Supraventricular Premature Beats and Short Atrial Runs Predict Atrial Fibrillation in Continuously Monitored Patients With Cryptogenic Stroke

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Background and Purpose—Supraventricular premature beats (SPBs) may help to assess the risk of atrial fibrillation (AF) in patients with cryptogenic stroke and therefore guide therapy.

Methods—An internal loop recorder was implanted in consecutive patients with acute cryptogenic stroke. The occurrence and quantity of SPBs and short supraventricular runs (SVRs) in 24-hour ECG in patients with and without future AF were analyzed. We evaluated the relative risk of the upper quartile of SPB and SVR patients against the remainder and used binary logistic regression to evaluate a possible independent influence of SPBs and SVRs on AF occurrence.

Results—Twelve of 70 included patients (mean age, 59±13 years) experienced development of AF during a mean monitoring duration of 536±212 days. Patients with AF had a median of 22.8 SPBs/h versus 1.2 SPBs/h (P<0.0001) in patients without AF and a median of 0.7 SVRs/h (AF) versus 0 SVR/h (non-AF). Patients in the upper quartile of SPBs (>14.1/h) and SVRs (>0.2/h) demonstrated a relative risk of 3.9 (95% confidence interval, 1.1–14.6; P=0.04) and 6.9 (95% confidence interval, 1.8–26.7; P=0.005) for future AF, respectively. In binary logistic regression, SPBs (P=0.02) and SVRs (P=0.05) remained significant independent predictors for occurrence of AF.

Conclusions—Numerous SPBs and SVRs demonstrated a high risk for future AF in patients with cryptogenic stroke.

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Key Words: atrial fibrillation • atrial premature complexes • stroke

It has been suggested that cardioembolic events attributable to paroxysmal atrial fibrillation (AF) may be responsible for many cases of cryptogenic stroke. However, the diagnosis of asymptomatic AF is often difficult because of the intermittent occurrence of the disease and the low diagnostic yield of intermittent diagnostics (eg, 24-hour ECG).1,2 Newly developed methods for continuous rhythm monitoring might significantly improve AF diagnostics. In fact, recently 2 studies using internal loop recorders (ILRs) reported AF in ≤25% in patients with cryptogenic stroke.2,3

Supraventricular premature beats (SPBs) have been shown to be associated with a higher risk for AF.4,5 A major drawback in past studies investigating an association between SPBs and future AF, however, is the limited ECG diagnostics (mostly only 24 hours of monitoring during long-term follow-up) in an intermittently diagnosable and commonly asymptomatic arrhythmia. This imprecision leads to underdiagnosis and, consequently, undertreatment of AF.

Therefore, we investigated the predictive values of SPBs on the occurrence of AF in a prospective study of continuously ECG-monitored patients with cryptogenic stroke. From an electrophysiological point of view, supraventricular runs (SVRs) might even be more closely linked to AF; therefore, we analyzed the influence of SVRs on future AF as well.

Materials and Methods

Study Population

The study population consisted of 70 consecutive patients from a previously published pilot study investigating the occurrence of AF in patients with cryptogenic stroke. The precise diagnostic work-up and the follow-up procedure are described in detail elsewhere and are summarized briefly. Patients classified with acute cryptogenic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were included. All patients had embolic stroke patterns on cerebral imaging. Patients with lacunar strokes were excluded. Pre-existing causes for embolism were excluded by Doppler ultrasound and transesophageal and transthoracic echocardiography. Patients were ECG-monitored for 72 hours on our stroke unit, and a 24-hour ECG (Spider View; Ela Medical, Sorin Group, Milan, Italy) was performed during the first 5 days after hospital admission. The 24-hour ECG was analyzed using Synescope version 3.10 (Ela Medical). One electrophysiologist reviewed the analyzed software.

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SVRs were defined as >3 consecutive supraventricular beats with an accelerated cycle length lasting <30 s. Only patients without AF were included, and a validated ILR (Reveal XT; Medtronic, Minneapolis, MN) was implanted. Two experienced electrophysiologists reviewed the episodes from the ILR and had to independently judge it as AF. The study was approved by the local ethics committee.

Apart from baseline characteristics, we also measured left atrial (LA) parameters (LA diameter and volume index) and diastolic dysfunction in all patients as potential predictors of future AF. Measurements of LA volume index and diameter were performed by only one of the authors (D.G.D.) to avoid possible poor interobserver agreement. For LA volume index, we used the Simpson method in apical 4-chamber and apical 2-chamber views. We evaluated diastolic function using the E/A ratio from the mitral valve inflow pattern and the ratio (E/E') of early diastolic mitral inflow (E) to early diastolic mitral annular tissue velocity (E').

**Statistical Analysis**

We used IBM SPSS Statistics 20.0 (IBM Corporation, Somers, NY) for statistical analysis.

Departure from normality was evaluated by Shapiro–Wilk statistic. We compared means, proportions, and dichotomous variables using the Mann–Whitney U test and the Fisher exact test, respectively. We calculated the relative risk of the upper quartile SVRs and SPBs against the 3 other quartiles. We used binary logistic regression to evaluate a possible independent influence of SPBs and SVRs and data and approved the results.

### Table. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Atrial Fibrillation</th>
<th>No Atrial Fibrillation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>70</td>
<td>12</td>
<td>58</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.8±13.4</td>
<td>57.7±13.4</td>
<td>64.2±12.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>27 (39)</td>
<td>7 (58)</td>
<td>20 (35)</td>
<td>0.19</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>2.9±0.8</td>
<td>3.0±0.9</td>
<td>2.9±0.8</td>
<td>0.80</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3.8±1.3</td>
<td>4.4±1.2</td>
<td>3.7±1.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Supraventricular extrasystoles/h, median (IQR)</td>
<td>1.5 (0.4–9.1)</td>
<td>22.8 (3.2–106.9)</td>
<td>1.2 (0.4–3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supraventricular runs/h, n, median (IQR)</td>
<td>0.0 (0.0–1.3)</td>
<td>0.7 (0.1–2.8)</td>
<td>0.0 (0.0–0.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Figure.** Receiver operating characteristic curve of supraventricular premature beats and supraventricular runs.

CHADS indicates congestive heart failure, hypertension, age, diabetes, stroke; IQR, interquartile range; and VASc, vascular disease, age, sex.
used receiver operating characteristic curve to evaluate these variables. Statistical significance was defined as a 2-sided P value <0.05.

Results
Demographic and other characteristics are summarized in the Table. The study population with a complete work-up consisted of 70 patients (27 women). A total of 12 patients experienced development of AF during a mean monitoring duration of 536±212 days. Mean age was 59±13 years. The first documented AF episode in the ILR occurred after a median of 81 days (interquartile range, 7–118 days; range, 1–556 days) after ILR implantation. Patients with and without AF during follow-up did not significantly differ regarding baseline characteristics, cardiovascular risk factors or known cardiovascular disease, and LA dimensions (Table).

SPBs and SVRs
SPBs and SVRs showed a skewed distribution. The median number of SPBs per hour was 1.5 (interquartile range, 0.4–9.1), and the median of number SVRs was 0.0 (interquartile range, 0.0–0.4; mean, 0.99 SVRs/h). There was a highly significant difference in the occurrence of SPBs (P<0.0001) and SVRs (P<0.0001) between groups (Table). Patients with and without AF during follow-up had medians of 22.8 SPBs/h and 0.7 SVRs/h versus medians of 1.2 SPBs/h and 0.0 SVRs/h in the group without AF.

For future AF diagnosis, patients in the upper quartile of SPBs (>14.1/h) and SVRs (>0.2/h) demonstrated a relative risk of 4.0 (95% confidence interval, 1.1–14.6; P=0.04) and 6.9 (95% confidence interval, 1.8–26.7; P=0.005), respectively.

In binary logistic regression, we forced sex, age, SVR or SPB, and a parameter of LA size or diastolic function into the model. SPBs (P=0.02) and SVRs (P=0.05) remained a significant independent predictor in all statistical models, whereas female sex showed a statistically nonsignificant trend (P=0.07). Age (P=0.18) and LA parameters were not independently predictive.

To analyze the diagnostic usefulness of SVRs and SPBs, we calculated a receiver operating characteristic curve. The area under the curve was 0.82 for SPBs and 0.92 for SVRs, demonstrating good and excellent diagnostic test accuracy (Figure).

Discussion
ILRs are a great advance in the diagnostics of AF because they allow continuous rhythm monitoring with high sensitivity for AF diagnosis. Especially in patients with cryptogenic stroke, this is a major improvement compared with current diagnostic concepts and allows an effective secondary prevention of stroke recurrence. Although implantation of an ILR is secure and patient compliance is usually excellent, it seems reasonable to identify factors that further determine patients who will benefit from invasive rhythm monitoring.

The presented results from our prospectively designed study with a long follow-up demonstrate that the number of SPBs and SVRs in the widely available and easy-to-use 24-hour ECG can be a powerful tool to estimate the risk of future AF in patients with cryptogenic stroke.

In the presented cohort of patients, the negative predictive value (and sensitivity) for the occurrence of AF during follow-up, for example, was 100% in patients with <40 SPBs. Applying this cutoff value in our group of patients would have excluded 36 of 70 patients. Therefore, our results could help to select patients who would benefit most from costly long-term monitoring and therefore might have a significant benefit on cost-effectiveness and patient care because patients with a low SPBs or SVR burden do not seem to have a clinically relevant risk of AF. On the contrary, >1660 SPBs predicted future AF, with a positive predictive value of 85% and a specificity of 98%, indicating the urgent need for continuous rhythm monitoring.

A potential limitation of our study is the moderate sample size, thereby increasing the risk of bias in our statistical analysis. We found, however, strong and consistent associations across our 70 consecutively included patients.

Conclusion
SPBs and SVRs in simple-to-use 24-hour ECG are statistically and clinically significant predictors of future AF in patients with cryptogenic stroke during long-term follow-up using continuous rhythm monitoring.

Disclosures
None.

References
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