Left Atria Strain Is a Surrogate Marker for Detection of Atrial Fibrillation in Cryptogenic Strokes

Jorge Pagola, MD; Teresa González-Alujas, MD; Alan Flores, MD; Marian Muchada, MD; David Rodriguez-Luna, MD; Laia Seró, MD; Marta Rubiera, MD; Sandra Boned, MD; Marc Ribó, MD; José Álvarez-Sabin, MD; Arturo Evangelista, MD; Carlos A. Molina, MD

After complete diagnostic workup, a quarter of ischemic strokes are regarded as undetermined pathogenesis at discharge with a substantial rate of mortality in some cases. Paroxysmal atrial fibrillation (PAF) is the most frequent occult cause resulting in significant morbidity and costs when is under diagnosed. Recent studies have shown that extending the cardiac monitoring duration with subcutaneous implantable monitors and selecting patients for prolonged monitoring significantly increased the PAF detection in ischemic strokes. The left atria volume (LAv) has been used to assess the left atrial function. Nevertheless, the left atria dimension is predictive of stroke but become nonsignificant after adjustment for the older age. The left atria function can be also obtained by the analysis of the left atria walls deformation, also called strain of the left atria. The speckle tracking is an echocardiographic technique that uses standard B-mode images for the analysis of the acoustic backscatter generated by the ultrasound beam. The changes between speckles are assumed to represent the strain. The published intraobserver and interobserver variability of left atria strain (LAS) is 7.8%, and 8.9%, respectively. The LAS profile has been previously described in patients with >140/90 mm Hg, age ≥75, diabetes, prior stroke. However, it has never been studied in cryptogenic ischemic strokes.

The same blinded sonographer performed the studies with the echocardiographic platform GE EchoPac Clinical ultrasound software. The LAS analysis was performed from the apical 4-chamber view, placing the 3.5-MHz multiphase array probe at the apex of the left ventricle. The atrial endocardium wall was first traced manually and followed by automatic estimation of the epicardial atrial surface. The atrial wall was divided into 6 segments by the software. Each 2 segments corresponded to the atrial septum, lateral wall, and the roof of the left atrium. The speckle tracking required 3 cardiac cycles digitally stored with a minimum of 50 frames per second. Those studies with inaccurate loop image were excluded. The software calculated the median longitudinal peak atrial strain (peak positive strain), which corresponded to the left atria diastensibility. We decided to select the positive peak atrial strain as the optimal point for the better interobserver agreement (Figure 1). A receiver operating characteristic curve was displayed to find the optimal LAS cutoff point to predict the PAF occurrence. In the analysis, the LAv was measured by biplane Simpson method considering LA enlarged if the volume was >50 mL from the apical 4-chamber view. The LAv was not body surface adjusted because of lack of information on the exact patient’s height and weight in most cases.

According to left ventricle strain analysis, the LAS was correlated with the left atria size by the LAS/LAv ratio. The LAS cutoff point obtained classified a group of cryptogenic stroke patients (CRYPTO group) in patients with low LAS and high LAS. The rate of PAF detection was assessed by 72-hour telemetry monitoring. The CHA2DS2VASC score (congestive heart failure, hypertension, age ≥75: 2, diabetes, stroke: 2, vascular disease, sex female) was calculated according published criteria. The rate of complex aortic atheroma (plaque thicker than 4 mm or with mobile components) was also registered.

Statistical significance for intergroup differences for categorical variables was assessed by χ² test using the SPSS 17.0 statistical package. For continuous variables, the Mann–Whitney U test or Student t test was selected as appropriated. The receiver operating characteristic curve was displayed using...
The left atria strain analysis. A, The left atria traced by the speckle tracking software. B, The dot line is the median left atria strain profile. White arrow points the peak positive strain value (↓).

Results of Pilot Testing
A total of 54 patients with acute strokes were studied in the first part of the protocol. Although 4 patients were excluded because of poor imaging quality for LAS analysis and 3 patients did not complete the whole monitoring, there were no differences in the baseline variables between the patients included (n=47): PAF group (n=34) and non-PAF group (n=13) except for lower percentage of LAS in PAF group (23% versus 34%; P=0.042; Table 1). This result has been previously reported in patients with decreased LAS and diagnosis of PAF. LAS measures the lack of distensibility and contractility observed in the atrial remodeling effect, which trends to trigger atrial fibrillation. In addition, patients who experience PAF episodes before the stroke may have had lower degree of atria contractility compared with those who remained in sinus rhythm. A receiver operating characteristic curve showed LAS cutoff point of 25.83%, which predicted PAF with sensitivity of 70% and specificity of 75%. The percentage of LAS independently predicted PAF detection regardless of age (odds ratio, 15 [95% CI, 1.54–145.2]; P=0.019) or enlarged LAv (odds ratio, 6.66 [95% CI, 1.45–30.64]; P=0.015). Some scales score the age of the patient as a marker for detecting PAF; however, most stroke causes are also related with the older people, therefore, an age-unrelated marker focused only in atria functionality, as LAS parameter, is valuable in these cases. The LAS/LAv ratio was also lower in the PAF group (0.47 [interquartile range, 0.32–0.88]) compared with non-PAF group (1.27 [interquartile range, 0.82–1.83; P=0.002]. A LAS/LAv<0.79 predicted the PAF detection with a sensitivity of 75.9% and specificity of 83.3%. The positive and negative likelihood ratio were 4.55 (95% CI, 1.26–16.39) and 0.29 (95% CI, 0.145–0.579), respectively.

From the 90 patients with cryptogenic stroke, 2 patients were excluded for inappropriate thoracic window for LAS analysis and 5 patients for incomplete cardiac telemetry monitoring. Table 2 shows baseline clinical characteristics of patients included in the CRYPTO group (n=83). The LAS cutoff point value 25.83% discriminated patients with low LAS (n=44) and high LAS (n=39). The overall rate of PAF diagnosis was 25.3% (n=21). The percentage of PAF detection was higher in patients with low LAS (n=17; 38.6%) compared with with high LAS (n=4; 10.3%; P=0.003). Patients with low LAS tended to be older, although LAS≤25.83% independently predicted the PAF detection regardless of age of the patients (odds ratio, 5.5 [95% CI, 1.66–18.27]; P=0.005). The median CHA2DS2-VASC score was higher in patients with low LAS: 5 points (interquartile range, 4–6) versus 4 points (interquartile range, 3–6; P=0.042). In our protocol, we assumed that patients with higher CHA2DS2-VASC score and no other stroke cause could have had occult PAF as the presumed cause.

There was a trend toward higher detection of complex aortic atheroma in the high LAS group (24.3%) versus (7%; P=0.064). Probably it was the occult cause of the cryptogenic stroke in these cases.

The percentage of LAS was inversely correlated with the LAv (Spearman ρ =−0.32; P=0.004; Figure 2). In our opinion, the larger the size of the left atria, the lower contractility is shown by lower LAS. Considering those patients without left atria enlarged (n=71; 85.5%), the PAF detection was higher in

Table 1. Baseline Clinical Characteristics of PAF and Non-PAF Groups

<table>
<thead>
<tr>
<th>Value</th>
<th>PAF Group</th>
<th>Non-PAF Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>71 (65–80)</td>
<td>62 (53–78)</td>
<td>0.138</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>16 (48.5)</td>
<td>5 (38.5)</td>
<td>0.539</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (53.3)</td>
<td>7 (58.3)</td>
<td>0.769</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (20)</td>
<td>4 (33.3)</td>
<td>0.359</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>2 (7.7)</td>
<td>1 (25)</td>
<td>0.283</td>
</tr>
<tr>
<td>Enlarged LAv, n (%)</td>
<td>9 (29)</td>
<td>1 (8)</td>
<td>0.150</td>
</tr>
<tr>
<td>LAS, % (IQR)</td>
<td>23 (16–33)</td>
<td>34 (23–46)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Percentage of LAS was lower in patients with PAF. The LAv (left atria volume enlarged) was defined as a volume >50 mL. IQR indicates interquartile range; LAS, left atria strain; LAv, left atria volume; Non-PAF, patients without paroxysmal atrial fibrillation; and PAF, paroxysmal atrial fibrillation.

Table 2. Baseline Clinical Characteristics of CRYPTO Group According Low (LAS<25.83%) and High LAS (LAS>25.83%)

<table>
<thead>
<tr>
<th>Value</th>
<th>Low LAS</th>
<th>High LAS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>75 (65–79)</td>
<td>70 (62–77)</td>
<td>0.067</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>22 (50)</td>
<td>19 (48.7)</td>
<td>0.907</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28 (63.6)</td>
<td>22 (56.4)</td>
<td>0.502</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (29.5)</td>
<td>10 (25.6)</td>
<td>0.692</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>3 (7.1)</td>
<td>1 (7.7)</td>
<td>0.925</td>
</tr>
<tr>
<td>Enlarged LAv, n (%)</td>
<td>11 (25)</td>
<td>1 (2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

There were more patients with enlarged LAv in low LAS group. CRYPTO indicates cryptogenic stroke patients; IQR, interquartile range; LAS, left atria strain; and LAv, left atria volume.
Conclusions and Limitations

Measurement of LAS in patients with cryptogenic stroke may be a useful tool to detect patients with occult PAF. Still, LAS parameter has also some limitations: it relies on frame-dependent technology and requires an optimal 2-dimensional image quality. However, only 5% of patients in our study were excluded because of lack of imaging quality. The CRYPTO group underwent 72-hour monitoring because it is the standard of care in our center, thus a false-negative result in PAF detection could not be ruled out. The performance of the LAS analysis required special Echo software; nevertheless, the software applied is frequently used for prevalent ventricle diseases as ischemic cardiomyopathy studies. Finally, the number of patients was small because the protocol was planned as a pilot study to launch new surrogate markers to improve the selection of patients for prolonged monitoring. Furthermore, LAS may be complemented in further protocols with other cardio embolic markers to improve the detection of occult PAF what makes secondary prevention more effective.

Disclosures

None.

References


Key Words: cardiovascular imaging agents/techniques • cerebrovascular disease/stroke • echocardiography • embolic stroke
Left Atria Strain Is a Surrogate Marker for Detection of Atrial Fibrillation in Cryptogenic Strokes
Jorge Pagola, Teresa González-Alujas, Alan Flores, Marian Muchada, David Rodriguez-Luna, Laia Seró, Marta Rubiera, Sandra Boned, Marc Ribó, José Álvarez-Sabin, Arturo Evangelista and Carlos A. Molina

Stroke. published online June 26, 2014; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2014/06/26/STROKEAHA.114.005540.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/