Frequent Atrial Premature Beats Predict Paroxysmal Atrial Fibrillation in Stroke Patients
An Opportunity for a New Diagnostic Strategy

Dieter Wallmann, MD; David Tüller, MD; Kerstin Wustmann, MD; Pascal Meier, MD; Jörg Isenegger, MD; Marcel Arnold, MD; Heinrich P. Mattie, MD; Etienne Delacrézat, MD

Background and Purpose—For patients having suffered ischemic stroke, the current diagnostic strategies often fail to detect atrial fibrillation as a potential cause of embolic events. The aim of the study was to identify paroxysmal atrial fibrillation in stroke patients. We hypothesized that patients with frequent atrial premature beats (APBs) recorded in 24-hour ECG will show more often atrial fibrillation when followed by repeated long-term ECG recordings than patients without or infrequent APBs.

Methods—127 patients with acute ischemic stroke and without known AF were enrolled in a prospective study to detect paroxysmal AF. Patients were stratified according to the number of APBs recorded in a 24-hour ECG (>70 APBs versus <70 APBs). Subsequently, they all underwent serial 7-day event-recorder monitoring at 0, 3, and 6 months.

Results—Serial extended ECG monitoring identified AF in 26% of patients with frequent APBs but only in 6.5% when APBs were infrequent (P=0.0021). A multivariate analysis showed that the presence of frequent APBs in the initial 24-hour ECG was the only independent predictor of paroxysmal AF during follow-up (odds ratio 6.6, 95% confidence intervals 1.6 to 28.2, P=0.01).

Conclusions—In patients with acute ischemic stroke, frequent APBs (>70/24 hours) are a marker for individuals who are at greater risk to develop or have paroxysmal AF. For such patients, we propose a diagnostic workup with repeated prolonged ECG monitoring to diagnose paroxysmal AF. (Stroke. 2007;38:2292-2294.)

Key Words: atrial fibrillation  ■  embolic stroke  ■  stroke prevention

Up to 20 to 25% of ischemic strokes occur because of embolic complications of atrial fibrillation (AF).1,2 In the presence of AF after ischemic stroke or transient ischemic attacks, patients are at especially high risk to suffer recurrent strokes, whether atrial fibrillation is paroxysmal or permanent. Both patients with paroxysmal and permanent atrial fibrillation benefit from anticoagulation substantially.3-4 Therefore it is imperative to identify paroxysmal AF after stroke or transient ischemic attack and use anticoagulation in such patients. Twenty-four–hour ECG recordings are routinely used to look for paroxysmal AF in stroke victims, but the test has a relatively low sensitivity.5-7 However, often abnormal electrical activity that triggers paroxysmal AF can be demonstrated in 24-hour ECG recordings.8 In a previous study, we demonstrated an association between frequent atrial premature beats (APBs) in 24-hour ECG recordings and an increased incidence of paroxysmal AF in patients with ischemic stroke.9

Having shown the association between APBs and paroxysmal AF in stroke patients we hypothesized that serial long-term ECG recordings would be efficient to identify AF in patients with frequent APBs on 24-hour ECG recording.
odds ratio of 6.6 (95% confidence intervals 1.6 to 28.2, among patients with frequent APBs remained significant with an
regression model the increased incidence of paroxysmal AF
ings (odds ratio 5.1; 95% CI 1.7 to 15.3, the documentation of paroxysmal AF in the follow-up record-
7-day event-recorder monitoring there was no difference of
statistical analyses were performed using Statview 4.5
cant. All statistical analyses were performed using Statview 4.5
presence of a patent foramen ovale or its treatment with an occluder
atrial enlargement, left ventricular hypertrophy, impaired left ven-
terior probability value <0.05 was considered signifi-
Continuous values are presented as means (SD). The Mann–Whitney
Statistical Considerations
Continuous values are presented as means (SD). The Mann–Whitney
U test and χ² test were used for comparisons between groups when
appropriate. Backward stepwise multiple logistic regression analysis
was performed to assess the relation between frequent APBS and
subsequent AF with adjustment for covariates. The assumption of
proportional hazards for the Cox regression model was checked for
valid. All statistical analyses were performed using Statview 4.5
(APB indicates atrial premature beats; ns, nonsignificant.
number of APBs per 24 hours and allocated to 2 groups that had been
defined according to the results of a previous retrospective study. One
group included patients with less than 70 APBs, and the other patients
with 70 or more APBs per 24 hours. Frequent APBs refer to the
presence of ≥70 APBs per 24 hours. All patients underwent serial 7-day
Event-recorder monitoring at 0, 3, and 6 months to detect asymptomatic
AF episodes. Moreover, they were requested to contact their physician
if they felt any palpitations to try to document arrhythmias. Occurrence
of AF was defined as the documentation of 1 AF episode lasting at least
30 seconds. The incidence of AF episodes were compared in both
groups with and without frequent APBs in the initial 24-hour ECG.

Results
We compared 50 patients with frequent APB (≥70 APB/24 hours) and 77 controls with infrequent APBs (<70 APB/24
hours; Table). Patients with frequent APBs were older, had
arterial hypertension more often, and a higher LV mass index
than patients without or infrequent APBs. Seven-day event-recorder monitoring identified paroxysmal AF in 13 patients (26%)
with frequent APBs and in 5 patients (6.5%) with infrequent
APBs (P=0.0021). The cumulative incidence of paroxysmal AF
in both groups is shown in the Figure. Frequent APBs, on the
other hand, were present in 72% of patients who were found to
have paroxysmal AF, but in only 34% of patients without
paroxysmal AF (P<0.004). In the univariate analysis, frequent
APBs on the initial 24-hour ECG were strongly associated with
the documentation of paroxysmal AF in the follow-up recordings
(odds ratio 5.1; 95% CI 1.7 to 15.3, P=0.004).

After adjustment for clinical covariates in a multiple logistic
regression model the increased incidence of paroxysmal AF
among patients with frequent APBs remained significant with an
odds ratio of 6.6 (95% confidence intervals 1.6 to 28.2, P=0.01).
In patients with documented paroxysmal AF (n=18) on
7-day event-recorder monitoring there was no difference of
age, gender, prevalence of cardiovascular risk factors, prev-
ulence of hypertension, and echocardiographic characteristics,
including left atrial size, left ventricular mass index, and
LV ejection fraction, when compared with patients without
identifiable paroxysmal AF (n=109).

Discussion
Frequent APBs in a 24-hour ECG identify stroke patients
who are at increased risk of having or developing paroxysmal
atrial fibrillation (PAF). Serial 7-day ECG recordings revealed
paroxysmal AF in 26% of patients with frequent
APBs, 5 times more often than in patients without or
infrequent APBs (<70/24 hours). Multivariate analysis
demonstrates that APBs represent a risk factor for paroxysmal AF
that is independent of other factors commonly associated with
AF such as age, left atrial enlargement, and hypertension. Thus, the results of our study support a new diagnostic
strategy to identify paroxysmal AF in stroke patients, which
would remain unidentified with the current diagnostic
approaches: First, 24-hour ECG recording to count the number
of APBs, and then serial 7-day ECG recordings selectively in
patients with ≥70 APBs per 24 hours.

For patients having suffered an ischemic stroke, the current
diagnostic strategies often fail to detect paroxysmal AF as a
potential cause of embolic events, though unrecognized
paroxysmal AF is a major and when diagnosed treatable risk
factor for recurrent stroke. Therefore, improvement in the
detection of paroxysmal AF in stroke victims is essential.

<table>
<thead>
<tr>
<th>Patient Characteristics With Respect to the No. of APBs</th>
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<tbody>
<tr>
<td>Age, y</td>
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<td>--------------------------------------------------------</td>
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<tr>
<td>Male , n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<td>Left atrial enlargement, n (%)</td>
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<td>Left ventricular mass-index, g/m²</td>
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<td>Left ventricular ejection fraction, n (%)</td>
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<tr>
<td>Paroxysmal atrial fibrillation, n (%)</td>
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Cumulative incidence of paroxysmal atrial fibrillation (in %) detected at serial follow-up (F/U) with 7-day event recording.
Twenty-four–hour ECG detects atrial fibrillation in 1% to 5% of unselected patients with stroke, and because of its low sensitivity its clinical value is controversial.6,7,12

The rationale to correlate the presence of arrhythmogenic triggers with an increased incidence of paroxysmal AF is supported by recent advances in the understanding of the pathophysiology of atrial fibrillation. A large array of evidence demonstrates that AF is triggered by multifocal abnormal electrical activity, usually originating in the pulmonary veins.6,8,13,14 Other studies have shown the association of frequent APBs, AF, and stroke. In a population-based cohort, frequent APBs in 68-year-old patients were associated with a relative risk of 1.9 to suffer a stroke.15 Patients with frequent APBs after bypass surgery had a higher risk to develop AF as well,16 and in a more recent study, frequent atrial extrasystoles (≥1/min) after exercise predicted AF in patients with left ventricular hypertrophy.17 In a retrospective study, we showed that frequent APBs were associated with AF in patients with acute ischemic stroke,10 and the present prospective study confirms even that frequent APBs are strongly associated with AF. Furthermore, the study results permit to suggest an algorithm to detect paroxysmal AF efficiently with serial 7-day ECG recordings selectively in patients with frequent APBs, ie, in patients with a high probability of AF. Factors that commonly predict the risk to develop AF such as age, hypertension, left ventricular hypertrophy, etc. were not associated with AF in our study. This may be because of the sample size. In a larger cohort these associations would probably have been found. In fact, however, this emphasizes the stratification power of frequent APBs, which reliably predicted paroxysmal AF even in a relatively small study. The strong association between repetitive APBs and the presence of paroxysmal AF reflects their pivotal role as AF triggers.

Uncovering AF in patients with stroke is important. However, our study does not necessarily establish AF as cause of stroke in the patient studied. The association of AF with ischemic stroke is not exclusively related to cardiogenic embolism, and in some stroke patients with AF concurrent other potential stroke causes are found.18

The suggested diagnostic algorithm to use serial 7-day ECG recordings may detect a stroke population which is not at the same risk of recurrent stroke as patients in whom paroxysmal AF is detected already in a 24-hour ECG recording. It is likely that such patients derive also a benefit from long-term anticoagulation as patients who had been randomized to antithrombotic trials in AF. However, the question of optimal secondary prevention in these patients will have to be addressed in new trials.

Conclusions
Frequent APBs mark stroke patients who are likely to have or to develop paroxysmal AF. For patients with frequent APBs on 24-hour ECG, we propose to use serial 7-day ECG recordings at distinct intervals to look for paroxysmal AF. Such an approach is efficient to identify AF in stroke patients who would potentially benefit from anticoagulation and sustain less recurrent strokes.

Sources of Funding
Etienne Delacretaz is supported by a Swiss National Research Foundation grant.

Disclosures
None.

References
14. Vincenti A, Brambilla R, Fumagalli MG, Merola R, Pedretti S. Onset of unselected patients with stroke, and because of its low sensitivity its clinical value is controversial.6,7,12

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*Stroke*. 2007;38:2292-2294; originally published online June 21, 2007; doi: 10.1161/STROKEAHA.107.485110

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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