Implication of Left Ventricular Diastolic Dysfunction in Cryptogenic Ischemic Stroke

Jae-Young Seo, MD; Kyung Bok Lee, MD, PhD; Jung-Gon Lee, MD; Ji-Sun Kim, MD; Hakjae Roh, MD; Moo-Young Ahn, MD; Byoung Won Park, MD; Min Su Hyon, MD

Background and Purpose—Left ventricular diastolic dysfunction (LVDD) is a predictor for atrial fibrillation (AF). This study was aimed to investigate whether LVDD in cryptogenic ischemic stroke (CS) could be a clue to stroke mechanism.

Methods—The clinical and echocardiographic findings of 1589 consecutive patients with acute ischemic stroke or transient ischemic attack between 2004 and 2013 were reviewed. LVDDs among stroke subtypes were graded by transthoracic echocardiography into 4 groups by severity: normal, abnormal relaxation (grade I), pseudonormal (grade II), and restrictive diastolic filling (grade III), whereas severe LVDD was defined as grade III. We classified the lesion pattern of CS into cardioembolism-mimic or non–cardioembolism-mimic and determined whether cardioembolism-mimic lesions were associated with severe LVDD.

Results—The fraction of severe LVDD in CS was not different from that of stroke with AF (27.3% versus 37.1%; P=0.173) but was significantly higher than that of stroke without AF (27.3% versus 13.4%; P=0.008). Cardioembolism-mimic CS had more severe LVDD than non–cardioembolism-mimic CS (41.4% versus 11.5%; P=0.013). LVDD of grade II (odds ratio, 4.37; 95% confidence interval, 2.99–6.41) and grade III (odds ratio, 5.60; 95% confidence interval, 3.42–9.17) were independently related to stroke with AF after adjusting covariates.

Conclusions—The severe LVDD could be a predictor of stroke with AF, and its frequency was similar between CS and stroke with AF. Cardioembolism-mimic CS had significantly more severe LVDD than non–cardioembolism-mimic CS. LVDD could be helpful to discriminate the stroke mechanism in the patients with acute CS.

Key Words: atrial fibrillation ■ echocardiography ■ stroke

Ischemic strokes that have no clearly definable cause despite extensive evaluation and are termed cryptogenic ischemic stroke (CS). As the rate of recurrence after a ischemic stroke of uncertain cause was reported to be >30% during the first 5 years after the index event, accurate determination of stroke cause is important for proper therapeutics and prognosis. The cause of some CS may be cardioembolism even though the initial diagnostic evaluation was negative. Several studies have suggested that 5% to 20% of patients with CS may have paroxysmal atrial fibrillation (AF) in long-term cardiac monitoring as a likely contributing cause. From these findings, there is the potential for more existence of AF in CS, and it is highly likely that AF could be a larger cause of CS.

As previous studies have tried to detect the factors associated with the prediction of AF because AF may be transitory, left ventricular diastolic dysfunction (LVDD) is one of the most important constituents of them. LVDD frequently occurs in patients with AF and is associated with progression and symptom severity of AF. LVDD favors left atrial enlargement (LAE), which results in a higher risk of atrial thrombogenicity, proarrhythmia, and cardioembolism. The presence and severity of LVDD are independently predictive of first documented nonvalvular AF in the elderly and may suggest the presence of undetected AF.

We sought to estimate the frequency and severity of LVDD in CS and compare them with those in stroke with AF or without AF. In addition, we compared the proportion of severe LVDD between 2 CS subgroups divided by the lesion pattern on diffusion-weighted MRI (DWI): cardioembolism-mimic CS and non–cardioembolism-mimic CS.

Study Subjects

From January 2004 to March 2013, the patients with acute (<7 days from onset) ischemic stroke or transient ischemic attack were consecutively enrolled in the prospective registry in Soochunhyang University Hospital. This Web-based registry contains clinical characteristics, laboratory/imaging findings, and cardiovascular outcomes after discharge. Patients who had transient ischemic attack without acute lesion on DWI or did not undergo transthoracic echocardiography (TTE) within 7 days from onset were excluded (Figure). CS was defined as stroke with no clearly definable cause even after extensive work ups: head/neck angiography, transesophageal echocardiography, and 24-hour ECG monitoring. The presence of AF documentation in medical records, ECG, or echocardiography

Key Words: atrial fibrillation ■ echocardiography ■ stroke

Methods

Study Subjects

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were regarded as stroke with AF. There was no discrimination among paroxysmal, persistent, or permanent AF. Extensive evaluation was performed for stroke mechanism in our registry: 95.8% for head and neck MR angiography, 90.3% for TEE, 54.1% for TEE, and 86.7% for Holter monitoring. In case one of the work ups was missed in determining stroke subtype, the subject was regarded as incomplete study and was excluded. The patients with high-risk sources of cardioembolism other than AF were also excluded because of the probable influence on LVDD: mechanical prosthetic valve, mitral stenosis, sick sinus syndrome, recent myocardial infarction, atrial myxoma, dilated cardiomyopathy, akinetic left ventricular segment, and infective endocarditis. Stroke without AF refers to stroke with relevant (>50% arterial stenosis in intracranial or extracranial vessel referable to the infarct) large artery atherosclerosis or lacunar infarct (<1.5 cm sized; Figure). The study design was approved by the Soonchunhyang Institutional Review Board before investigation.

Echocardiographic Data
The Philips iE33 (Philips Medical Systems, Bothell, WA) with 5-MHz transducers were used for M-mode and doppler TTE in all patients. TTE was performed by 2 cardiologists (H.M.S. and P.B.W.), who were blinded to information of the study purpose and the patient’s stroke subtypes. TTE parameters consisted of M-mode–based parasternal long-axis LA diameter, LV end-systolic/eddiostolic dimensions, LV septal/posterior wall thickness during diastolic phase, LV ejection fraction, and LV fractional shortening. LAE was defined as LA diameter >44 mm.

Doppler mitral valve inflow was obtained by pulsed wave from the apical window, with a 1- to 3-mm sample volume placed between the tips of the mitral leaflets during diastole. Mitral peak E velocity and peak A velocity, deceleration time (DT) of mitral early velocity, and E/A ratio were measured from the transmitral flow tracing. Early diastolic mitral peak E’ velocity was estimated by tissue Doppler imaging measurements at the mitral annulus. The ratio of transmitral early LV filling velocity to early diastolic tissue Doppler imaging velocity of the mitral annulus (E/e’) was calculated.

Diagnosis and Grading of LVDD
The transmitral Doppler flow profiles and tissue Doppler profiles were used for the assessment of LVDD. The grading outline was normal, abnormal relaxation, pseudonormal, and restrictive LV filling pattern. Grade of LVDD was determined by different parameters according to the presence of atrial contraction.

Normal LV filling was defined by the presence of mitral e’<10 cm/s, E/A ratio 0.8–1.5, and DT of 160–200 ms. A mild form of LVDD (grade I: abnormal relaxation) was mitral e’<10 cm/s and E/A ratio 0.8–1.5 or DT>200 ms. With more severe LVDD (grade II: pseudonormal), e’<10 cm/s and E/e’ ratio is 9 to 12, whereas E/A ratio (0.8–1.5) and DT (160–200 ms) were within normal range. In a patient with the most severe form of LVDD (grade III: restrictive LV filling) occurs with E/e’>13 cm/s and E/A ratio ≤1.5 or DT<160 ms.

However, because peak A velocity is unmeasurable because of no atrial contraction, E/A ratio could not be applied in patients with persistent AF. However, E’, DT, and E/e’ ratio, which were independent of atrial effect, were correlated with filling pressure and were used as valuation basis of LVDD. Normal LV filling was defined by the presence of e’≥10 cm/s. In patient with mild LVDD (grade I), annular E’ is <10 cm/s, E/e’ ratio is ≤8, or DT is >240 ms. In a more severe LVDD (grade II), E’ is <10 cm/s, E/e’ ratio is >12, or DT is <160 ms. As majority of studies suggested that the patients with LVDD, especially grade III, indicate high risk of incident AF, we categorized the patients with severe LVDD as grade III.

Lesion Pattern of CS on DWI
DWI was performed using a 1.5-T magnetic resonance system with 7-mm-thick axial-oblique slices. The lesion pattern of CS was classified into 2 subgroups (cardioembolism-mimic or non-cardioembolism-mimic). Cardioembolism-mimic suggested a cardioembolic infarction (1) corticostriocortical territorial lesion or (2) multiple lesions, which were defined as multiple noncontiguous lesions in the vascular territories of both anterior and posterior circulations. DWI lesion patterns were determined by 2 readers (S.J.Y. and L.J.G.; κ=0.87) who were blinded to clinical data, and a third reader’s (L.K.B.) interpretation was adopted in cases of disagreement.

Statistical Analysis
Categorical variables are reported as frequencies, and continuous variables as mean±SD. One-way ANOVA was used to compare baseline clinical and echocardiographic parameters, and 2 set of χ² test to analyze LVDD distribution between CS and stroke with or without AF. χ² test was also used to analyze association of stroke subtypes with severe LVDD or LAE, and the lesion pattern among 3 groups. To determine LVDD as an independent predictor of stroke with AF, multivariable logistic regression was applied adjusting covariates of major clinical risk factors and echocardiographic variables. The level

Figure. Flow diagram for subtype classification of the ischemic stroke. AF indicates atrial fibrillation; CE, cardioembolism; CS, cryptogenic stroke; DWI, diffusion-weighted MRI; TIA, transient ischemic attack; and TTE, transthoracic echocardiography. *Transthoracic echocardiography (TTE) (+), but insufficient data for grading left ventricular diastolic dysfunction. *Incomplete study: one of the work ups (head/neck angiography, TEE, and 24-hour ECG monitoring) was missed.
of statistical significance was set at \( P < 0.05 \). All statistical analyses were done with SPSS version 18.0 (SPSS, Inc, Chicago, IL).

**Results**

**Study Patients and Baseline Characteristics**

Among 1901 patients with acute ischemic stroke or transient ischemic attack, 312 patients were excluded: no acute lesion on DWI (n=97), other high cardioembolic sources (n=41), and no TTE (n=174) Among stroke without AF or lacunes or relevant artery stenosis, 84 patients who had not undergone one of the work ups were excluded (incomplete study). After classification of stroke subtype, 97 of 407 (21.4%) in stroke with AF, 72 of 1041 (6.9%) in stroke with AF, and 2 of 57 (3.5%) in CS were additionally excluded because of insufficient TTE data for grading LVDD. Finally, a total 310 TTE data of stroke with AF, 969 TTE data of stroke without AF, and 55 TTE data of CS were analyzed (Figure).

The baseline characteristics and TTE data of the study population are summarized in Table 1. The mean age was 58.05±14.71 years in CS. Stroke with AF had more hypertension (70.2%; \( P < 0.001 \)) and diabetes mellitus (42.1%; \( P = 0.006 \)) than other groups. There was no significant difference in sex and the time from onset of symptom to TTE examination among 3 groups.

**Distribution of LVDD and LAE**

Distribution of LVDD in each stroke subtype is demonstrated in Table 2. When severe LVDD was defined as grade III, stroke with AF had more severe LVDD than stroke without AF (37.1% versus 13.4%; \( P < 0.001 \)). The proportion of severe LVDD in CS was not different from that of stroke with AF (27.3% versus 37.1%; \( P = 0.104 \)), but was significantly higher than that of stroke without AF (27.3% versus 13.4%; \( P = 0.007 \); Table 2).

LAE was predominantly detected in stroke with AF (38.4%; \( P < 0.001 \)), whereas the frequency was not different between CS and stroke without AF (7.7% versus 7.8%; \( P = 0.974 \)).

**Lesion Patterns of Infarct and Severe LVDD in CS**

Among 55 DWI lesion patterns in CS, 29 was cardioembolism-mimic (17 corticosubcortical territorial lesion, 12 multiple lesions in the territories of both anterior and posterior circulations), and 26 was non–cardioembolism-mimic. The proportion of severe LVDD in cardioembolism-mimic was significantly higher than that of non–cardioembolism-mimic (41.4% versus 11.5%; \( P = 0.013 \)).

**Factors Associated With Stroke and AF**

Multivariable logistic regression analysis was performed adjusting age, sex, hypertension, diabetes mellitus, smoking, hyperlipidemia, LAE, and patent foramen ovale. Values in Table 3 are odds ratios and 95% confidence intervals. LVDD of grade II (odds ratio, 4.37; 95% confidence interval, 2.99–6.41) and grade III (odds ratio, 5.60; 95% confidence interval, 3.42–9.17) were significantly associated with stroke with AF independent of covariates.

### Table 1. Baseline Clinical and Echocardiographic Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke With AF (n=310)</th>
<th>Stroke Without AF (n=969)</th>
<th>CS (n=55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.57±11.14</td>
<td>66.41±12.83</td>
<td>58.05±14.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, men</td>
<td>159 (51.3%)</td>
<td>549 (56.7%)</td>
<td>34 (61.8%)</td>
<td>0.163</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>213 (68.7%)</td>
<td>680 (70.2%)</td>
<td>24 (43.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>103 (33.2%)</td>
<td>408 (42.1%)</td>
<td>16 (29.1%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking</td>
<td>82 (26.5%)</td>
<td>350 (36.1%)</td>
<td>20 (36.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>50 (16.1%)</td>
<td>201 (20.7%)</td>
<td>12 (21.8%)</td>
<td>0.190</td>
</tr>
<tr>
<td>Symptom onset-to-TTE time, d</td>
<td>2.87±1.87</td>
<td>3.05±2.37</td>
<td>3.21±2.69</td>
<td>0.308</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>53/305 (17.3%)</td>
<td>87/969 (9.0%)</td>
<td>1/55 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTE parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-mode LA diameter, mm</td>
<td>41.66±7.74</td>
<td>35.97±5.38</td>
<td>35.33±6.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>30.58±8.56</td>
<td>27.64±5.37</td>
<td>27.12±4.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>48.29±8.31</td>
<td>47.32±5.54</td>
<td>47.12±5.34</td>
<td>0.057</td>
</tr>
<tr>
<td>LV septal wall thickness, diastolic, mm</td>
<td>10.43±2.21</td>
<td>10.56±2.09</td>
<td>10.01±1.72</td>
<td>0.138</td>
</tr>
<tr>
<td>LV posterior wall thickness, diastolic, mm</td>
<td>10.20±2.21</td>
<td>10.22±1.95</td>
<td>9.51±1.43</td>
<td>0.043</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>60.82±12.03</td>
<td>66.19±8.08</td>
<td>66.78±6.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>37.27±9.25</td>
<td>41.75±7.4</td>
<td>42.60±5.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral inflow peak E velocity, cm/s</td>
<td>77.99±31.29</td>
<td>62.99±19.51</td>
<td>65.68±47.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral inflow peak A velocity, cm/s</td>
<td>74.21±29.98</td>
<td>79.22±20.72</td>
<td>69.09±21.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral inflow peak E’ velocity, cm/s</td>
<td>5.65±2.35</td>
<td>5.21±1.98</td>
<td>6.24±2.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral DT, ms</td>
<td>194.19±87.26</td>
<td>215.91±70.32</td>
<td>202.11±57.71</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are n (%) or mean±SD values. AF indicates atrial fibrillation; CS, cryptogenic ischemic stroke; DT, deceleration time; LA, left atrial; and TTE, transthoracic echocardiography.

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Discussion

The reasons of undetermined causes in CS are that the cause is transitory or reversible; investigations did not look for all possible causes, or some causes truly remain unknown.1 Among them, transitory or reversible properties might be undetected paroxysmal cardioembolic sources. There have been some evidences indicating that cardioembolic causes are a contributor to CS. Cardioembolism is the most probable cause of CS studied by gene expression profiles.21 In analysis of DWI patterns, large subcortical territorial lesions suggests cardioembolism and represents similar percentages between cardioembolic stroke and CS.20

Among the probable causes of cardioembolic, undetected paroxysmal AF was proposed as the most common cause of CS.7,22–24 Prolonged holter monitoring,22 21-day outpatient cardiac telemetry24 and insertable cardiac monitor implantation23 was used to detect paroxysmal AF. However, these investigations are not always available, and the detection rate of AF is weakly increased considering the time and effort involved. Therefore, we need to find the contributing and preceding factors of AF, which are consistent and unaffected by timing of investigation.

It is noteworthy that LVDD is well established as a risk factor for incident AF.32 One consistent observation with progressive LVDD has demonstrated that LAE occurs concurrently.33 However, in our study, LAE was less frequent in CS than that in stroke with AF in populations without structural heart disease suggest that increased filling pressures may represent important mechanisms of the development of AF.9,28 However, there has been little evidence that LVDD is related to acute stroke with AF. In this study, LVDD of grade II and III was associated with stroke with AF after adjusting multiple vascular risk factors, LAE, and patent foramen ovale.

In this first study to compare the prevalence of LVDD between CS and other stroke subtypes, we found that severe LVDD in CS and stroke with AF was significantly higher than that in stroke without AF. Furthermore, the comparison of severe LVDD between 2 subgroups of CS based on DWI lesion patterns provided the significant association between cardioembolism-mimic lesions and severe LVDD. This observation suggests that more CS, especially those with LVDD, might have undetected AF. This result could be a need for further cardiac monitoring to detect AF as a source of cerebral embolism and could encourage anticoagulation in CS with LVDD. Two-year rate of recurrent stroke or death was lower in patients with CS receiving warfarin than those receiving antiplatelet therapy.29

The importance of LAE has also been described as a risk factor for incident AF.30,31 LAE is associated with structural and functional atrial tissue changes that develop the propagation of AF.32 One consistent observation with progressive LVDD has demonstrated that LAE occurs concurrently.31 However, in our study, LAE was less frequent in CS than that in stroke with AF in spite of similar fraction of severe LVDD between the 2. Because LA diameter regarded as a biomarker of chronicity of LVDD,34 our result may be because of much shorter periods of LVDD morbidity in relatively young patients with CS. Meanwhile, LVDD was a predictor of stroke with AF independent of LAE.

This study has some limitations. First, because the clinical data were obtained by retrospective chart review, biases of selection (eg, exclusion of disproportionately high number of insufficient TTE data in stroke with AF), misclassification, or information are possible. Second, study design was single center based, and the number of subjects with CS was relatively small. The reason why the proportion of CS was much lower than that documented in previous studies1,3 is that more extensive evaluation for stroke mechanism in our registry and exclusion of many undetermined cause with incomplete study. Actually, previous

Table 2. Distribution of LVDD Among 3 Stroke Subtypes

<table>
<thead>
<tr>
<th>Grade of LVDD</th>
<th>Stroke With AF (n=310)</th>
<th>P Value</th>
<th>CS (n=55)</th>
<th>P Value</th>
<th>Stroke Without AF (n=969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>36 (11.6%)</td>
<td>...</td>
<td>3 (5.5%)</td>
<td>...</td>
<td>36 (3.7%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>127 (41.0%)</td>
<td>...</td>
<td>19 (34.5%)</td>
<td>...</td>
<td>565 (58.3%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>32 (10.3%)</td>
<td>...</td>
<td>18 (32.7%)</td>
<td>...</td>
<td>238 (24.6%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>115 (37.1%)</td>
<td>...</td>
<td>15 (27.3%)</td>
<td>...</td>
<td>130 (13.4%)</td>
</tr>
<tr>
<td>Severe LVDD (grade III)</td>
<td>115 (37.1%)</td>
<td>0.173</td>
<td>15 (27.3%)</td>
<td>0.008</td>
<td>130 (13.4%)</td>
</tr>
<tr>
<td>LAE</td>
<td>119 (38.4%)</td>
<td>&lt;0.001</td>
<td>4 (7.7%)</td>
<td>0.974</td>
<td>75 (7.8%)</td>
</tr>
</tbody>
</table>

Data are n (%). Grade I, abnormal relaxation; grade II, pseudonormal; and grade III, restrictive LV filling. AF indicates atrial fibrillation; CS, cryptogenic ischemic stroke; LAE, left atrial enlargement; and LVDD, left ventricular diastolic dysfunction.

Table 3. Multivariable Logistic Regression Model for Stroke With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exp (β)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.05-1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>1.11</td>
<td>0.78-1.57</td>
<td>0.561</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.85</td>
<td>0.61-1.20</td>
<td>0.367</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.71</td>
<td>0.51-0.98</td>
<td>0.035</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.96</td>
<td>0.64–1.44</td>
<td>0.84</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.7</td>
<td>0.48–1.03</td>
<td>0.07</td>
</tr>
<tr>
<td>LVDD normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>0.83</td>
<td>0.45–1.51</td>
<td>0.535</td>
</tr>
<tr>
<td>Grade II</td>
<td>4.37</td>
<td>2.99–6.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade III</td>
<td>5.6</td>
<td>3.42–9.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAE</td>
<td>5.19</td>
<td>3.67–7.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LAE, left atrial enlargement; and LVDD, left ventricular diastolic dysfunction.
studies have made no distinction between cryptogenic stroke and incomplete study and led to somewhat higher prevalence of cryptogenic stroke.\textsuperscript{1,2,10} Our study was aimed to reveal the echocardiographic characteristics of true cryptogenic stroke because incomplete study could not represent CS and was liable to include more noncardiogenic embolic stroke. Finally, we were unable to incorporate many recent tools for measuring LVDD, including strain rate and strain analysis, and LA volume index, which were not available in our echocardiographic data.

In conclusion, we have found that the frequency of severe LVDD in CS was similar to those in stroke with AF but different from that in stroke without AF. And, the cardioembolism-mimic lesion pattern of CS was significantly associated with severe LVDD, which was independently related to stroke with AF. This result suggests that more CS might result from undetected AF, and LVDD could be helpful to discriminate the stroke mechanism in the patients with acute CS. This warrant a further prospective study to establish the implication of LVDD in acute CS for predicting mechanism.

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**Disclosures**

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**References**

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