Prevalence and Predictors of Paroxysmal Atrial Fibrillation on Holter Monitor in Patients With Stroke or Transient Ischemic Attack

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Background and Purpose—Our aims were to quantify the yield of Holter monitor for detection of paroxysmal atrial fibrillation (PAF) in patients with stroke and TIA, and to determine potential predictors of PAF to allow more focused testing.

Methods—We reviewed records of 1128 consecutive patients attending a university stroke clinic from September 2005 to September 2006 and identified 426 patients with definite TIA or stroke. We abstracted clinical, cardiac imaging, and neuroimaging data. Logistic regression analysis was performed to determine independent predictors of PAF on Holter monitor.

Results—Overall, 413 of 426 patients (65 ± 15 years; male, 49.8%) with a definite TIA (53%) or stroke (47%) underwent Holter monitoring for a mean of 22.6 hours. PAF occurred in 39 patients (9.2%) all older than age 55 years. PAF lasting >30 seconds was evident in 11 patients (2.5%). The other 28 patients had PAF <30 seconds (6.5%). In multivariate analyses, number of acute (odds ratio [OR], 1.7 for each 1 lesion increase; 95% confidence interval [CI], 1.2–2.6; P = 0.0047) and chronic (OR, 1.6 for each 1 lesion increase; 95% CI, 1.2–2.3; P = 0.0001) infarcts on brain CT, number of chronic infarcts on MRI (OR, 3.0 for each 1 lesion increase; 95% CI, 1.7–5.1; P < 0.0001), and any acute cortical infarct on imaging (OR, 5.8; 95% CI, 1.9–17.8; P = 0.0023) were associated with PAF.

Conclusions—PAF is present in 9.2% of patients with definite stroke or TIA. Age older than 55 years and presence of acute or chronic brain infarcts on neuroimaging are strongly associated with PAF. (Stroke. 2010;41:2596-2600.)

Key Words: atrial fibrillation • diagnostic imaging • Holter monitor • ischemic stroke
Subjects and Methods

Study Population
The research protocol was approved by our Health Research Ethics Board. Our tertiary-level stroke prevention clinic keeps a prospective registry of all consecutive patients. Patients are referred to our stroke prevention clinic from emergency departments in the northern half of the province, our inpatient stroke service, or a family physician’s office with the presumptive diagnosis of stroke or TIA. The charts of 1128 consecutive new patients presenting over a 1-year period of time (from September 2005–September 2006) were reviewed, and all patients without a diagnosis of definite ischemic stroke or TIA as determined by a board-certified stroke neurologist were excluded (n = 702). In addition, patients with any history of chronic AF or PAF were excluded. Furthermore, our case definition required that, in addition to having a neurologist diagnosis of definite stroke or TIA, the patient’s symptoms would have to include acute focal neurological dysfunction. Patients with stroke had either deficits lasting >24 hours or brain imaging confirmation of acute infarcts and those with TIA had resolution within 24 hours and no evidence of infarction on brain imaging.20,21 This left us with 426 symptomatic patients with definite stroke or TIA. Of these patients, 13 did not undergo HM and, although included for baseline characteristics, they were excluded from further analysis, leaving our final sample of 413 patients.

Patients were seen in the stroke prevention clinic on average 1 to 3 weeks after their index events. All patients underwent routine history, physical examination, laboratory tests, and various imaging and ancillary tests, including HM during the process of clinical investigation. We used a standardized case report form and abstracted a number of clinical and demographic variables, including age, date of the event, risk factors for stroke, medications, cardiac history, congestive heart failure, coronary artery disease, myocardial infarction, previous stroke or TIA, neurological symptoms, and neurological examination findings. We also documented infarct pattern on CT or MRI, carotid ultrasound results, electrocardiogram (ECG) results, transthoracic echocardiogram and transesophageal echocardiogram results (ejection fraction <30%, left atrial and ventricle thrombus, left atrial size >42 mm, left atrial blood velocity <30 cm/sec, patent foramen ovale and presence of shunt, atrial septal aneurysm, vegetations, and aortic arch plaque <4 mm, >4 mm, or mobile), and HM results.

Neuroimaging Data
All brain CT scans and MRI scans were interpreted by board-certified neuroradiologists independent of our study team and without knowledge of the diagnosis of PAF. Acute lesions on CT scan were identified as brain hypodensities with associated cytotoxic edema.22,23 Acute lesions on MRI were identified as acute by restricted diffusion on diffusion-weighted imaging sequences and low signal on apparent diffusion coefficient sequences.22,23 The number of acute lesions was recorded, as well as the involvement of cerebral cortex (cortical) or just cerebral white matter (subcortical). Similarly, chronic infarcts on brain CT were defined as hypodense lesions without an associated cytotoxic edema pattern. Chronic infarcts on brain MRI involved increased signal on fluid-attenuated inversion recovery or T2-weighted sequences without evidence of restricted diffusion on diffusion-weighted imaging sequences.22,23

Measurement and Definition of AF
HM was performed from a few days to up to 3 months after the stroke/TIA event depending on whether it was performed during an inpatient stay or was organized by the clinic on an outpatient basis. All HM was reported by board-certified cardiologists who were independent of our study team and unaware of clinical and neuroimaging results. Bursts of AF on HM were reported either by the duration of each occurrence or by the number of beats of each occurrence or both. AF on HM was defined by irregular ventricular response in the absence of p-waves or with fibrillatory waves.16,25 Atrial flutter was defined by clear flutter waves with regular or irregular ventricular rate.16 We calculated the mean number of beats per burst and/or the mean duration of bursts of AF for each patient. The HM test was considered “positive” for PAF if any AF was present. We additionally defined individual bursts of AF lasting <30 seconds as brief PAF.

Statistical Analysis
We calculated descriptive statistics using means and proportions, and present results were stratified by the presence or absence of PAF. We then performed univariate logistic regression on all clinical, cardiac imaging on TTE and TEE, ECG, and neuroimaging variables to determine potential predictors of PAF on HM. Of those variables with P < 0.1 in univariate analysis, we conducted multivariate logistic regression analysis, adjusting for age and gender. Statistical analyses were performed with the Statistical Package for Social Science (version 15 for Windows; SPSS) and SAS version 9 (SAS Institute).

Results
There were 426 patients with definite TIA or stroke included in our sample. Their mean age was 65 ± 14.8, and 73.9% were older than 55 years; 212 patients were male (49.8%). Two-hundred twenty-seven patients had TIA (53.3%) and 199 patients had stroke (46.7%). Twenty-seven patients had previous stroke (6.3%) and 34 had previous TIA (8%). Only 2 patients (0.4%) had valve disease (1 aortic stenosis and 1 aortic regurgitation). One patient had a mechanical heart valve (0.2%) and 4 had porcine valves (1%). Seven patients (1.7%) had congestive heart failure.

Diagnostic Imaging
All patients had carotid ultrasound and 15 patients (3.5%) had symptomatic carotid stenosis >50%. All patients had CT of the brain completed. The mean number of acute CT lesions was 0.5 (SD, 0.77; range, 0–4). The mean number of chronic infarcts on CT was 0.29 (SD, 0.74; range, 0–4). A total of 238 patients (55.9%) also underwent brain MRI. The mean number of acute MRI lesions was 0.35 (SD, 0.73; range, 0–3). The mean number of chronic MRI infarcts was 0.20 (SD, 0.67; range, 0–3). Thirty-nine out of 227 patients (17.2%) with recent TIA had chronic infarcts seen on brain CT, whereas 31 of 199 patients (15.6%) with new stroke had chronic infarcts on brain CT (P = 0.6).

HM
Overall, 413 out of 426 patients had HM completed for a mean of 22.6 hours; 9.2% (39/426) had bursts of definite AF and, based on these results, they were all subsequently fully anticoagulated by stroke neurologists. Definite occurrences of PAF lasting >30 seconds were evident in 2.5% (11/426) patients. The other 28 patients (6.5%) had brief PAF lasting <30 seconds, with variable numbers of beats during the monitoring period. In those with brief PAF lasting <30 seconds, the mean number of beats overall was 59.9. Characteristics of patients stratified by the presence or absence of bursts of PAF on HM are presented in Table 1. Paroxysmal AF occurred in no patients 55 years of age or younger but occurred in 39 or 306 (12.7%) of those older than 55 years.
Predictors of PAF

All clinical cardiac imaging and neuroimaging characteristics were tested in univariate logistic regression analysis. Only those with \( P \leq 0.1 \) were tested in subsequent analysis adjusted for age and gender. In the multivariate-adjusted analyses, only acute and chronic infarcts on CT, acute cortical infarcts on MRI, acute cortical infarcts on either MRI or CT, and chronic infarcts on MRI were associated with PAF on HM (Table 2). Age remained significantly associated with PAF in all models. We also examined number of brain infarcts as a categorical variable as a form of “dose-response” analysis.

For brain CT, 2 acute lesions compared to 0 acute lesions was a significant predictor of PAF on HM after adjustment for age and gender (odds ratio [OR], 2.9; 95% confidence interval [CI], 1.2–6.8; \( P = 0.0179 \)). The same applies for brain MRI; 3 acute lesions compared to 0 acute lesions was a significant predictor of PAF on HM after adjustment for age and gender (OR 2.1; 95% CI, 1.1–4.1; \( P = 0.0278 \)). Increasing numbers of chronic infarcts on CT scan were strongly associated with positive HM for PAF (Figure).

None of the other variables was independently associated with PAF, including other risk factors, congestive heart failure, MI, previous stroke or TIA, clinical presentation, specific arterial territories of infarcts on brain CT or MRI, or any of the ECG variables. Similarly, the presence of infarcts in \( >1 \) vascular territory on brain CT or MRI was a slightly more common finding in those with PAF (2.56%) than those without PAF (1.6%), but this difference was not significant.

However, patients older than 55 years with any infarct present

| Table 1. Baseline Characteristics Based on the Presence of PAF on Holter Monitoring |
|---------------------------------|-------------------------------|
| Baseline Characteristics | Without PAF (n=387) | With PAF (n=39) |
| Age, mean (SD) | 63.9 (14.9) | 75.4 (8.1)* |
| Male, n (%) | 187 (50) | 19 (48.7)* |
| Hypertension, n (%) | 217 (58) | 31 (79.4) |
| Hyperlipidemia, n (%) | 174 (46.5) | 22 (56.4) |
| CAD, n (%) | 53 (14.2) | 7 (17.9) |
| MI, n (%) | 24 (6.4) | 5 (12.8) |
| CHF, n (%) | 5 (1.3) | 2 (5.1) |
| DM, n (%) | 54 (14.4) | 6 (15.4) |
| Smoking, n (%) | 47 (12.6) | 1 (11.1) |
| Previous stroke, n (%) | 23 (6.2) | 4 (10.3) |
| Previous TIA, n (%) | 30 (8.0) | 4 (10.3) |
| Any ECG abnormality, n (%) | 16 (4.3) | 3 (7.7) |
| Mechanical valve, n (%) | 1 (0.3) | 0 (0) |
| Porcine valve, n (%) | 4 (1.1) | 0 (0) |
| Diagnosis of stroke, n (%) | 169 (45.2) | 23 (59.0) |
| Diagnosis of TIA, n (%) | 205 (54.8) | 16 (41.0) |

*\( P \leq 0.1 \) in univariate logistic regression.

| Table 2. Logistic Regression to Predict Paroxysmal Atrial Fibrillation on Holter Monitor |
|---------------------------------|-------------------------------|
| | Univariate‡ | Adjusted for Age and Gender |
| | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) |
| Age‡ | 1.1 (1.0, 1.1) | <0.0001* | | |
| Male | 1.0 (0.5–1.8) | 0.88 | | |
| Hypertension | 2.4 (1.1, 5.2) | 0.0256* | 1.4 (0.6, 3.2) | 0.4108 |
| N of acute infarcts on CT‡ | 1.5 (1.1, 2.2) | 0.0223* | 1.7 (1.2, 2.6) | 0.0047* |
| N of chronic infarcts on CT‡ | 1.9 (1.4, 2.5) | 0.0001* | 1.6 (1.2, 2.3) | 0.0045* |
| Acute cortical infarcts on MRI | 6.1 (1.1, 34.2) | 0.0404* | 11.1 (1.4, 86.4) | 0.0220* |
| N of chronic infarcts on MRI‡ | 2.3 (1.5, 3.7) | 0.0003* | 3.0 (1.7, 5.1) | <0.0001* |
| Acute cortical infarcts on CT or MRI | 3.6 (1.3, 9.7) | 0.0113* | 5.8 (1.9, 17.8) | 0.0023* |
| Left atrial enlargement on TEE | 2.9 (1.0, 9.0) | 0.0610 | 2.3 (0.7, 8.0) | 0.1853 |

*Significant at \( P < 0.05 \).
‡For each 1-unit increase in the independent variable.
‡‡All clinical, demographic, cardiac imaging and neuroimaging variables were examined in univariate analysis (see Subjects and Methods and Table 1). Presented are all of those with \( P < 0.1 \) in univariate analysis.

TEE indicates transesophageal echocardiogram.
on neuroimaging had a prevalence of PAF of 23.2% and represented >55% of all positive HM (P<0.001).

Discussion
In a large study of consecutive patients with a definite stroke or TIA seen at a tertiary care stroke prevention clinic, we found that almost 10% of patients had PAF on their HM test. The yield was realized entirely in persons 55 years of age and older. The yield of HM to detect paroxysmal AF is similar to the yield of carotid ultrasound to detect carotid stenosis in the stroke patient population. Our results are broadly consistent with the few previous studies that have tried to examine this question while overcoming some limitations of the studies included in a recent systematic review of the topic.7–15 Specifically, we restricted our population to those with definite stroke or TIA, reported a larger number of patients, and we defined clinical variables associated with PAF on HM. Baseline ECG was not helpful in identifying any case of AF in our study’s population, which contrasts with a previous report by Douen et al26 that reported that serial ECG assessments within the first 72 hours of an acute stroke significantly improve the detection of AF (17.5%). The discrepancy might be because of differences in practice patterns in inpatient stroke at our center compared with those of Douen et al. Patients with AF present on EKG would not receive subsequent HM at our institution because the diagnosis of AF has already been made. Therefore, this group of patients would have been excluded from our final study sample. The other explanation is that serial EKG were not performed systematically in our inpatients unless there was a cardiac indication and the yield of a single EKG is expected to be less than that of serial tests.26

Surprisingly, other than age, there were no sociodemographic, clinical, or ECG characteristics that were associated with PAF. Conversely, we found that bursts of PAF on HM were associated with abnormal neuroimaging results. Specifically, multiple acute and chronic brain infarcts on CT and MRI of the brain were associated with PAF, and it appeared that the greater the burden of infarcts, the greater the prevalence of PAF after adjustment for age and gender. Based on our data, as a simple rule of thumb, of patients with definite stroke or TIA aged 55 years of age and older who have ≥1 infarcts on neuroimaging, nearly one-quarter will have bursts of AF on HM. This subgroup of patients might represent a high-yield population for future studies of HM that include follow-up studies for stroke recurrence and randomized trials of anticoagulation. Our results indicate that performing HM in those younger than 55 years of age is unlikely to be useful given the zero yield for AF in our study. Current guidelines define AF as episodes lasting >30 seconds; therefore, briefer bursts are generally not considered to represent AF requiring treatment.16 Our results imply that brief bursts of AF may be clinically important for 2 reasons. First, the association with a cardioembolic infarct pattern on imaging (ie, multiple lesions) suggests that these bursts may be markers of a cardioembolic source of embolism. Either the brief bursts alone may contribute to atrial thrombus formation or, more likely, they are markers of longer periods of AF occurring outside of the monitoring period. Further studies are needed to define this phenomenon. Second, both intuitively and based on the literature, multiple brain infarcts are associated with cognitive dysfunction and dementia.27–29 For this reason, the addition of brief PAF to current definitions of AF should be considered, if only for the purposes of study because the importance of this phenomenon needs to be further characterized.

Because anticoagulant treatment dramatically reduces the rate of recurrent stroke, detection of AF after stroke is essential.17 Studies have clearly shown that patients with PAF and previous ischemic stroke or TIA have a risk of recurrent stroke and benefit from anticoagulation in an identical manner to that of patients with chronic AF.17–19 Unfortunately, AF remains underdiagnosed because it is often asymptomatic; up to 30% of patients with AF are unaware of their diagnosis and 25% of those with AF-associated stroke have no previous diagnosis of AF.30,31 Whether patients with short-duration PAF or brief PAF will benefit in the same manner is unclear.

Although our study represents a consecutive series of patients with rich clinical and diagnostic data, and it is nearly as large by itself as a recent systematic review on the topic, there are several limitations. First, we did not record the exact timing of the HM; however, some were performed within a few days of the index stroke and others were arranged on an outpatient basis 5 to 12 weeks after the index stroke. Because HM was performed in many outpatients, our results may differ from those of other studies examining HM entirely in the acute setting. Second, some of the brief occurrences of AF may represent stroke-induced arrhythmias rather than being the cause of the stroke (ie, reverse causality). However, whether PAF occurred before or after the stroke will always be difficult to clarify because prestroke monitoring is, of course, not available. Third, the relationship we report between PAF on HM and multiple infarcts on brain imaging is cross-sectional. However, we think the results are still of importance because increasing infarct burden on brain imaging is undesirable and is associated with worsening patient prognosis.7–29 Last, our decision to include only patients with definite stroke or TIA might have led to an overestimation of the yield of HM test relative to an overall stroke prevention clinic population. However, it is our opinion that this limitation is outweighed by the benefit of understanding the yield of HM in a well-defined population in which it is most indicated.

Conclusion
In summary, the yield of routine HM in patients with definite stroke or TIA is high. We found that age older than 55 years and neuroimaging are the strongest predictors of PAF bursts on HM. In resource-constrained settings, this may help physicians better-rationalize the use of HM. Nevertheless, further prospective study is required to determine long-term stroke risk in those with brief occurrences of AF which lasts less than 30 seconds on HM, and the condition seems common enough in the setting of stroke or TIA work-up that we suggest that a randomized trial of anticoagulation be considered. Until randomized trial evidence becomes available, the pattern of practice at our center is to fully anticoagulate stroke and TIA patients with brief occurrences of PAF.
Disclosures

None.

References

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Abstract 9

뇌졸중 또는 일과성혈혈발작이 있는 환자에서 Holter 감시를 통한 발작성 심방세동의 유병률과 예측 인자

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(Stroke. 2010;41:2596-2600.)

Key Words: atrial fibrillation ■ diagnostic imaging ■ Holter monitor ■ ischemic stroke

배경과 목적
본 연구의 목적은 뇌졸중이나 일과성혈혈발작(paroxysmal ischemic attack, TIA)이 있는 환자에서 발작성 심방세동(paroxysmal atrial fibrillation, PAF)의 발견을 위한 Holter 감시(Holter monitor)의 성과를 정량화하고, 더 명확한 감사를 하기 위한 PAF의 강력한 예측 인자 결정을 위한 것이었다.

방법

결과
명백한 TIA (53%) 또는 뇌졸중 (47%)이 있는 환자 426명 (65±15세; 남성, 49.8%; 증 413명이 Holter 감시를 평균 22.6시간 동안 수행하였다. PAF는 39명 (9.2%)에서 발견되었고, 모두 55세 이상이었다. 30초 이상 지속된 PAF는 11명 (2.5%)에서 명백하였다. 다른 28명의 환자는 30초 미만의 PAF가 있었다 (6.5%). 다변량 분석에서 뇌 CT에 의한 급성 (OR, 1개 병변 증가당 1.7; 95% CI, 1.2~2.6; P=0.0047) 및 만성 (OR, 1개 병변 증가당 1.6; 95% CI, 1.2~2.3; P=0.0001) 경색의 수, MRI에서 만성 경색의 수 (OR, 1개 병변 증가당 3.0; 95% CI, 1.7~5.1; P=0.0001) 및 모든 급성 피질 경색 (OR 5.8; 95% CI, 1.9~17.8; P=0.0023)이 PAF와 관련이 있었다.

결론
PAF는 명백한 뇌졸중 또는 TIA 환자의 9.2%에서 나타났다. 55세 이상 및 신경영상에서 급성 또는 만성 뇌경색이 PAF와 관련이 같다.
Figure. Results of dummy variable regression showing that increasing numbers of chronic brain lesions on CT are associated with the presence of brief bursts of paroxysmal atrial fibrillation on Holter monitor. The probability values for the odds ratios are as follows: 1 infarct vs 0 infarcts, $P = 0.9407$; 2 infarcts vs 0 infarcts, $P = 0.0043$; 3 infarcts vs 0 infarcts, $P = 0.0213$; and 4 infarcts vs 0 infarcts, $P = 0.0142$.

Table 2. Logistic Regression to Predict Paroxysmal Atrial Fibrillation on Holter Monitor

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<th>Univariate†</th>
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<th>Adjusted for Age and Gender</th>
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<td>OR (95% CI)</td>
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<td>OR (95% CI)</td>
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<tr>
<td>Age†</td>
<td>1.1 (1.0, 1.1)</td>
<td>&lt;0.0001*</td>
<td>1.4 (0.6, 3.2)</td>
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<td>Male</td>
<td>1.0 (0.5–1.8)</td>
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<td>Hypertension</td>
<td>2.4 (1.1, 5.2)</td>
<td>0.0256*</td>
<td>1.7 (1.2, 2.6)</td>
<td>0.0047*</td>
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<td>N of acute infarcts on CT†</td>
<td>1.9 (1.4, 2.5)</td>
<td>0.0001*</td>
<td>1.6 (1.2, 2.3)</td>
<td>0.0045*</td>
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<tr>
<td>N of chronic infarcts on CT†</td>
<td>6.1 (1.1, 34.2)</td>
<td>0.0404*</td>
<td>11.1 (1.4, 86.4)</td>
<td>0.0220*</td>
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<tr>
<td>Acute cortical infarcts on MRI</td>
<td>2.3 (1.5, 3.7)</td>
<td>0.0003*</td>
<td>3.0 (1.7, 5.1)</td>
<td>&lt;0.0001*</td>
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<tr>
<td>N of chronic infarcts on MRI†</td>
<td>3.6 (1.3, 9.7)</td>
<td>0.0113*</td>
<td>5.8 (1.9, 17.8)</td>
<td>0.0023*</td>
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<tr>
<td>Left atrial enlargement on TEE</td>
<td>2.9 (1.0, 9.0)</td>
<td>0.0610</td>
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<td>0.1853</td>
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*Significant at $P < 0.05$.
†For each 1-unit increase in the independent variable.
‡All clinical, demographic, cardiac imaging and neuroimaging variables were examined in univariate analysis (see Subjects and Methods and Table 1). Presented are all of those with $P < 0.1$ in univariate analysis.

TEE indicates transesophageal echocardiogram.