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

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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 atrial fibrillation (hypertension >140/90 mm Hg, age ≥75, diabetes, prior stroke), but it has never been studied in cryptogenic ischemic strokes.

Description of the Innovation

We aimed to describe the left atria functionality assessed by LAS parameter in cryptogenic strokes to improve the detection of occult PAF. With the purpose to obtain the best LAS cutoff point to differentiate patients with and without PAF, we planned the comparison as a case–control study. Accordingly, the selection of patients without PAF (non-PAF group) was made considering consecutive patients with cryptogenic stroke after complete workup evaluation with no PAF episodes in 3-year cardiac monitoring with Holter Reveal Tx to reduce the chance of a false-negative result. A group of patients with previously known PAF composed the PAF group. An informed consent was obtained from the patient or relatives. 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.

For continuous variables, the Mann–Whitney U test or Student t test was selected as appropriate. 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 appropriate. The receiver operating characteristic curve was displayed using 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 dis-tensibility. 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.
LAS cutoff point of 25.83%, which predicted PAF with trigger atrial fibrillation. In addition, patients who experience PAF episodes before the stroke may have had lower degree of atrial fibrillation. A receiver operating characteristic curve showed the test variable as the detection rate of PAF and state variable as peak atrial strain in 4-chamber view. Variables associated in the univariate analysis or clinically relevant in investigator’s judgment (as the age of the patients or the LAv) were entered into a forward stepwise logistic regression model to identify variables independently associated with PAF detection (odds ratio [95% confidence interval (CI) for exp(B) %]). The study protocol was approved by the ethics committee of the Vall d’Hebron Hospital Research Institute.

**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 monitorization, 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 atrial fibrillation 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, 1.263–16.399) 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 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 CHA2DS2VASC 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>Age, median (IQR)</th>
<th>PAF Group</th>
<th>Non-PAF Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 (65–80)</td>
<td>62 (53–78)</td>
<td></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>Age, median (IQR)</th>
<th>Low LAS</th>
<th>High LAS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 (65–79)</td>
<td>70 (62–77)</td>
<td></td>
<td>0.067</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>22 (60)</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.
the low LAS group (33.3%) versus the high LAS group (7.9%; P=0.007). Despite that the left atria size is a powerful predictor of PAF in our study, only 14.4% (n=12) had an enlarged LAv. Moreover, the sensitivity seemed to be low because half of patients had nonenlarged left atria but PAF detection. Therefore, LAS analysis may play a role to select patients with normal size left atria for prolonged cardiac monitoring. In addition, most patients with PAF had low LAS, so this parameter may be an early predictor of left atria impairment. Finally, patients with LAS/LAv ratio≤0.79 showed higher detection of PAF (41.9%) versus (8.6%; P=0.001).

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 myocardopathy studies. Finally, the number of patients was small because the protocol was planned as a pilot study to launch new surrogates 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
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