

Usefulness of Ambulatory 7-Day ECG Monitoring for the Detection of Atrial Fibrillation and Flutter After Acute Stroke and Transient Ischemic Attack

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Background and Purpose—Although atrial fibrillation is the most frequent cause of cardioembolic stroke, this arrhythmia remains underdiagnosed, as it is often asymptomatic or intermittent and, thus, may not be detected on standard 12-lead ECG or even 24-hour ECG recording (Holter). In this study, we hypothesized that 7-day ambulatory ECG monitoring using an event-loop recording (ELR) device would detect otherwise occult episodes atrial fibrillation and flutter (AF) after acute stroke or transient ischemic attack (TIA).

Methods—One hundred forty-nine consecutive patients admitted to our neurology department with an acute stroke or TIA were systematically screened for emboligenic arrhythmias using standard ECG. In the absence of AF on standard ECG, patients underwent 24-hour ECG recording (Holter), which was followed by a 7-day ambulatory ECG monitoring (ELR) in patients with a normal Holter. Patients with previously documented persistent AF, with primary hemorrhagic stroke, or with acute large vessel dissection were not included in the study.

Results—AF was detected in 22 patients. Standard ECG identified AF in 2.7% of the cases at admission (4/149 patients) and in 4.1% of remaining patients within 5 days (6/145). Holter disclosed AF in 5% of patients with a normal standard ECG (7/139 patients), whereas ELR detected AF in 5.7% of patients with a normal standard ECG and normal Holter (5/88 patients).

Conclusions—Following acute stroke or TIA, ELR identified patients with AF, which remained undetected with standard ECG and with Holter. ELR should, therefore, be considered in every patient in whom a cardioembolic mechanism is suspected. (*Stroke*. 2004;35:1647-1651.)

Key Words: atrial fibrillation ■ diagnostic tests ■ electrocardiography
■ prevention and control ■ stroke, cardioembolic

Atrial fibrillation and flutter (AF) account for $\approx 10\%$ of all strokes and 50% of cardioembolic strokes.¹ Stroke associated with AF carries a poor prognosis as more than 50% of the survivors remain with a severe deficit, and recurrence may be as high as 12% per year.² Because anticoagulant treatment dramatically reduces the recurrence rate, detection of this arrhythmia after stroke is essential.³ Unfortunately, AF remains underdiagnosed as it is often asymptomatic: up to 30% of patients with AF are unaware of their diagnosis,⁴ and 25% of those with AF-associated stroke have no prior diagnosis of AF.^{5,6} Moreover, the fibrillation pattern is intermittent in 30% of patients with stroke and may not appear on a single recording.⁵⁻⁷

Because of the rather poor sensitivity of single standard ECG for paroxysmal AF, 24-hour ECG recording (Holter) is often used, allowing the detection of previously unrecognized AF in $\approx 2\%$ of stroke patients.⁸⁻¹⁰ Further extending the ECG

recording time from 24 to 72 hours increases the prevalence of paroxysmal AF after stroke from 1.2% to 6.1%, suggesting that the probability of detecting AF increases with the duration of the heart rhythm monitoring.¹¹⁻¹³

An event-loop recording (ELR) device is designed to monitor the heart rhythm for 1 week or longer in an ambulatory patient (Figure 1b). This 2-lead device performs an event-triggered (eg, onset of AF) or patient-triggered (eg, onset of palpitations) sampling of the ECG during the period of use, with a total storage capacity of ≈ 20 minutes.¹³⁻¹⁵ This tool is, thus, well suited to capture paroxysmal events such as intermittent AF.

In this study, we examined whether 7-day ambulatory ECG monitoring (ELR) allows further detection of AF in patients admitted with an acute stroke or transient ischemic attack (TIA) in whom standard ECG and Holter produce normal results.

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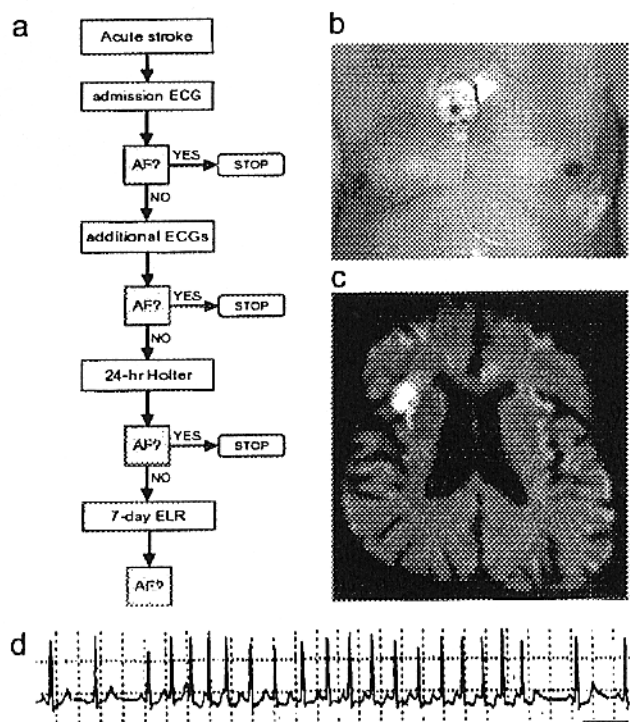


Figure 1. Study design and sample case. a, Study flowchart. Cerebral CT scan and MRI, extracranial carotid duplex ultrasonography, transcranial Doppler, transcranial Doppler with right-to-left shunt detection, transthoracic echocardiography, transoesophageal echocardiography, standard laboratory tests, and advanced coagulation tests were also performed. ECG refers to standard 12-lead ECG. See Patients and Methods section for details. b, ELR device, in front, with second recording lead on the side (first lead is built into the recording case). c, Diffusion-weighted MRI showing an acute right insular cortical infarct. This patient presented with vertigo. d, Sample ELR recording in the same patient showing paroxysmal AF rhythm. 12-lead ECG and Holter were normal. This patient had several other AF paroxysms lasting up to 30 hours. Scale bar indicates 80 ms.

Patients and Methods

We enrolled 169 consecutive patients admitted between February and December 2002 with a suspicion of acute stroke or TIA to the Neurology Department of the University Hospital, Geneva, Switzerland, a primary care center. The consent forms and the protocol were approved by the local ethics committee. Patients with previously documented persistent AF, with recent (<12 months) AF paroxysm, with primarily hemorrhagic stroke, or with acute large vessel dissection were not included in the study. Twenty patients, for whom the initial suspicion of stroke was not confirmed and an alternative diagnosis established, were retrospectively excluded, leaving 149 patients in the study cohort. Study design is summarized in Figure 1a.

All patients were assessed by use of a structured questionnaire regarding main risk factors and medical history and had a neurological examination, extracranial carotid duplex ultrasonography, and standard laboratory tests. Cerebral CT scan was performed on admission in all but 11 patients who directly had cerebral MRI. MRI was performed in all patients within 10 days of admission except for 5 patients (3 because of refusal and 2 because of agitation). In addition, transcranial Doppler (n=138, 92.6%), transcranial Doppler with right-to-left shunt detection (n=62, 41.6%), transthoracic echocardiography (n=86, 59.7%; 21/22 for patients with AF), transoesophageal echocardiography (n=14, 9.4%; 2/22 for patients with AF), and coagulation tests (n=54, 36.2%) were also performed when indicated.

Clinical Data and Analysis

Clinical findings were described using the Oxfordshire Community Stroke Project Classification,¹⁶ and stroke severity was rated using the National Institutes of Health (NIH) Stroke Scale,¹⁷ with scores <5 defined as corresponding to a light deficit. Stroke etiology was rated independently by D.J. and R.S. ($\kappa=0.87$) using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification¹⁸ as follows: cardioembolic (29.5%, n=44), lacunar (26.2%, n=39), large vessel pathology (20.1%, n=30), and undetermined origin (24.2%, n=36). TIA was defined as a neurological deficit lasting less than 24 hours with no acute lesion visible on diffusion-weighted MRI.

Electrocardiographic Studies

All patients had a standard 12-lead ECG at admission. In the absence of AF on the initial ECG, heart rate was measured hourly for 24 hours in patients with TIA (n=60, 40.3%) and for 48 hours in those with suspected stroke (n=89, 59.7%). Additional ECGs (1 additional ECG in 40 patients [27.4%], 2 additional ECG in 12 patients [8.2%]) were performed when an arrhythmia was suspected on clinical grounds. A 24-hour 3-channel ECG recording (Holter) (Avia, Del Mar Reynolds Medical Systems) was performed in all patients without evidence for AF after these examinations. An ambulatory ELR (R-test Evolution II, Novacor) was scheduled in patients without evidence for AF after Holter. This device has a total recording time of ≈ 20 minutes. The ELR was programmed to store irregular RR-interval strips that could correspond to AF paroxysms. Parameters for event-triggered recording were as follows: 50 s for absolute pauses (RR interval >2.5 s); 175 s for relative pauses (RR interval >150% previous RR interval); 500 s for premature beats (RR interval <[mean RR - 12.5% \times mean RR]); 60 s for bradycardia (R frequency <50 minutes⁻¹); 250 s for runs (RR interval <[RR - 12.5% \times RR] for >3 beats); and 30 s for ST shift (<1 mm or >3 mm). 120 s were devoted to patient-triggered recording. AF was identified by manual reviewing of the ECG recordings. Heart rate was stored throughout the whole period of use and variations in heart frequency were, therefore, recorded continuously.

Statistical Analysis

We used 2-tailed *t* tests for comparisons of means and Fisher 2-tailed exact test for comparisons of proportions. Ninety-five percent CIs were calculated using the modified Wald method. Cumulative AF risk was calculated by Kaplan-Meier analysis using the GraphPad Prism software (GraphPad Software Inc).

Results

The baseline characteristics of the 149 patients with acute stroke or TIA are summarized in Table 1. We found 22 cases of AF among the 149 patients. Patients with AF were significantly older and more often had a remote (>12 months) history of paroxysmal AF (Table 1). Twenty-two patients (3 in the AF group and 19 in the non-AF group, $P=1$) were taking an antiarrhythmic drug, including amiodarone (2 patients), β -blockers (22 patients), and digoxine (1 patient). Indication for use of an antiarrhythmic drug was mainly high blood pressure. In 2 cases, it was used for paroxysmal AF (1 in the AF group and 1 in the non-AF group). Although the proportion of patients with TIA was similar in both groups, acute lesion on admission CT and total anterior stroke syndromes were more frequent in patients with AF, whereas none presented with a lacunar syndrome. Left atrial dilatation was more frequent in patients with AF (Table 1). Enlargement was slight (42 to 48 mm) in 5/9 cases, moderate (48 to 52 mm) in 3/9 cases, and severe (>52 mm) in one case. In patients with left atrial enlargement but no AF, enlargement was slight in all cases (n=7). Finally, palpitations in the acute phase or history of palpitations or both were not associated with a greater risk of having AF.

TABLE 1. Patient Characteristics

	Non-AF n=127	AF n=22	P
Sex ratio (M/F)	86/41	15/7	NS
Mean age, y (age range)	66 (37–93)	72 (56–91)	0.02
Hypertension	76 (60%)	11 (50%)	NS
Hypercholesterolemia	74 (58%)	9 (41%)	NS
Smoking	47 (37%)	5 (23%)	NS
Diabetes	22 (17%)	3 (14%)	NS
Acute palpitations	8 (6%)	1 (5%)	NS
History of palpitations	11 (9%)	5 (23%)	NS
History of paroxysmal AF	3 (2%)	4 (19%)	0.01
Previous stroke	20 (16%)	5 (23%)	NS
Positive HHD	19 (13%)	6 (27%)	NS
Positive FHS HD	12 (8%)	1 (5%)	NS
TIA	51 (40%)	9 (41%)	NS
NIHSS \leq 5	19 (15%)	6 (27%)	NS
PACS	56 (44%)	12 (45%)	NS
TACS	7 (6%)	5 (23%)	0.02
LACS	32 (25%)	0 (0%)	0.005
POCS	32 (25%)	5 (23%)	NS
Left atrial dilatation* (n=86)	7 (11%)	9 (43%)	0.02
Acute lesion on CT (n=156)	16 (13%)	7 (33%)	0.05
Acute lesion on MRI (n=144)	68 (55%)	15 (75%)	NS

*Defined as a left atrium >42 mm on transthoracic echocardiography.

AF indicates atrial fibrillation or flutter; HHD, history of heart disease; FHS HD, family history of stroke or heart disease; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; LACS, lacunar stroke; POCS, posterior circulation stroke; CT, head computerized tomography; MRI, head magnetic resonance imaging.

Standard ECG Recording

Four cases of AF were identified on the initial standard ECG (4/149 patients, 2.7%; 95% CI, 0.8 to 6.1), whereas 6 other cases were identified on standard ECG performed within 5 days of admission (6/145 patients, 4.1%; 95% CI, 1.7 to 8.9) (Tables 2 and 3). Two of the latter cases were detected on the first day, 1 on day 3, 2 on day 4, and 1 on day 5.

24-Hour ECG Recording (Holter)

Seven cases of AF were detected among the 139 patients who underwent Holter recording (5.0%; 95% CI, 2.3 to 10.2) (Tables 2 and 3). The median delay before Holter recording was 8 days (range 1 to 29 days), and the heart rate was recorded on average for 21 hours (range 6.1 to 25.5). AF was persistent in 3 patients and paroxysmal in 4. In the latter cases, 2 patients had 1 single episode of AF of \approx 10 hours duration, and 2 patients had several^{2–5} shorter episodes lasting several seconds to several minutes. Five patients (3.6%) reported symptoms during the recording period (eg, dizziness, palpitation), but in only 1 patient did the presence of symptoms correspond to the onset of AF (Table 2).

7-Day Ambulatory ECG Monitoring (ELR)

Ambulatory ELR was scheduled for the 132 patients without evidence of AF after Holter. Among this cohort, 10 patients were lost for follow-up, 1 patient died before the test was performed, and 1 patient could not have the test for technical reasons. Eighty-eight patients had this investigation, whereas 32 patients (26.7%) refused the test, yielding a compliance of 73.3% (95% CI, 64.8 to 80.5). Importantly, patients who had ELR did not differ significantly from the rest of the population as for clinical, paraclinical, or epidemiological characteristics. The median time interval between admission and ELR was 55 days.

Five cases of AF were detected among the 88 patients (5.7%; 95% CI, 2.1 to 12.9) (Tables 2 and 3; Figure 1c), for an average monitoring time of 159 hours (range 35 to 191) (Table 2). In 4 cases, the arrhythmia was intermittent, beginning 5.5 (patient illustrated in Figure 1c and 1d), 17, and 28 hours after the onset of the monitoring, whereas in 1 patient, AF was present during the whole recording (Table 2). The duration and number of the AF paroxysms was inferred from the duration of tachyarrhythmic episodes on the continuous heart rate recording (see Patients and Methods); in the 4 patients with a paroxysmal AF pattern, at least 1 to 4 episodes were recorded, each lasting from a few tenths of seconds to several hours, with a median duration of 1.5 hours (Figure 1d). As was the case for Holter, symptoms (17 patients, 19.3%) or patient-triggered recording (22 patients, 25.0%)

TABLE 2. Electrocardiographic Investigations

	Admission ECG n=149	Additional ECGs n=52	24-hr Holter n=139	7d-ELR n=88
Mean monitoring time	20 s	22 s	21 hr	159 hr
Median delay (d)	0	1	8	55
Sinus rhythm	145 (97.3%)	46 (88.5%)	132 (95.1%)	83 (94.3%)
Sinus rhythm + atrial flutter	0	0	1 (0.7%)	1 (1.2%)
Sinus rhythm + atrial fibrillation	0	0	3 (2.1%)	3 (2.3%)
Atrial flutter	0	0	1 (0.7%)	1 (1.2%)
Atrial fibrillation	4 (2.7%)	6 (11.5%)	2 (1.4%)	0
Complaints	NA	NA	5 (3.6%)	19 (21.6%)
Patient-triggered recording	NA	NA	NA	22 (25.0%)

ECG, standard 12-lead electrocardiogram; ELR, event-loop recording; NA, not applicable.

TABLE 3. Tests Comparison

	Standard ECG	24-hr Holter*	7d-ELR†
% AF positive (95% CI)	6.7 (3.6–12.1)	5.0 (2.3–10.2)	5.7 (2.1–12.9)
NNS (95% CI)	15 (9–28)	20 (10–44)	18 (8–48)
% total AF cases	45.5	31.8	22.7
Cumulative AF risk, % (95% CI)	6.7 (3.6–12.1)	10.6 (5.6–14.6)	16.4 (8.7–20.1)
Monitoring time needed to detect 1 event‡	6.9 minutes	18 days	117 days

*With normal standard ECG.

†With normal standard ECG and 24-hr Holter.

‡(Monitoring time per patient × n monitored patients)/(n recordings with AF). ELR indicates event-loop recording; NNS, number needed to screen.

were not usually associated with electrocardiographic abnormalities.

Discussion

In the present study, AF was detected in 22 of 149 patients with acute stroke or TIA, accounting for 50% (22/44) of all cardioembolic strokes. Standard ECG identified this arrhythmia in 6.7% of the patients, in about half of the cases at admission (5/11 patients), and in the remaining cases within the first 5 days. Holter disclosed AF in an additional 5% of the patients presenting a normal standard ECG. Finally, ELR allowed further detection of this arrhythmia in 5.7% of the patients, thus identifying AF in 1 of 18 patients having a normal standard ECG and Holter (Table 3). The calculated risk of AF in this study was 16.9% (Table 3, Figure 2), with about one third of the cases (8/22 patients, 36.3%) showing a paroxysmic dysrhythmic pattern, in agreement to what is usually reported.^{5–7,19}

Several factors were significantly associated with an increased risk of AF detection, namely older age, left atrial dilatation, and history of paroxysmal AF, as previously described.² Among the 7 patients with a remote history of paroxysmal AF, 4 cases of AF were documented during the

study period. One case of AF was detected on 12-lead ECG and 3 cases were detected with Holter. No case was identified using ELR. Acute lesions were more frequently detected on brain CT in these AF patients (Table 1, Figure 1c), probably in relation to the larger size of infarcts of cardioembolic origin.²⁰ Larger infarct size in the AF population is also reflected by a higher prevalence of total anterior stroke syndromes (Table 1) and a higher proportion of patients with a severe neurological deficit (NIH stroke scale ≥ 10 ; n=4 without AF [3.1%], n=5 with AF [22.7%], $P=0.003$).^{21,22}

Our data, thus, demonstrate that ELR allows identification of AF in cases that remain undetected using other ECG recording techniques. Among the 22 patients with AF, 8 had no sign of heart disease on transthoracic echocardiography (8/21 tested patients, 38.1%). Three of these patients were younger than 65 years old and had neither hypertension nor diabetes, thereby satisfying criteria for "lone AF."¹⁹ Four fifths of patients with ELR-detected AF had a normal transthoracic echocardiography, 1 of which had "lone AF."

The decision for anticoagulation treatment after discovery of AF was taken according to our local guidelines.²³ Oral anticoagulation was introduced in all ELR-detected cases; in 2 patients, diagnosis after Holter was "stroke of undetermined origin" and identification of the arrhythmia justified preventive anticoagulation. Stroke etiology in 2 other cases was classified as likely cardioembolic, but without sufficient arguments for anticoagulation. In the fourth case, discovery of AF avoided endovascular closure of a foramen ovale. A follow-up study performed 13 months after introduction of oral anticoagulation revealed that persistent or paroxysmal AF was still present in 2/5 of these patients (40%) even after pharmacological cardioversion and chronic amiodarone treatment versus 56% for patients with AF who were diagnosed with ECG or Holter ($P>0.05$). The natural history of cases detected with ELR, therefore, does not differ from the AF population of this or other^{23,24} studies.

As the number needed to screen (NNS) values for Holter and ELR are comparable (18 versus 20), one may be tempted to replace Holter by ELR and use the latter as the first choice for investigation after standard ECG. In our opinion, however, a stepwise sequential workup should be preferred. Indeed, the sensitivity of these 2 techniques has not been compared. ELR would, therefore, not necessarily identify all cases detected by Holter, as suggested by a recent study where 2/6 patients with Holter-documented AF had a normal

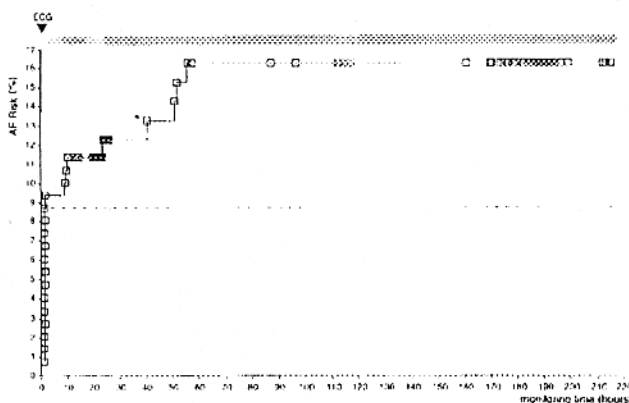


Figure 2. Risk of atrial fibrillation for various ECG monitoring times. Cumulative monitoring times for each patient (open squares) are reported on the x axis, whereas risk of AF in the cohort at this time point, as calculated by Kaplan-Meier analysis, is reported on the y axis. Risk of AF after ECG alone is 6.7%, after ECG + Holter, 10.6%; after ECG + Holter + ELR, 16.7% (see Table 3). The asterisk-tagged open square corresponds to the data from the patient illustrated in Figure 1. Dashed line indicates the lower limit of the 95% CI of AF risk at longest monitoring time.

4-day ELR.²⁵ Furthermore, within 7 days of admission (ie, within a delay shorter than the mean ELR monitoring time), Holter was able to detect 22% of the AF cases that were not disclosed by standard ECG, allowing rapid introduction of appropriate treatment. Starting the workup with a time-consuming examination such as ELR would have postponed the detection of these early cases. In addition, patients with TIA, having no residual deficit, may be reluctant to wear the ELR device for 7 days, whereas outpatient appointments may be difficult to organize for severely impaired patients, as illustrated by the 73% compliance rate for ELR.

The ideal timing and duration of ELR are so far not determined. Although a prolonged delay between admission and the ambulatory investigation may render the causal link between arrhythmia and stroke debatable, the detection of AF in some of our patients several weeks after the acute event still prompted us to introduce an anticoagulant treatment, considering the likelihood of a stroke of cardioembolic origin. Early cases, on the other hand, are probably more readily detected by standard ECG or Holter. Although AF may occasionally be a consequence rather than a cause of stroke,^{7,23,26} in this study the median delay between stroke and AF detection with ELR was 55 days. Given this time span, it seems unlikely that the arrhythmia was secondary to the cerebrovascular event.

In conclusion, we have shown that 7-day ambulatory ECG monitoring is useful and detects AF in 5.7% of patients with normal standard ECG and 24-hour ECG recording (Holter). This finding modified the therapeutic options in all cases. By improving detection of AF after acute stroke or TIA, ELR allows introduction of the most appropriate treatment, which should result in better secondary prevention.

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