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 atheroma.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 increased 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 neurological 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 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 electrocardiography 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 multiplane, and images were independently reviewed by 2 experienced cardiologists. Multiple standard tomographic planes were imaged, and LA 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 LAA.

A 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 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
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.

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,

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></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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<tr>
<td>Age, y</td>
<td>57.9±12.2</td>
<td>59.6±11.9</td>
<td>64.1±11.2*</td>
<td>70.1±10.2**†‡</td>
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<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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<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>
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<td>Hypertension, n (%)</td>
<td>47 (58)</td>
<td>31 (72)</td>
<td>27 (63)</td>
<td>61 (76)*</td>
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<td>Diabetes mellitus, n (%)</td>
<td>24 (30)</td>
<td>14 (33)</td>
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<td>Dyslipidemia, n (%)</td>
<td>22 (27)</td>
<td>8 (19)</td>
<td>10 (23)</td>
<td>12 (15)</td>
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<td>Smoking, n (%)</td>
<td>26 (32)</td>
<td>15 (35)</td>
<td>15 (35)</td>
<td>27 (33)</td>
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<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>
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<td>Type of stroke, n (%)</td>
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<td></td>
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<tr>
<td>Large artery atherosclerosis</td>
<td>27 (33)</td>
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<td>14 (32)</td>
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<td>Cardioembolism</td>
<td>13 (16)</td>
<td>8 (19)</td>
<td>6 (14)</td>
<td>29 (36)*†‡</td>
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<tr>
<td>Lacunar</td>
<td>23 (28)</td>
<td>14 (33)</td>
<td>11 (26)</td>
<td>13 (16)</td>
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<tr>
<td>Cryptogenic</td>
<td>19 (34)</td>
<td>9 (21)</td>
<td>12 (28)</td>
<td>14 (19)</td>
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<td>Systolic blood pressure, mm Hg</td>
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<td>137±17</td>
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<td>Diastolic blood pressure, mm Hg</td>
<td>81±15</td>
<td>84±14</td>
<td>81±13</td>
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<tr>
<td>Pulse pressure, mm Hg</td>
<td>55±17</td>
<td>59±17</td>
<td>56±12</td>
<td>61±16*</td>
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<tr>
<td>Brachial ankle PWV, m/s</td>
<td>1797±497</td>
<td>1802±361</td>
<td>2067±652†</td>
<td>2111±425†</td>
</tr>
</tbody>
</table>

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.
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/m²; $P<0.01$) 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 al3 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 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
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, comorbidity, 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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SUPPLEMENTAL MATERIAL

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.

<table>
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<tr>
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<th>LA volume index, ml/m²</th>
<th>Global LA LS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.304</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.108</td>
<td>0.090</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>-0.233</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.394</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e' velocity</td>
<td>-0.008</td>
<td>0.896</td>
</tr>
<tr>
<td>S' velocity</td>
<td>-0.370</td>
<td>&lt;0.001</td>
</tr>
<tr>
<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

Darae Kim, MD; Chi Young Shim, MD, PhD; Geu-Ru Hong, MD, PhD; Mi-Hyun Kim, MD; Jiwon Seo, MD; In Jeong Cho, MD; Young Dae Kim, MD, PhD; Hyuk-Jac Chang, MD, PhD; Jong-Won Ha, MD, PhD; Ji Hoe Heo, MD, PhD; Namsik Chung, MD, PhD

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、主动脉斑块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/m²；曲线下面积 0.823；敏感度 75%；灵敏度 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

（Stroke. 2016;47:1444-1451. 浙江大学医学院附属第一医院神经内科 计仁杰 译 魏瑞理 罗本燕 校）
斑点追踪成像技术

每个患者均行左心房的二维斑点追踪成像。摄影帧频设置为每秒60~80帧，记录连续3次心动周期并取其平均值。数据分析采用离线的专业软件 (EchoPAC PC；GE Medical Systems)。从四腔和二腔切面视图手动追踪左心房心内膜边界的运动。因为左心房顶部的2个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TEE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动周期图、左心耳收缩速度、左心房及左心室有无血栓、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获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峰值速度。

统计分析

连续变量以均值±标准差表示，分类变量以绝对和相对频率（%）表示。不同组间连续变量的比较采用t检验（组2）和方差分析（组4），分类变量间的比较采用χ²分析或方差分析。本研究构建受试者工作特征曲线确定总LALS或左心房容积指数的诊断效能。
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

表2描述了超声心动图参数，根据左心房容积指数和总LALS将患者分成4组，故左心房容积指数和总LALS在该4组中差异有显著性。LALS达峰时间在组1中显著短于其他分组，组4患者A′速度显著低于其他组。左心房容积指数及总LALS对心源性栓塞高风险的诊断价值

<table>
<thead>
<tr>
<th>组别</th>
<th>n=81</th>
<th>n=43</th>
<th>n=43</th>
<th>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>全LALS，%</td>
<td>31.2±4.9</td>
<td>28.4±3.9*</td>
<td>18.5±4.7**</td>
<td>14.7±6.7**</td>
</tr>
<tr>
<td>达峰时间LALS，ms</td>
<td>379±66</td>
<td>483±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>LVESD，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>67±7</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>e′速率，cm/s</td>
<td>6.3±2.1</td>
<td>5.9±1.4</td>
<td>5.2±1.7*</td>
<td>5.5±2.0*</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±1.6**</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>组别</th>
<th>n=81</th>
<th>n=43</th>
<th>n=43</th>
<th>n=81</th>
</tr>
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<tbody>
<tr>
<td>总心率（LAA）</td>
<td>69.7±21.5</td>
<td>65.5±17.7</td>
<td>67.4±21.2</td>
<td>45.1±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>总体</td>
<td>3（4）</td>
<td>1（2）</td>
<td>1（2）</td>
<td>28（35）**</td>
</tr>
<tr>
<td>轻度</td>
<td>0（0）</td>
<td>0（0）</td>
<td>0（0）</td>
<td>0（0）</td>
</tr>
<tr>
<td>中度</td>
<td>0（0）</td>
<td>0（0）</td>
<td>0（0）</td>
<td>6（7）*</td>
</tr>
<tr>
<td>重度</td>
<td>0（0）</td>
<td>0（0）</td>
<td>0（0）</td>
<td>6（7）*</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±1.1**</td>
</tr>
<tr>
<td>主动脉钙化斑块，数目（％）</td>
<td>35（44）</td>
<td>20（48）</td>
<td>24（56）</td>
<td>55（71）*</td>
</tr>
<tr>
<td>总体</td>
<td>35（44）</td>
<td>20（48）</td>
<td>24（56）</td>
<td>55（71）*</td>
</tr>
<tr>
<td>轻度</td>
<td>22（28）</td>
<td>12（29）</td>
<td>15（35）</td>
<td>28（36）</td>
</tr>
<tr>
<td>中度</td>
<td>13（16）</td>
<td>9（19）</td>
<td>9（21）</td>
<td>27（35）*</td>
</tr>
<tr>
<td>重度</td>
<td>37（46）</td>
<td>11（26）*</td>
<td>19（44）*</td>
<td>18（21）*</td>
</tr>
</tbody>
</table>

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。注：A′：舒张晚期二尖瓣环；S′：收缩期二尖瓣环；E：舒张早期二尖瓣环流入率；e′：舒张期二尖瓣环流入率；LA：左心房；LAA：左心耳；LALS：左心房纵向应变；LV：左心室；LVEDD：左心室舒张末期内径；LVESD：左心室收缩末期内径；SEC：自发声学显影。

*P < 0.05, 与组1相比。
†P < 0.05, 与组2相比。
‡P < 0.05, 与组3相比。

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有较高的诊断价值。根据TTE参数，组4患者的左心耳排空速度显著降低，其栓塞的发生率及左心房或左心耳的自发超声显影与其他组存在显著差异。组1或组2患者均未有左心房或左心耳血栓。主动脉壁厚度在组1至组4中逐渐上升，组4中主动脉钙化斑块的发生率显著增加。组1或组2患者均未有左心房或左心耳血栓。主动脉壁厚度在组1至组4中逐渐上升，组4中主动脉钙化斑块的发生率显著增加。组4患者左心耳排空速度显著降低，其栓塞的发生率及左心房或左心耳的自发超声显影与其他组存在显著差异。
对于左心耳排空速度 < 20 cm/s 的患者，其容易形成血栓，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 < 0.01）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 56%；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。第一眼影像高风险患者的不同左心房容积指数（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见表 3。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 呈正相关。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 BA 波 (r=0.169；P=0.008) 及 S’ 波 (r=0.445；P < 0.001) 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。多因素回归分析显示年龄、左心室射血分数、S’ 波流速、左心房容积指数及 baPWV 为总 LALS 的独立决定因素（表 3）。

图 1 左心房的大小和机械功能与左心房或左心耳出现血栓有一定关系。A：左心房或左心耳存在血栓的受试者工作特征曲线；B：左心房或左心耳没有血栓患者的总 LALS 分布和左心房容积指数。注：LALS：左心房纵向应变力；LA：左心房；LAA：左心耳。

<table>
<thead>
<tr>
<th>表 3 左心房机械功能的决定因素</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>总 LALS (R²=0.444)</td>
<td>β</td>
<td>T</td>
<td>P值</td>
</tr>
<tr>
<td>年龄</td>
<td>-0.219</td>
<td>-3.20</td>
<td>0.002</td>
</tr>
<tr>
<td>男性</td>
<td>-0.061</td>
<td>-1.11</td>
<td>0.269</td>
</tr>
<tr>
<td>体重指数</td>
<td>-0.096</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 倍收缩指数</td>
<td>0.095</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 舒张指数</td>
<td>-0.376</td>
<td>-5.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>肱 - 踝脉 PWV</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’：舒张期二尖瓣环；S’：收缩期二尖瓣环；LA：左心房。
图 2 根据心源性栓塞存在高风险时，左心房的大小和机械特性。A: 左心房容积指数; B: 左心房总的纵向应变力。

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和卒中相关。尽管具体机制目前仍不清楚，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具有临床意义。二维斑点追踪是一项新技术，它能更直接的测量心房内膜的收缩和被动变形情况。

图 2 心源性栓塞风险(-) 心源性栓塞风险(+)

左心房容积指数 (ml/m^2)

总左心房纵向应变力(%) Diff

心源性栓塞风险(-) 心源性栓塞风险(+)

* 心源性栓塞风险: 在左心房 / 左心房 + 左心耳存在血栓时，排空速度<20 cm/s + 复杂斑块

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密切联系，比如心脏衰竭、心肌梗死、心肌病和房颤。左心房容积指数和许多心血管疾病的预后有密切联系，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和卒中相关。尽管具体机制目前仍不清楚，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具有临床意义。二维斑点追踪是一项新技术，它能更直接的测量心房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 比左心房容积指数更敏感地反映左心房功能。

本研究结果证实，总 LALS 的损害与左心耳排空流速的降低、血液瘀滞、左心房或左心耳血栓、或复杂的主动脉粥样硬化有关。值得注意的是，总 LALS 对左心房或左心耳血栓的诊断能力明显优于左心房容积指数。在我们的队列研究中，8 例左心房或左心耳血栓患者，其左心房容积指数相对广泛分布，而其 LALS < 11.5%。因此，在真正的临床实践过程中，当一个卒中患者由于各种原因（TEE 禁忌证、过高的费用或者神经系障碍等）不能进行 TEE 时，总 LALS 可能是排除血栓可能性的一种替代方法，并决定进一步的影像学评估。对左心房或左心耳血栓，总 LALS 可能提供有价值的信息。因此，如果一个患者 LALS < 11.5%，那么需要进一步进行 TEE 证实血栓并且决定是否需要抗凝治疗。如果不能进行 TEE，其他替代的影像学检查，如心尖 CT 或磁共振，对显示左心房机械性功能不全的患者来说也是昂贵的检查。

从我们的研究结果来看，总 LALS 和左心房容积指数对左心耳排空流速 < 20 cm/s 的患者都有良好的诊断性能，且两指标无显著差异。然而，当诊断左心房或左心耳血栓、左心耳排空流速 ≥ 40 cm/s 时，总 LALS 的诊断效能明显高于左心房容积指数。左心房病变不同的阶段和总 LALS 对检测左心房功能不全更高的敏感性能解释上述情况。总 LALS 比左心房容积指数更能好的反映左心房的功能，即使是在左心耳排空流速 < 40 cm/s 的临床阶段。当左心房功能损害严重导致左心耳排空流速 < 20 cm/s，此时常合并左心房扩大，在该阶段，总 LALS 的诊断能力逐渐超过左心房容积指数。因此，总 LALS 的临床使用可能在早期或晚期的左心功能不全患者中更被青睐，LALS 较左心房容积指数能提供更多新的信息。

主动脉僵硬度与左心房功能的联系

既往针对不同人群的研究一致揭示了动脉僵硬度与左心室舒张功能不全的相关性。本研究结果显示 LALS 与 baPWV 具有相关性 (r = 0.36; P < 0.01)，这与既往研究结果一致，有助于加深对心房心室动脉耦合的理解。左心房及左心室功能损害被认为是心房心室异常耦合的早期征象，而这两症往往与具有心血管危险因素但尚未发生临床事件患者的动脉僵硬度相关；进一步结果分析显示，左心室收缩期的左心房峰值应变率与颈动脉僵硬度显著相关。本研究显示，在多因素回归分析中，通过控制校正年龄、性别、体重指数、共存病及左室功能参数后，baPWV 仍与总 LALS 呈独立相关性。本研究同样显示了总 LALS 与主动脉斑块存在与否具有密切关系，我们目前谨慎地认为这一相关性可能与卒中负担增高相关。主动脉斑块是 CHA2DS2-VASc 评分中的一项重要指标，被公认为是卒中发生的高危因素之一。近期的研究已经显示了总 LALS 与 CHA2DS2-VASc 评分具有相关性，尽管这些研究的纳入人群都仅局限于房颤患者。此外，主动脉粥样硬化的患者往往合并存在其他一些潜在的心血管疾病，比如高血压，而后者同样能够影响左室舒张功能及左房功能。因此，我们认为当 TEE（经食道超声心动图）作为一种半侵入式的评估手段不适用于临床实践时，总 LALS 可以作为一种潜在的替代技术用于心血管危险分层评估及探寻复杂主动脉粥样斑块的存在，我们的上述研究为此提供了证据。
From this research, left atrial mechanical function is an important factor. In multiple regression analysis, normalized left atrial volume and LALS change were independently associated with stroke recurrence.

The conclusion is that left atrial mechanical function is an important factor in the development of stroke recurrence.

**References**

