Paroxysmal atrial fibrillation in young cryptogenic ischemic stroke: A 3-week ECG Holter monitoring study

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Background. Atrial fibrillation is known very frequent cause of ischemic stroke. Undetected paroxysmal atrial fibrillation (PAF) is thus often considered a possible cause of cryptogenic ischemic stroke (CIS). The aim of this prospective study was to detect PAF using ECG Holter monitoring and determinate whether prolongation of the Holter monitoring to 3 weeks would increase the detection rates of PAF in young CIS patients ≤ 50 years.

Methods. The study set consisted of IS patients ≤ 50 years enrolled in the HISTORY (Heart and Ischemic StROke Relationship studY) study (NCT01541163). CIS was defined according to the TOAST criteria including the absence of ultrasonographic or angiographic signs of atherosclerosis, vasculitis or dissection. Admission ECG, serum levels of high sensitive Troponin T (hs TnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP), markers of thrombophilia, transoesophageal echocardiography (TEE) and 24-hour ECG-Holter monitoring were performed in all patients. In case of negative 24-h ECG Holter, an additional 3-weeks monitoring was done.

Results. Of the 105 enrolled patients ≤ 50 years, 95 (90%) were identified as cryptogenic (49 males, mean age 39.1 ± 8.2 years). All CIS patients had normal admission ECG. In total, PAF was detected in 9 (9.5%, 95% CI: 3.5% - 17.8%) patients; in two during 24-h ECG Holter and in seven during 3-weeks Holter monitoring. Patients with PAF had more frequently elevated admission hs TnT and NT-proBNP levels (P - 0.0001).

Conclusions. PAF was detected in 9.5% of young CIS patients and 3-weeks ECG Holter monitoring increased the detection rate.

Key words: cryptogenic ischemic stroke, paroxysmal atrial fibrillation, ECG Holter monitoring, young stroke

INTRODUCTION

The cause of ischemic stroke (IS) remains often unclear (cryptogenic) despite an extensive diagnostic panel\textsuperscript{1}. In young patients, cryptogenic ischemic stroke (CIS) represents more than one third of all ischemic strokes\textsuperscript{2-4}. Embolism due to cardiac abnormalities, particularly atrial fibrillation (AF), represents a very frequent cause of IS in these patients\textsuperscript{5-6}, therefore undetected paroxysmal AF (PAF) is often considered the cause in CIS patients\textsuperscript{7-8}. Patients with AF (including transient or paroxysmal forms) have a high risk for recurrent IS and oral anticoagulation is highly effective in secondary prevention\textsuperscript{9,10}. Thus, a diagnostic effort should be made to detect PAF in patients with IS. A standard ECG has a limited ability to detect PAF, while a continuous ECG Holter monitoring may increase \textsuperscript{7,8,11,12}.

The frequency of AF in young IS patients has not been studied in depth, however undetected AF is considered a cause of IS. A few previous studies have shown the presence of AF in approx. 3.4% of young IS patients up to 50 years at the time of hospitalization\textsuperscript{14,15}. In spite of the greater rate of detected AF using a 24-h ECG Holter monitoring\textsuperscript{16}, the presence of AF in young patients may be underestimated due to insufficient detection of PAF.

The aim of this prospective study was to report detection rates of PAF using an ECG-Holter monitoring in young CIS patients ≤ 50 years and determine whether prolongation of continuous monitoring (up to 3 weeks) would increase the detection rates of PAF. We assumed our findings might contribute to discussion about an optimal duration of ECG-Holter monitoring for PAF detection in young CIS patients.

MATERIALS AND METHODS

Patients

The study set consisted of consecutive acute IS patients ≤ 50 years, who were enrolled in the prospective single-center observational HISTORY (Heart and Ischemic StROke Relationship studY) study registered on ClinicalTrials.gov (identifier NCT01541163) between years 2011 and 2014 (ref.\textsuperscript{15}). In all patients, brain ischemia was confirmed on
20 rolled in the HISTORY study and 105 (16%) of them
medians, and interquartile ranges. All tests used an α-level
non-normal distributions are presented a means ± SD,
checked using the Shapiro-Wilk test. All parameters with
used for statistical analysis. Normality of distribution was
Statistical analysis
pattern more consistent with an alternative diagnosis
as at least 1 period of > 30 seconds’ duration of an abso
Loop Holter were processed in an external medical data
(Philips, Netherlands) and a 3-weeks monitoring us
24-hour monitoring was performed using a Holter
monitor Philips-Zymed DigiTrack plus/DigiTrack XT
in our study was lower than the previously reported
in elderly population
higher rates of detected PAF with a prolongation of ECG-
monitoring to the first detection of PAF was 11.5 ± 3.4 days.
patients with detected AF had elevated both cardiac mark
were ≤ 50 years (54 males, 41.2 ± 8.1 years). In this patient
two (1.9%) patients presented with AF on admission. Eight (7.6%)
other known cause of IS (3 patients had a symptomatic arterial
tissue had a severe dilatational cardiomyopathy with thrombus in the left ventricle, one patient had an artificial valve replacement with insufficient anticoagulation, two patients had a confirmed severe thrombophilia; one patient had detected resistance of ac-
the other had antiphospholipid syndrome [lupus anticoagulant]). The remaining 95 (88.7%) patients (49 males, 39.1 ± 8.2 years) were identified as
cryptogenic and comprised the study set.
In total, PAF was detected in 9 (9.5%, 95% CI: 3.5% -
17.8%) CIS patients during ECG-Holter monitoring. The
demographic and baseline characteristics of these patients
are shown in Table 1. There was no significant difference
between PAF and CIS patients in these parameters.
A 24-hour ECG-Holter was started after a median of 5.3
days (interquartile range 4.1 – 8.3 days) after admission. 3-week ECG-Holter was performed after a median of 42
days (interquartile range 25 – 96 days) after admission. No
interruptions of Holter monitoring and no significant tech-
nical difficulties occurred and patients tolerated long-term
monitoring. Paroxysmal AF was detected in two patients
during 24-h ECG-Holter and in another 7 patients during
3-week monitoring. Mean time from start of 3-week moni-
toring to the first detection of PAF was 11.5 ± 3.4 days.
Patients with detected PAF had elevated admission
serum levels of hs TnT and NT-proBNP (Table 2) sig-
nificantly more frequently than patients without detected
AF (56% vs. 2% and 56% vs. 3.5%, \( P=0.0001 \)). Two (22%)
patients with detected AF had elevated both cardiac mark-
ters. There was no difference between groups in terms of
a patent foramen ovale (PFO) with an evident right-left
shunt on TEE (Table 2).
In all patients with detected PAF, oral anticoagulant
therapy was initiated.

DISCUSSION
The results of our study showed a clear trend towards
higher rates of detected PAF with a prolongation of ECG-
Holter monitoring also in young stroke patients, while
this trend was reported previously in elderly population
only. Nevertheless, the rate of detected PAF (9.5%) in
our study was lower than the previously reported
rates achieved during 7-day Holter monitoring (12-13%)
(ref. \[7,20\]). This difference may be due the fact that our study
population was selected from patients with CIS only and
was substantially younger (≤ 50 years). Previously re-
ported age-dependent yields of screening for undetected
AF in stroke patients suggested this explanation. In the
recently reported randomized EMBRACE (Cardiac
Event Monitor Belt for Recording Atrial Fibrillation after
a Cerebral Ischemic Event) study, PAF was detected
in 16.1% of patients over 55 years with cryptogenic stroke
using a 30-day ECG-Holter monitoring. 

RESULTS
In total, 652 consecutive acute IS patients were en-
rolled in the HISTORY study and 105 (16%) of them
were excluded. The study protocol was in compliance with
the current Declaration of Helsinki and study was ap-
proved by the Ethics Committee of the hospital.

Data collection and clinical evaluation
Medical history, baseline characteristics, epidemi-
ologic data, and risk factors were recorded in all patients
at admission or during hospitalization. Stroke severity
was quantified using the National Institutes of Health
Stroke Scale (NIHSS) at admission. All patients under-
went following diagnostic work-up: 1) brain CT or MRI
on admission and 24 h later 2) serial laboratory samples,
3) admission ECG, 4) ultrasound of cervical and cerebral
arteries within first 48 h, 4) transoesophageal echocar-
diography (TEE), 5) 24-h ECG Holter monitoring.
The serial laboratory panel used contained the fol-
lowing samples: 1) standard laboratory panel, 2) basic
cogulation parameters and standard screening panel of
thrombophilia including genetic screening, 3) serum car-
diac markers ≤ 12 h after stroke onset (N-terminal pro-
brain natriuretic peptide [NT-proBNP], high sensitive
Troponin T [hs TnT]), 4) serum levels of glycosylated
hemoglobin and lipids ≤ 60 h after stroke onset. The
details and normal values of the specific methods have been
published.
CIS was defined according to the Trial of Org 10172
in Acute Stroke Treatment (TOAST) classification without
presence of any known stroke cause including any ultrasonographic or angiographic signs of atherosclerosis,
vasculitis or dissection.
All admission ECGs were evaluated by blinded
cardiologists (M.H., M.F.). All patients with CIS and
negative 24-hour ECG Holter monitoring underwent
subsequent 3-week ECG-Holter monitoring. A 24-hour monitoring was performed using a Holter
monitor Philips-Zymed DigiTrack plus/DigiTrack XT
(Philips, Netherlands) and a 3-weeks monitoring us-
ing a Holter monitor MDT Vitaphone Loop 3100 BT
(Vitaphone GmbH, Germany). All records from 3-week
Loop Holter were processed in an external medical data
transfer (MDT) center and evaluated by specially trained
and blinded cardiologists. The presence of AF was defined
as at least 1 period of ≥ 30 seconds’ duration of an abso-
lute arrhythmia without detectable P waves and without a
pattern more consistent with an alternative diagnosis.

Statistical analysis
SPSS software (version 15.0; SPSS Chicago) was
used for statistical analysis. Normality of distribution was
checked using the Shapiro-Wilk test. All parameters with
non-normal distributions are presented a means ± SD,
medians, and interquartile ranges. All tests used an α-level
of 0.05 for significance.

RESULTS
In total, 652 consecutive acute IS patients were en-
rolled in the HISTORY study and 105 (16%) of them
were ≤ 50 years (54 males, 41.2 ± 8.1 years). In this patient
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a Cerebral Ischemic Event) study, PAF was detected
in 16.1% of patients over 55 years with cryptogenic stroke
using a 30-day ECG-Holter monitoring.
Table 1. Demographic and baseline stroke characteristics of CIS patients and PAF patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CIS</th>
<th>PAF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>86</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Age (yrs), mean ± SD</td>
<td>40.3 ± 6.2</td>
<td>43.1 ± 3.2</td>
<td>0.903</td>
</tr>
<tr>
<td>Males</td>
<td>44 (51 %)</td>
<td>5 (56 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline NIHSS (Median + interquartile range)</td>
<td>9 (3-18)</td>
<td>8 (4-16)</td>
<td>0.986</td>
</tr>
<tr>
<td>Stroke in anterior circulation</td>
<td>61 (71 %)</td>
<td>6 (67 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of prior TIA/stroke</td>
<td>2 (2.3 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (8.1 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (1 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (14 %)</td>
<td>1 (11 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoking</td>
<td>21 (24 %)</td>
<td>2 (22 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2 (2 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135 ± 7</td>
<td>132 ± 9</td>
<td>1.000</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>69 ± 14</td>
<td>74 ± 11</td>
<td>0.978</td>
</tr>
<tr>
<td>IV thrombolysis</td>
<td>36 (42 %)</td>
<td>6 (67 %)</td>
<td>0.205</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td>12 (14 %)</td>
<td>1 (11 %)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

IV = intravenous, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, TIA = transient ischemic attack

Table 2. Laboratory parameters and TEE findings of CIS and PAF patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CIS patients</th>
<th>PAF patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP &gt; 125 ng/L</td>
<td>3 (3.5 %)</td>
<td>5 (56 %)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hs TnT &gt; 0.014 μg/L</td>
<td>2 (2 %)</td>
<td>5 (56 %)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Creatinine &gt; 90 μmol/L</td>
<td>2 (2 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline serum level of GLU &gt; 5.6 mmol/L</td>
<td>46 (54 %)</td>
<td>5 (56 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Glycosylated hemoglobin &gt; 40mmol/L</td>
<td>2 (2 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline serum level of CH &gt; 5.0 mmol/L</td>
<td>25 (29 %)</td>
<td>2 (22 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Left atrial diameter (mm) (mean + SD)</td>
<td>35 ± 5</td>
<td>36 ± 8</td>
<td>1.000</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55</td>
<td>60</td>
<td>0.989</td>
</tr>
<tr>
<td>PFO with significant right-left shunt</td>
<td>25 (29 %)</td>
<td>2 (22 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other defect of atrial septum</td>
<td>3 (3 %)</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

CH = cholesterol, CIS = cryptogenic ischemic stroke, GLU = glucose, Hs TnT = high sensitive Troponin T, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAF paroxysmal atrial fibrillation, PFO = patent foramen ovale, SD = standard deviation, TEE = transoesophageal echocardiography

In young IS patients < 50 years, previous studies showed a frequency of AF up to 5% (ref.2,3,20,22). The use of a 24-h ECG Holter and a prolonged ECG Holter monitoring (up to 7 days) did not increase this low frequency in these patients2,20,24,25. In our study, the prolongation of Holter monitoring up to 3 weeks increased substantially the detection rate of PAF with the mean time of 11.5 ± 3.4 days from the start of monitoring to the first detection of PAF.

In our study, the loop recorder was used for the detection of PAF. This type of recorder detects arrhythmias triggered by a patient only. Thus the detection rate may be limited in case of an asymptomatic episode of AF. Continuous telemetric or implantable monitors may provide a more accurate PAF detection. These devices are able to record user-defined, automatic and patient-activated episodes of AF or other arrhythmias26. However, in the recently published randomized CRYSTAL AF (Cryptogenic Stroke and Underlying AF) study, the rate of detected PAF did not exceed 10% during a 6-month period of continuous monitoring27.

Paroxysmal AF represents the same risk for a recurrent IS as a permanent form of AF (ref.28). Moreover, the frequency of episodes of PAF increases over time and AF may become persistent29. The duration of AF is considered necessary for thrombus formation, however the TEE-based studies showed that short intervals of AF may also generate a thrombus30,31. Although PAF has been defined as an episode of AF in duration > 30 s (ref.17,18), we assume that shorter periods of AF (< 30 s) may be also relevant for detection of PAF. We agree with the suggestion that very short AF episodes may be associated
with longer undetected AF episodes of sufficient duration, which result in thrombus formation and subsequent embolization. The presence of PFO with evident right-left shunt on TEE was registered only in one patient with detected PAF. Regarding the fact that the thrombus formation due to AF occurs in the left atrium and ventricle primarily, we suggest there is no relevance of PFO in CIS patients with detected PAF. Moreover, the relevance of PFO as a risk factor for IS has been still discussed. Although PFO is more prevalent in IS patients, recently published results from the PC Trial showed no significant benefit of the PFO closure for patients with CIS (ref. 31). Similarly, results from the RESPECT trial were negative in the primary intention-to-treat analysis. However, the additional results from the per-protocol analysis suggested a certain benefit of closure. The elevation of serum hs TnT and NT-proBNP in our PAF patients may correspond to the reported findings that elevation of hs TnT is associated with AF and that NT-proBNP was found to be a robust predictor of AF, especially in younger patients. Thus, we suggest the serum elevation of hs TnT and NT-proBNP might help to better identify IS patients with undetected PAF, in whom a diagnostic effort with a sufficient length of ECG-Holter monitoring is needed for detection of PAF.

The study has limitations. A single center study design with a small sample size was used. Nevertheless, the incidence of IS in young patients is generally low and most previously reported studies with young CIS patients < 50 years had similar sample sizes. The interval from stroke onset to start of 24-h and 3-week ECG Holter was relatively longer. For a 3-week monitoring, the loop recorder with a limited ability to record arrhythmias was used. Thus we cannot exclude the possibility of a higher detection rate if continuous telemetry or implantable recorders were used.

In conclusion, AF (including its transient or paroxysmal forms) is more prevalent in IS patients, recently published results from the EMBRACE Investigators and Coordinators. Atrial Fibrillation in young adults: classification and risk factors. J Neurol 2012;259:653-9.

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