Paroxysmal atrial fibrillation in cryptogenic stroke

Neha S Dangayach1
Kevin Kane2
Majaz Moonis3

1Saint Vincent Hospital, 2University of Massachusetts Medical School, 3University of Massachusetts Memorial Health Center, Worcester, MA, USA

Introduction: Paroxysmal atrial fibrillation (PAF) is perhaps the most underdiagnosed mechanism of apparent cryptogenic stroke (CS). Various studies have shown that increasing the duration of monitoring can increase the diagnosis of PAF in CS.

Methods: We compared demographic and risk factors for ischemic stroke across different TOAST (Trial of ORG 10172 in Acute Stroke Treatment) stroke subtypes to look for clinical differences between other subtypes and CS and subsequently performed periodic Holter monitoring and imaging studies in apparent CS patients.

Results: Of the 298 patients with ischemic stroke, 17% had CS. Periodic holter monitoring enabled diagnosis of PAF in 29% of patients. Five of 51 patients with CS had recurrent ischemic stroke and all 5 were demonstrated as PAF on repeated Holter monitoring.

Conclusions: Long-term periodic rhythm monitoring in patients with apparent CS showed PAF in a significant percentage of CS patients, which altered subsequent treatment.

Keywords: cryptogenic stroke, atrial fibrillation, stroke of undetermined etiology

Introduction

Understanding the etiological basis of acute ischemic stroke is important in optimizing treatment to reduce the chances of recurrent ischemic stroke (RIS).1 Warfarin is the accepted treatment for cardioembolic stroke,2 while antiplatelet drugs with or without carotid endarterectomy or carotid artery stenting are the appropriate treatment for large artery atherosclerosis (LAA).3

Even with the most comprehensive in-patient evaluation, 20% to 30% of ischemic stroke has undefined etiologies: cryptogenic stroke (CS).4-8 These patients are often randomly assigned to treatment options depending upon the perceived etiology of the stroke by their physician. The American Heart Association/American Stroke Association (AHA/ASA) guidelines8 help in identifying structural causes for stroke such as atherothrombosis or known cardiac causes (eg, known atrial fibrillation, low ejection fraction).

However, one of the most neglected aspects of stroke evaluation is intermittent rhythm disorders such as paroxysmal atrial fibrillation (PAF), which may not be evident within the suggested 24-hour telemetry period and is as important as chronic atrial fibrillation (CAF) as a risk factor for stroke. Therefore, we prospectively investigated the prevalence of PAF in apparent CS.

Methods

Patients with a first-ever ischemic stroke admitted to the University of Massachusetts Memorial Health Center were worked up as per the standard ASA/AHA acute care
guidelines\(^9\) for a period of 7 years from 2002 to 2009 and were classified into subtypes according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria and definitions.\(^1\) Transient ischemic attacks (TIA), while not a part of the TOAST classification, were nevertheless included since they constitute a high risk group for subsequent stroke and may have PAF or CAF as an underlying mechanism. The study remains an ongoing project and data collected between 2002 and 2009 were analyzed. Patients seen in the stroke prevention clinic with a diagnosis of CS were included in the study for periodic follow-ups. Patients with hemorrhagic stroke were excluded. The entire cohort of patients was transitioned from the inpatient service to follow-up in the stroke prevention clinic. All patients had a transthoracic echocardiogram followed by magnetic resonance imaging (MRI) of the brain where noncontrast CT was normal.

### Protocol

At each 6-monthly visit, a comprehensive evaluation and medical reconciliation were performed. The evaluation consisted of fasting lipid panel, glucose, C-reactive protein, Doppler studies of the neck, and 48-hour Holter monitoring.

PAF was defined as episodes of AF that lasted for less than 1 week and resolved spontaneously.\(^10\) To detect PAF, patients underwent periodic 48-hour Holter monitoring every 6 months. Stroke-related risk factors (hypertension, diabetes mellitus, hyperlipidemia, past history of myocardial infarction [MI], coronary artery disease [CAD]), demographics, and medication use were compared across different subtypes to assess for possible clinical differences between patients with CS and other stroke subtypes.

A subgroup analysis of all patients determined to have cardioembolic stroke (including newly diagnosed PAF and CAF) was performed to look for possible clinical similarities and differences between patients with CS with later defined PAF and those presenting as obvious cardioembolic stroke at onset. We also compared the subgroup of patients with CS and PAF and the subgroup of patients with CS without PAF to identify any differences that might again help to predict which patients with CS have an underlying cardiac arrhythmia, namely PAF.

### Statistical methods

One way analysis of variance (age) and Chi-square tests (risk factors, medications, gender) were used to compare the variables in the different groups, and a P-value < 0.05 was regarded as significant.

### Results

Two hundred ninety-eight patients with ischemic stroke were evaluated. The mean age of the subjects was 63.16 ± 15.85 years, and 56.7% of the patients with ischemic stroke were males. Subtype classification showed 54 (17%) cardioembolic stroke, 74 (25%) LAA, 87 (29%) small artery disease, 51 (17%) CS, and 32 (11%) TIA. A comparative analysis of demographics and risk factors including hypertension, hyperlipidemia, CAD, diabetes mellitus, past history of MI, and past history of TIA, yielded significant difference in age between the 5 groups (P = 0.043) (Table 1). A post-hoc Tukey test showed that patients with SAD were older than patients with CS (P = 0.076), but this difference did not reach significance. There were no other significant differences between the groups. Two patients with initial CS developed early subsequent PAF and therefore for

### Table 1

Demographic and risk factors compared across the 5 subgroups of ischemic stroke and transient ischemic attack

<table>
<thead>
<tr>
<th></th>
<th>LAA</th>
<th>CE</th>
<th>SAD</th>
<th>TIA</th>
<th>CS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.59 ± 14.94</td>
<td>65.66 ± 17.33</td>
<td>66.03 ± 14.73</td>
<td>64.89 ± 16.46</td>
<td>58.22 ± 15.94</td>
<td>0.043</td>
</tr>
<tr>
<td>Gender</td>
<td>29 (39.2%)</td>
<td>22 (40.7%)</td>
<td>40 (46.0%)</td>
<td>9 (28.1%)</td>
<td>29 (56.9%)</td>
<td>0.102</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>45 (60.8%)</td>
<td>32 (59.3%)</td>
<td>47 (54.0%)</td>
<td>23 (71.9%)</td>
<td>22 (43.1%)</td>
</tr>
<tr>
<td>HTN</td>
<td>40 (54.1%)</td>
<td>29 (53.7%)</td>
<td>49 (56.3%)</td>
<td>18 (56.3%)</td>
<td>18 (35.3%)</td>
<td>0.149</td>
</tr>
<tr>
<td>Hyper-lipidemia</td>
<td>42 (56.8%)</td>
<td>27 (50.0%)</td>
<td>42 (48.3%)</td>
<td>16 (50.0%)</td>
<td>24 (47.1%)</td>
<td>0.813</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (9.5%)</td>
<td>4 (7.4%)</td>
<td>4 (4.6%)</td>
<td>2 (6.3%)</td>
<td>3 (6.0%)</td>
<td>0.805</td>
</tr>
<tr>
<td>A-Fib</td>
<td>2 (3.8%)</td>
<td>14 (35.0%)</td>
<td>5 (8.6%)</td>
<td>4 (14.8%)</td>
<td>2 (7.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (18.9%)</td>
<td>11 (20.4%)</td>
<td>15 (17.2%)</td>
<td>5 (15.6%)</td>
<td>8 (16.0%)</td>
<td>0.965</td>
</tr>
<tr>
<td>CAD</td>
<td>9 (12.2%)</td>
<td>10 (18.5%)</td>
<td>9 (10.3%)</td>
<td>7 (21.9%)</td>
<td>7 (15.7%)</td>
<td>0.446</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; CAD, coronary artery disease; CE, cardioembolic stroke; CS, cryptogenic stroke; HTN, hypertension; LAA, large artery atherosclerotic stroke; MI, myocardial infarction; SAD, small artery disease; TIA, transient ischemic attack.
other anti-HtN 21 (28.4%) 27 (50.0%) 32 (36.8%) 12 (37.5%) 16 (31.4%) 0.138
ACe-inhibitors 24 (32.4%) 21 (38.9%) 31 (35.6%) 9 (28.1%) 13 (25.5%) 0.596
statins 43 (58.1%) 31 (57.4%) 51 (58.6%) 14 (43.8%) 21 (41.2%) 0.184
Warfarin 10 (13.5%) 24 (44.4%) 4 (4.6%) 7 (21.9%) 7 (13.7%)
Clopidogrel 12 (16.2%) 4 (7.4%) 9 (10.3%) 5 (15.6%) 7 (13.7%) 0.565
dipyridamole
AsA/extended-release
AsA 25 (33.8%) 19 (35.2%) 26 (29.9%) 13 (40.6%) 17 (33.3%) 0.860
embolic etiology for stroke.
bihemispheric subcortical infarcts vessel consistent with an
RIS was on warfarin. MRI in 4 of these patients also showed
demographic differences among groups.
not included in the analysis. There were no significant
differences among patients (Table 3).

During the follow-up of patients with CS, based on
48-hour Holter monitoring, 29% patients were diagnosed
with PAF within a period of 1 year from initial evaluation.
Patients with brief <30-second nonrecurring PAF were
not included in the analysis. There were no significant
demographic differences among groups.

RIS was seen in 5 patients (10% of all CS patients). All
were associated with newly diagnosed PAF. No patient with
RIS was on warfarin. MRI in 4 of these patients also showed
bihemispheric subcortical infaracts vessel consistent with an
embolic etiology for stroke.

Table 3 Comparison of demographics, risk factors, and stroke
recurrence in patients with cryptogenic stroke with and without
paroxysmal atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>PAF present</th>
<th>PAF absent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15 (29.4%)</td>
<td>36 (70.6%)</td>
<td>0.375</td>
</tr>
<tr>
<td>Age</td>
<td>61.5 ± 16.28</td>
<td>56.7 ± 15.85</td>
<td>0.751</td>
</tr>
<tr>
<td>Gender</td>
<td>8 (53.3%)</td>
<td>14 (38.9%)</td>
<td>0.371</td>
</tr>
<tr>
<td>HTN</td>
<td>12 (90.0%)</td>
<td>12 (33.3%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (53.3%)</td>
<td>16 (44.4%)</td>
<td>0.759</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1 (6.7%)</td>
<td>2 (5.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (26.7%)</td>
<td>4 (11.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>RIS</td>
<td>5 (33.3%)</td>
<td>0</td>
<td>0.213</td>
</tr>
<tr>
<td>CAD</td>
<td>4 (26.7%)</td>
<td>4 (11.1%)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

Note: *No comparison was made for the number.

Abbreviations: CAD, coronary artery disease; HTN, hypertension; MI, myocardial
infarction; PAF, paroxysmal atrial fibrillation; RIS, recurrent ischemic stroke.

Discussion
AF and atrial flutter account for about 10% of all strokes and
50% of cardioembolic strokes.11,12 Patients with PAF have
many episodes of asymptomatic AF.13,14 Both CAF and PAF
are comparable for their risk of stroke.14,15 In patients with
CS periodic rhythm monitoring may identify new PAF in
approximately 1 in 20 patients.16

The incidence of CS in our study was 17%. Other
population-based studies have shown the incidence of CS
to be 30% to 40%5–8,17 which may be attributed to different
sampling methods.

Based on the treating physician’s perception of the stroke
subtype, patients with CS are often arbitrarily treated with
warfarin or antiplatelet agents, as in our study (warfarin 14%
and antiplatelet agents 53%).

We did not find any demographic differences between
different ischemic stroke subtypes in spite of some studies
suggesting that demographic data and risk factors may be
significantly different across subtypes.17,18 Patients who had
CS and were diagnosed with PAF had a higher incidence
of diabetes, CAD, and past history of MI than CS patients
without a diagnosis of PAF. Tayal et al also found that the
incidence of diabetes was higher in patients of CS/TIA
diagnosed with AF on mobile cardiac outpatient telemetry
(MCOT).19 However these differences, while important,
are not predictive of stroke subtype and are not helpful in
individual treatment decisions.

AF/atrial flutter is a strong risk factor for stroke and is
arguably the most important finding on cardiac work-up in
patients with stroke. Treatment with warfarin and other oral
anticoagulants provides a 44% greater relative risk reduction
in recurrent stroke compared with antiplatelet therapy.16
In spite of the importance of diagnosing PAF they are per-
haps the most under-studied mechanisms causing CS and no
definitive guidelines are yet available for the follow-up and
diagnoses of these disorders in patients with apparent CS.
With periodic 6-monthly Holter monitoring, we found PAF
in 29% of our CS cases within a year, which changed the treatment in these patients from antiplatelet drugs to warfarin. Interestingly, all 5 RIS that occurred during the follow-up period were all in patients with CS, and delayed detection of PAF.

Different short-term follow-up strategies for diagnosing underlying PAF, such as automatic cardiac event recorders, 20 7-day external loop recorders, 21 and 21-day MCOT, 19 have been studied. Barthelemy et al monitored CS and TIA patients continuously using automatic cardiac event recorders for a mean period of 70.1 ± 30.9 hours and found PAF in 4 out of 28 (14.3%) patients with CS. Approximately 33% of AF episodes were missed in spite of the currently recommended strategies for secondary prevention such oral anticoagulants in ischemic stroke patients with PAF.

In our study, RIS was seen exclusively in the CS with subsequent PAF. This underscores the importance of proper identification of stroke subtypes for initiating appropriate strategies for secondary prevention such oral anticoagulants in ischemic stroke patients with PAF.

While there may be no differentiating clinical features to distinguish CS patients who have PAF, some ECG findings seem to be more informative. Kolb et al, in a small study of 33 patients where 297 episodes of PAF were detected using 12-lead Holter monitoring, found that most of these episodes were triggered by monomorphic left atrial premature complexes. 23,24 Similar in some studies, patients with left atrial enlargement, spontaneous echo contrast were found to have a higher likelihood of PAF and cardioembolic events. 26,27 Some studies have identified patients with PAF poststroke that was short lived and associated with an intracerebral hematoma. The authors argue that these short-lived episodes of AF may be triggered by the stroke itself. However if there is no other explanation for the etiology of stroke and it happens to be ischemic, 28 PAF would still rank highly on the list as the underlying cause.

In conclusion, it seems that the present guidelines for rhythm monitoring for ischemic stroke are insufficient for detecting PAF, as shown by several studies as well as our own study. Increasing the duration of initial rhythm monitoring along with periodic rhythm monitoring (either with Holter or poststroke 30-day event monitoring) may increase the yield of PAF in CS. Based on our and other studies, to optimize detection of PAF, periodic 3- to 6-month monitoring seems reasonable, especially if there is history of intermittent palpitations, radiological evidence of bilateral infarcts, or ECG evidence of monomorphic premature atrial contractions without significant cardiac or atherosclerotic disease. A recent ongoing randomized prospective trial using standard arrhythmia monitoring versus an implantable device with a follow-up of 6 to 12 months may further enhance our knowledge of the prevalence of PAF in CS. 29

Disclosure
This study was approved by the Institutional Review Board.

The authors have no conflicts of interest to disclose.

The study was prospectively designed and data were collected from the stroke prevention clinic. The study was not supported by any funding agency or pharmaceutical company.

References

36 Therapeutics and Clinical Risk Management 2011:7

For personal use only.
Therapeutics and Clinical Risk Management 2011:7


