shown an association between global LALS and CHA2DS2-VASc although limited in AF population. Also, patients with aortic atheroma are likely to have other underlying cardiovascular diseases, such as hypertension, which may affect LV diastolic function, and decreased function of LA. Therefore, the results from our study provide potential role for global LALS for cardiovascular risk evaluation and the presence of complex aortic atheroma in aorta especially when TEE cannot be done because of its semi-invasive nature.

From our result, age was also an important determinant for LA mechanical function. Multivariate analysis showed independent correlation between age and global LALS after adjustment of other variables, which is consistent with previous studies. Normal aging is associated with reduced LV diastolic function and atrial fibrosis, which leads to deterioration of LA function. A previous study suggested that although normal aging is associated with enlargement of LA volume, it does not significantly alter LA volume index until the eighth decade of life. Global LALS may be more appreciated than LA volume index as it better reflects earlier change of LV function.

**Study Limitations**

A few limitations should be addressed in this study. First, this study is a cross-sectional study from a single center with a
limited number of patients who underwent TEE. Therefore, there would be a selection bias in this study’s stroke population because of the observational nature of our study. Further longitudinal study with larger population is needed to determine interactions of clinical variables with LA mechanical function, as well as the causality of the global LALS and clinical outcome. However, the results from our study provide insightful information for future investigations on LA mechanical function in relation to future risk of cardioembolism in patients with stroke. Second, the global LALS was analyzed in patients who had a sinus rhythm when TTE and TEE were performed. We excluded patients with paroxysmal AF; however, some of silent paroxysmal AF may have been underdiagnosed and classified into cryptogenic stroke in our cohort. Although 24-hour electrocardiography was not performed on the study patients to exclude paroxysmal AF, this limitation seems minimal as continuous electrocardiographic monitoring was done when the patients were first admitted to the stroke unit. Third, persistent AF, which constitutes a significant portion of patients with stroke, was excluded for quality control of acquired strain images, which may have biased the study population. This provides an explanation for the small incidence of thrombus in LA or LAA (8/248) in this study. Although it may not represent general stroke patient population, our data reflect real-world practice. Given the small percentage of thrombus in LA and LAA in stroke patients with sinus rhythm in the real world, results from our study suggest noninvasive, easily applicable, alternative method for evaluation of abnormal flow stasis or thrombus in LA or LAA in patients with stroke. Our study demonstrates possible application of the global LALS in real-world practice where TEE is difficult to perform. Fourth, a total incidence of cardioembolism stroke was not low although we only included patients with sinus rhythm. Considering the possibility of underdiagnosed incidence of paroxysmal AF and the mean age of our cohort, the incidence of cardioembolism stroke (22.6%) is not unusual. In addition, cardiac conditions other than AF may have contributed to cardioembolism stroke.

Conclusions
LA mechanical dysfunction is closely associated with high risks of cardioembolism. Global LALS assessed by TTE speckle tracking methods well discriminates the presence of LA or LAA thrombus detected from TEE in patients with acute ischemic stroke. Therefore, comprehensive assessment of LA size and mechanical function can be useful for risk stratification of cardioembolism in patients with acute ischemic stroke.

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Disclosures
None.

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Supplementary material for method

Speckle tracking echocardiography

The intra-observer and inter-observer reproducibility for the assessment of global LALS were determined by the Bland-Altman analysis. Intra-observer reproducibility was determined by repeating the strain measurements at two different time points by one experienced reader in 15 randomly selected patients. A second experienced reader performed the strain analysis in the same 15 patients, providing the inter-observer data. The Bland Altman analysis and intra-class correlation coefficient (ICC) showed good intra- and inter-observer agreement for global LALS. For inter-observer agreement of global LALS, the mean difference was 1.7 (-1.3, 4.4) and the ICC was 0.88; for intra-observer agreement, the mean difference was 1.2 (-2.0, 3.1) and the ICC was 0.90.

Supplementary material for results

Clinical determinants for LA or LAA thrombus and complex aortic plaques

Multiple regression analysis was performed to determine independent clinical parameters for LA or LAA thrombus and complex aortic plaques. From multiple regression analysis, the global LALS was the only significant determinant (p<0.01) for the presence of a LA or LAA thrombus, even after adjustment for age (p=0.18) and LA volume index (p=0.53). For complex aortic plaque, age was an independent determinant of complex aortic plaque (p<0.01), but the global LALS was not. This result might be explained by a significant mechanistic association among age, increased aortic stiffness which is often combined with complex aortic plaques, and the low global LALS.
**Supplementary Table I. Simple correlation analysis.**

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<th>LA volume index, ml/m²</th>
<th>Global LA LS, %</th>
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<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P-value</td>
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<td>Age</td>
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<td>E/e’</td>
<td>0.255</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic wall thickness</td>
<td>0.212</td>
<td>0.001</td>
</tr>
<tr>
<td>baPWV</td>
<td>0.172</td>
<td>0.008</td>
</tr>
</tbody>
</table>

LA, left atrium; LA LS, left atrial longitudinal strain; LV, left ventricle; e’, early diastolic mitral annular; S’, systolic mitral annular; baPWV, brachial-ankle pulse wave velocity.
卒中患者左心房机械功能障碍的临床意义及决定因素
Clinical Implications and Determinants of Left Atrial Mechanical Dysfunction in Patients With Stroke

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背景及目的: 经食道超声心动图(transesophageal echocardiography, TEE)可用于评估卒中患者心源性栓塞的来源，是一项极其关键却又半侵入式的检查。我们推测，经胸超声心动图(transthoracic echocardiography, TTE)评估左心房的大小和机械功能，可以为 TEE 上的心源性栓塞高风险卒中患者提供有用信息。此外，本文旨在明确此类患者左心房机械功能障碍的决定因素。

方法: 共有 248 例急性缺血性卒中患者(147 例男性; 64±13 岁)在二维斑点追踪 TTE 检查之后进行了 TEE 检查。

结果: 按左心房容积指数和总左心房收缩期纵向应变率(left atrium longitudinal strain, LALS)的中位数将患者分成 4 组, 左心耳排空速度、左心或左心耳血栓、主动脉瓣的患病率和脑栓塞的发病率表现出显著的组间差异。经 TEE 证实存在心源性栓塞高风险的患者左心房容积指数更大、总 LALS 更低。总 LALS (截断值 11.5%; 曲线下面积 0.947; 敏感度 100%; 特异度 91%; P < 0.001) 与左心房容积指数(截断值 36.2 ml/m 2; 曲线下面积 0.823; 敏感度 88%; 特异度 75%; P=0.002) 相比, 在诊断左心或左心耳血栓方面展现了更好的效能 (P=0.04)。年龄、左心室收缩功能、左心房容积指数和脉搏波传导速度是总 LALS 的独立决定因素。

结论: 左心房机械功能与心源性栓塞高风险的关联密切。通过二维斑点追踪 TTE 评估所得的总 LALS 指标能很好地区分急性缺血性卒中患者在 TEE 上左心房或左心耳血栓的存在。

关键词: 心耳; 经食道超声; 心房; 脉搏波分析; 卒中; 血栓形成
25~35 MHz 的相控阵扇形探头，检查期间同时进行 1 导联心电图连续监测，并根据美国超声心动图指南进行标准二维超声和多普勒超声检查。每节段纵向应变曲线明显低于其他 4 个节段，故在后续的统计分析中将此数据剔除，而取两个切面中其余 8 个节段数据的均值作为总峰值 LALS，同上记录 QRS 波出现到正向 LALS 峰值产生之间的平均时间间隔。行超声心动图检查的神经科医生对患者的信息未知。经食道超声心动图

行 TTE 检查后立即进行 TEE 检查，该系统配置了 5~7 MHz 的多平面探头，图像分别由两位经验丰富的神经科医生独立采集。采集的信息包括多个心房断面图像、左心耳收缩速度、左心房及左心房有无血栓、卵圆孔闭合情况、左心房或左心耳有无自发性造影回声。利用脉冲多普勒技术取样点深入左心耳开口约 1 cm 处连续测量 3 个心动周期的收缩期血流峰值速度并取其均值作为左心耳收缩期峰值速度。如果左心房或左心耳可见区别于心内膜和梳状肌的强回声团块，可诊断为左心房或左心耳血栓。如果左心房或左心耳可见特征性的动态烟雾状涡流回声，可诊断为左心房或左心耳自发性造影，严重程度参照以往研究分为 1~3 级。通过生理盐水造影，如果在 3 个心动周期中可见左侧心腔内出现气泡影，即可诊断为卵圆孔未闭。
结果

临床信息

患者平均年龄为 64±13 岁，其中男性占 58.3%。表 1 为 4 组的基线临床信息。组 4 为左心房增大及总 LALS 降低的患者，其年龄大于其他分组，差异有显著性。性别及共存病差异无显著性。关于卒中类型，栓塞性卒中在组 4 中比例较大，差异有显著性。组 4 患者收缩压及脉压显著高于组 1，baPWV 从组 1 至组 4 呈阶梯状上升。

超声心动图特点

根据超声心动图特征，患者被分为 4 组：组 1，保留 LALS 的小左房；组 2，保留 LALS 的大左房；组 3，LALS 受损的小左房；组 4，LALS 受损的大左房。表 2 为超声心动图参数，显示了 LALS 的达峰时间、A′和 S′速率及 LVEF 的差异。

左心房容积指数及总 LALS 对心源性栓塞高风险的诊断价值

总 LALS < 11.5%（曲线下面积 0.95；敏感性 100%；特异性 91%；P < 0.001）对诊断左心房或左心耳血栓的存在较左心房容积指数（截断点 36.2 ml/m²；曲线下面积 0.82；敏感性 88%；特异性 75%；P = 0.002；图 1A）更有效力。8 位存在左心房或左心耳血栓的患者 LALS 均 < 11.5%，而其左心房容积指数分布范围较宽（图 1B）。总 LALS < 11.5% 的患者其年龄较总 LALS > 11.5% 的患者显

<table>
<thead>
<tr>
<th>组别</th>
<th>组 1 (n=81)</th>
<th>组 2 (n=43)</th>
<th>组 3 (n=43)</th>
<th>组 4 (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>左心房容积指数，ml/m²</td>
<td>22.9±4.3</td>
<td>35.3±5.3*</td>
<td>21.3±5.2†</td>
<td>42.9±11.4**</td>
</tr>
<tr>
<td>总 LALS，%</td>
<td>31.2±4.9</td>
<td>28.4±3.9*</td>
<td>18.5±4.3**</td>
<td>14.7±6.7**</td>
</tr>
<tr>
<td>达峰时间 LALS，ms</td>
<td>379±66</td>
<td>48±65*</td>
<td>426±67*</td>
<td>417±71*</td>
</tr>
<tr>
<td>LVEDD，mm</td>
<td>48±4</td>
<td>50±5*</td>
<td>46±5*</td>
<td>50±5*</td>
</tr>
<tr>
<td>LVEF，mm</td>
<td>31±4</td>
<td>33±5*</td>
<td>31±5</td>
<td>34±7*</td>
</tr>
<tr>
<td>LV 射血分数，%</td>
<td>67±6</td>
<td>66±9</td>
<td>67±7</td>
<td>62±9**</td>
</tr>
<tr>
<td>LV 质量指数，g/m²</td>
<td>91.3±21.7</td>
<td>100.8±20.6*</td>
<td>67.3±16.5*</td>
<td>112.7±25.2**</td>
</tr>
<tr>
<td>A′速率，cm/s</td>
<td>8.7±1.5</td>
<td>8.8±1.6</td>
<td>8.5±1.3</td>
<td>7.9±1.8**</td>
</tr>
<tr>
<td>S′速率，cm/s</td>
<td>7.2±1.3</td>
<td>6.9±1.3</td>
<td>6.8±1.2</td>
<td>5.6±1.6**</td>
</tr>
<tr>
<td>E/e′</td>
<td>10.3±2.8</td>
<td>12.2±3.3*</td>
<td>10.7±3.3*</td>
<td>13.2±5.1**</td>
</tr>
<tr>
<td>LAA 排空速率，cm/s</td>
<td>69.7±21.5</td>
<td>65.5±17.7</td>
<td>67.4±21.2</td>
<td>451±21.7**</td>
</tr>
<tr>
<td>LA 或 LAA 血栓形成，数目（%）</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.3)</td>
<td>7 (8.6)**</td>
</tr>
<tr>
<td>LA 或 LAASEC，数目（%）</td>
<td>3 (4)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>28 (35)**</td>
</tr>
<tr>
<td>主动脉壁厚度，mm</td>
<td>1.7±0.9</td>
<td>1.9±0.9</td>
<td>2.2±1.0*</td>
<td>23±1.1**</td>
</tr>
</tbody>
</table>

*P < 0.05，与组 1 相比。
†P < 0.05，与组 2 相比。
‡P < 0.05，与组 3 相比。
著增大（71 ± 10 vs 62 ± 12 岁；P < 0.01）。

对于左心耳排空速度 < 20 cm/s 的患者，其易形成血栓，总 LALS（截断点 10.5%；曲线下面积 0.91；敏感性 80%；特异性 92%；P < 0.01）及左心房容积指数（截断点 41.6 ml/m²；曲线下面积 0.91；敏感性 80%；特异性 88%；P < 0.001）显示良好的诊断价值，但两参数差异无显著性（P=0.95）。另一方面，总 LALS（截断点 24.2%；曲线下面积 0.74；敏感性 55%；特异性 84%；P < 0.001）显示出左心耳排空速度 ≥ 40 cm/s 有更好的诊断性能相较于左心房容积指数（截断点 29.5 ml/m²；曲线下面积 0.64；敏感性 57%；特异性 73%；P < 0.01），差异有显著性（P=0.03）。

对于诊断复杂性主动脉斑块，总 LALS 和左心房容积指数均显示出现良好的诊断价值（曲线下面积 0.64；敏感性 72%；特异性 51%；P < 0.01 和曲线下面积 0.61；敏感性 61%；特异性 55%；P=0.011），且两参数间差异无显著性（P=0.44）。

图 2 描述了是否存在 TEE 探测的心源性栓塞高风险患者不同左心房大小及机械功能。心源性栓塞高风险患者的左心房容积更大（36 ± 14 vs 29 ± 10 ml/m²；P < 0.01）及低总 LALS（19 ± 9% vs 25 ± 8%；P < 0.01），差异有显著性。


### 左心房机械功能的决定因素

单因素相关分析结果在网上数据补充材料的表 I。总 LALS 与年龄、左心室质量指数、左心耳排空速度、主动脉弓壁厚度及 baPWV 呈负相关。总 LALS 与左心室射血分数、e′波流速及 S′波流速呈正相关。总 LALS 与左心房容积指数相比，与 S′波 (r=0.169; P=0.008) 及 S′波 (r=-0.445; P < 0.001) 具有良好的相关性。总 LALS 与左心房容积指数相比，与 baPWV (r=0.335; P < 0.001) 和主动脉弓壁厚度 (r=0.304; P < 0.001) 具有较好的相关性。

多线性回归分析显示年龄、左心室射血分数、S′波流速、左心房容积指数及 baPWV 是总 LALS 的独立决定因素（表 3）。

### 讨论

本研究的主要结果如下：（1）通过斑点追踪显像二维 TEE 评估的左心房增大及机械功能损害可反映急性缺血性卒中患者存在心源性栓塞高风险；（2）通过斑点追踪显像 TEE 得到总 LALS 对于诊断缺血性卒中中的血液瘀滞、左心房和左心耳的血栓及复杂性主动脉斑块具有较好的诊断性能；（3）左心房机械功能与年龄、左心室功能和左心房容积指数、主动脉僵硬度独立相关。

综上所述，通过全面的 TEE 评估左心房大小及机械功能对缺血性卒中患者的血栓性危险因素的评估具有重要价值。我们的研究显示左心房机械功能在卒中患者中的重要临床意义及总 LALS 在不能耐受 TEE 检查的急性卒中患者中的诊断应用价值。

### 表 3 左心房机械功能的决定因素

<table>
<thead>
<tr>
<th>因素</th>
<th>β</th>
<th>T</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄</td>
<td>-0.279</td>
<td>-3.20</td>
<td>0.002</td>
</tr>
<tr>
<td>性</td>
<td>-0.061</td>
<td>-1.11</td>
<td>0.269</td>
</tr>
<tr>
<td>体质量指数</td>
<td>-0.066</td>
<td>-1.78</td>
<td>0.076</td>
</tr>
<tr>
<td>合并高血压</td>
<td>-0.008</td>
<td>-0.13</td>
<td>0.894</td>
</tr>
<tr>
<td>合并糖尿病</td>
<td>-0.022</td>
<td>-0.40</td>
<td>0.687</td>
</tr>
<tr>
<td>LV 射血分数</td>
<td>0.148</td>
<td>2.53</td>
<td>0.012</td>
</tr>
<tr>
<td>LV 质量指数</td>
<td>0.055</td>
<td>1.53</td>
<td>0.127</td>
</tr>
<tr>
<td>e′速率</td>
<td>-0.013</td>
<td>-0.19</td>
<td>0.850</td>
</tr>
<tr>
<td>S′速率</td>
<td>0.187</td>
<td>2.96</td>
<td>0.003</td>
</tr>
<tr>
<td>LA 容积指数</td>
<td>-0.376</td>
<td>-5.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>baPWV</td>
<td>-0.137</td>
<td>-2.16</td>
<td>0.032</td>
</tr>
</tbody>
</table>

注：LALS：左心房纵向应变力；LV：左心室；PWV：脉搏波传导速度；e′：舒张早期二尖瓣环；S′：收缩期二尖瓣环；LA：左心房。
左心房机械功能在卒中患者中的临床作用

既往研究表明，左心房容积和许多心血管疾病的预后有关密切联系，比如心脏衰竭、心肌梗死、心肌病和房颤。有报道，左心房增大与原发性缺血性卒中、复发性心源性栓塞型卒中的病因有关。尽管具体机制目前尚不清楚，但左心房大小与卒中发生率之间的关系表明，对于卒中患者而言左心房功能有临床意义。二维斑点追踪是一项新技术，它能更直接的测量左心房心内膜的收缩和被动变形情况。由于功能改变先于形态改变，故总 LALS 比左心房容积更能敏感地反映左心房功能。

既往研究一致表明总 LALS 能预测房颤人群中血栓栓塞的风险。既往研究表明，左心房容积指数对左心房容积指数和左心房容积指数的中位数有良好的预测能力，且两者无显著差异。然而，当诊断左心耳或左心房血栓、左心耳血栓或左心房血栓时，总 LALS 比左心房容积指数的预测能力强。

主动脉僵硬度与左心房功能的联系

本研究显示，总 LALS 与 baPWV 具有相关性（r = 0.36; P < 0.01），这与既往研究结果一致，有助于加深对左心房心室动脉耦合的理解。左心房及左心室舒张功能损害被认为是心房心室异常耦合的早期征象，而左心室收缩期与颈动脉僵硬度显著相关。本研究显示，当 baPWV 增大时，总 LALS 呈负相关性，这可能与左心房心室动脉耦合有关。因此，总 LALS 可以作为一种潜在的替代方法用于心房心室功能不全患者的评估。
研究的局限性

本研究中仍存在以下不足。第一，本研究为单中心的横断面研究。完成 TEE 检查的患者数量有限，因此纳入样本量较少；同时，由于该研究属于观察性研究，不可避免的在选择患者时出现偏倚。未来需要大样本队列研究来进一步证实上述临床参数与左心房功能的相关性以及探究总 LALS 改变与临床结局的因果关系。然而，本研究为日后关于左心房机械功能对未来心源性脑栓塞风险评估的相关研究提供了重要信息。第二，研究排除了阵发性房颤的患者。因此，只有窦性心律的患者中完成了 TEE、TTE 检查及总 LALS 分析；部分无症状阵发性房颤患者虽未发现但被归入了隐源性卒中中。尽管入组患者中并没有实施 24 h 动态心电图以排除阵发性房颤，但这一缺陷对研究结果的影响较小。因所有患者在首次收入卒中中心时都曾有过持续心电监护。第三，为了获得良好的图像，持续性房颤的患者被排除在入组之外，这就可能导致入组样本的人群偏倚，这是造成研究中左心房及左心耳血栓发生率低的原因（8/248）。尽管不能代表普通的人群，我们的研究中确实有实际临床意义：考虑到临床实践中心律失常患者的心房及左心耳血栓发生率很低，我们所采用的技术正好可以作为一种非侵入、易实施的替代手段用于卒中患者评估心房及心耳血栓情况。第四，尽管入组的患者都是窦性心律，但最终确诊为心房颤中率的比率仍然不低。考虑到可能存在未被诊断的阵发性房颤患者混入以及入组患者的平均年龄，本研究心房颤中率的比率（22.6%）是可以接受的。此外，除房颤之外的其他心脏病也可能导致心房颤率中的发生。

结论

左心房机械功能不全被认为是发生心源性脑栓塞的高危因素，借助应变求解或成像技术，TEE 有可能能够获取总 LALS 参数，而后者很好地判别有无左心房或左心耳内血栓的形成（金标准 TEE 食道超声心动图可证实）。因此，对左心房大小以及机械功能的全面评估有助于确定急性缺血性卒中患者发生心源性栓塞的危险分层。

参考文献