Telemonitoring Boosts Atrial Fibrillation Detection in Cryptogenic Stroke Patients – Preliminary Findings

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Authors' contributions

All authors took participation in the design of the study. Authors IS and HM wrote the protocol. Data management was performed by the authors IS, HM, TK and LH. Authors IS, HM and ND managed the analyses of the study. Author IS performed the statistical analysis. Author IS wrote the first draft of the manuscript. Authors IS and HM managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Approximately 25% of strokes are cryptogenic in origin and identifying atrial fibrillation (AF) as an etiologic factor in this situation has major therapeutic implication. Standard Holter ECG has a low sensitivity for AF detection in this patient group.
Aim: To assess the diagnostic yield of prolonged ambulatory noninvasive ECG telemonitoring for AF detection in cryptogenic stroke or transitory ischemic attack (TIA) patients.
Methods and Results: We prospectively included 36 patients (mean age 53 ± 15 years, 17% women) with cryptogenic stroke or TIA in the previous 3 months and without previously documented episodes of AF. We employed a validated ECG telemonitoring system (TEMEO). The median monitoring period was 22 days, ranging from 13 to 36 days. AF was detected in 10 patients (27%): in 7 patients (70%) AF episodes lasted <30 sec and in the other 3 episodes of absolute arrhythmia were longer. AF runs were

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asymptomatic in 6 of the patients with arrhythmia detection (60%). The mean time from initiation of telemonitoring to AF detection was 10 days, ranging from 2 to 29 days. Anticoagulation therapy for secondary prevention of stroke and systemic embolism was initiated in all of the patients with AF detected during telemonitoring.

Conclusion: ECG telemonitoring after cryptogenic stroke or TIA results in AF detection in at least one in every four patients. Considering the important therapeutic implication of this finding we believe that prolonged ECG monitoring should become the standard of care in this patient group.

1. INTRODUCTION

Stroke still represents a major health problem and its prevalence and incidence are estimated to increase [1]. The Framingham Study showed that 1 in 5 women and 1 in 6 men aged 55 to 75 years will experience stroke sometime during their life [2].

In-hospital mortality rate on cardio-embolic stroke remains around 20% and it's the subtype of ischemic infarct with the highest in-hospital mortality. The short-term prognosis of patients with cardio-embolic stroke is poor in comparison with other ischemic stroke subtypes [3].

Approximately one of four strokes is considered cryptogenic. In these cases identifying atrial fibrillation (AF) as a main pathogenic factor in the embologenic etiology is a key priority in secondary stroke prevention because of important treatment implications [4, 5]. Introducing anticoagulation therapy with vitamin K antagonists results in a relative stroke risk reduction of 64% and all-cause mortality is also significantly reduced by 26% versus control, according to the results of a meta-analysis [6]. Novel oral anticoagulants show even better results for stroke prevention in patients with non-valvular AF compared to vitamin K antagonists [7-9].

AF is the most common form of sustained cardiac arrhythmia [10]. This rhythm disorder is associated with a five-fold increase of the risk of stroke and significantly higher mortality [11, 12]. AF-related strokes on the other hand carry a greater risk of disability and increased mortality compared with strokes of other etiologies [13].

Currently standard evaluation includes repeat Holter monitoring which, however, has low sensitivity for AF detection - about 5% [14-17]. AF could be even more difficult to detect if it is paroxysmal or asymptomatic.

Mobile cardiac outpatient telemetry systems provide home-based, real-time monitoring of symptomatic and asymptomatic arrhythmias. They represent a relatively new method for prolonged noninvasive and ambulatory patient monitoring and show promise in detection and diagnosis of rhythm disorders with sporadic and rare occurrence (e.g. paroxysmal AF).

Our hypothesis is that AF may be systematically underdiagnosed in patients with unexplained strokes and transitory ischemic attacks (TIA) employing standard diagnostic methods and that this problem could be overcome with the use of longer-term telemonitoring.

2. MATERIALS AND METHODS

2.1 Study Group

This was a prospective study of ambulatory patients. We screened patients with stroke or TIA, hospitalized in Clinic of Neurology in our institution and those of them who were deemed eligible (see below) entered a telemonitoring period after dehospitalization.

2.2 Inclusion / Exclusion Criteria

Patients could be included if they were ≥ 18 years of age and had an ischemic stroke (CT/MRI verified) or transitory ischemic attack (symptoms for less than 24 hours and no CT/MRI data for ischemic lesion) in the last 3 months before inclusion. Eligible patients should not be significantly disabled or dependent for their daily activities - modified Rankin score ≤ 3.

Exclusion criteria were significantly shortened life expectancy, permanent pacemaker, anatomical deformities precluding TEMEO installation, presence of absolute contraindications for antithrombotic prophylaxis, history of hemorrhagic stroke.

Documented episode of AF was an exclusion criterion. Some of the patients, however (see results), had a history of undocumented arrhythmia.

We have not included patients with positive findings for potential atheroembolic sources, such as aortic atheromatosis or carotid artery pathology. Presence of patent foramen ovale or aneurismal atrial septum deformation was an also exclusion criterion. Patients with diagnosed prothrombotic state (antiphosphoplipid syndrome, protein C or S deficiency, factor V Leiden, homocystinemy etc) were not included.

2.3 Calculation of Thromboembolic Risk

For the calculation of thromboembolic risk we used CHA_2DS_2-VASc score as recommended in current guidelines [11,12]: Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65–74, and Sex category (female).

2.4 Neurologic Assessment

Stroke-related neurologic deficit was assessed using National Institutes of Health Stroke Scale (NIHSS) - http://www.nihstrokescale.org/. It is applied in the acute stroke phase and represents a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extra ocular movement, motor strength, ataxia, dysarthria, and sensory loss.

2.5 Echocardiography

Standard transthoracic echocardiography was performed on the day of telemonitoring initiation in a left lateral position with scanners GE Vivid 9 and Aloka Prosound SDD- α 10. The following echocardiographic parameters were included in our analysis: left artial volume index (LAVI) (ml/m2) by two-plane area-length method in a four-chamber and two-chamber

apical views obtained just before mitral valve opening, ejection fraction (EF) (%) by biplane Simpson's method, mitral valve anatomy assessment and determination of regurgitation degree (if present), interatrial septum interrogation for PFO or septal aneurism, assessment of ascendic aorta and aortic arch from left and right parasternal views and suprasternal view for aortic atheromatosis and evaluation of carotid arteries bilaterally for the presence of atherosclerotic plaques or stenoses.

2.6 Telemonitoring

Telemonitoring was performed with TEMEO system, validated versus standard ECG and Holter ECG [18]. The design and mode of operation has been previously described [19]. Briefly: TEMEO is an ambulatory patient telemonitoring system, which consists of two components - a mobile handheld device for recording and transmitting data and an elastic belt, placed on the chest, for registering precordial electrical activity of the heart and detecting R-R intervals. Data from the belt is transmitted wirelessly to the mobile device. The handheld device is used also to record demand ECGs (single-channel ECG) which is easily achieved by the patient: placing the device to his / her chest and pressing a button.

By GSM network, within 5-minute intervals, recorded data is transmitted to the TEMEO electronic center for further analysis and visualization. Acquired ECG data is transfered immediately to the TEMEO center.

The mobile device has also an accelerometer for detection of physical activity (and therefore has the ability to differentiate between resting condition and physical exertion) simultaneously with R-R interval detection.

TEMEO electronic center consists of a server with developed software for automatic RR interval analysis [20, 21] – for rhythm detection (including atrial fibrillation), heart rate and premature beats. The algorhythms and software have been validated during development and afterwards on MIT ECG database. The electronic center is accessible via Internet, from any PC or smartphone with security access to the system. The telemonitoring system has the possibility to alert via SMS the monitoring doctor and the patient in case of significant deviation from normal values (e.g. heart rate less than 40 beats per minute, AF episode, etc).

2.7 Ethics

All patients signed an informed consent. The study is in accordance with the Declaration of Helsinki.

2.8 Statistics

We tested the distribution of continuous variables using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed data – as median and interquartile range (IQR) (the difference between the 25th and 75th percentile). Categorical variables were presented in percentage terms. Clinical variables between the two studied groups (with or without AF) were compared using an independent samples t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables, presented in percentage terms, were compared with Chi square test. Statistical analysis was performed using SPSS statistical software for Windows version 13.0.

3. RESULTS AND DISCUSSION

3.1 Results

We have evaluated 36 patients, 6 of them (17%) were women, and mean age in our group was 53 ± 15 years. Risk factor distribution, past medical history and baseline therapy are presented in Table 1.

Table 1. Baseline characteristics of the study group

Parameter	Whole group	AF pts	No AF pts	p
Arterial hypertension - number (%)	24 (67%)	14 (54%)	10 (100%)	0.008
Dyslipidemy - number (%)	24 (67%)	16 (62%)	8 (80%)	ns
Diabetes mellitus - number (%)	10 (28%)	6 (23%)	4 (40%)	ns
Smokers - number (%)	22 (61%)	16 (62%)	6 (60%)	ns
Body mass index - median (25th - 75th percentile)	24.7 (20.5-28.9)	24.7 (22.6-26.5)	25.5 (22.6-26.6)	ns
Coronary artery disease - number (%)	7 (19%)	2 (8%)	5 (50%)	0.002
History of arrhythmia - number (%)	14 (39%)	8 (31%)	6 (60%)	ns
Heart failure - number (%)	2 (6%)	0	2 (20%)	ns
Acetylsalicylic acid - number (%)	15 (42%)	9 (35%)	6 (60%)	ns
Beta blockers - number (%)	10 (28%)	2 (8%)	8 (80%)	<0.001
ACE inhibitors - number (%)	15 (42%)	9 (35%)	6 (60%)	ns
Angiotensin receptor blockers - number (%)	0			
Calcium channel blockers - number (%)	6 (17%)	6 (23%)	0	ns
Statins - number (%)	4 (11%)	2 (8%)	2 (20%)	ns
Clopidogrel - number (%)	16 (44%)	10 (38%)	6 (60%)	ns

Also in table 1 could be seen how the patients with and without AF during telemontoring differ in terms of their baseline characteristics – AF patients have more often arterial hypertension, coronary artery disease and were more likely to take beta-blockers.

Mean CHA_2DS_2-VASc score in our group was 3.44 ± 1.08. The distribution of patients according to their thromboembolic risk (CHA_2DS_2-VASc score) is presented in Table 2.

Table 2. Thromboembolic risk (CHA2DS2-VASc score)

CHA_2DS_2-Vasc score	Number (%)
2	5 (14%)
3	22 (61%)
4	2 (6%)
5	5 (14%)
6	2 (6%)

Echocardiographic findings showed that mean ejection fraction in our group was 59.8 ± 9.5%. Six of the patients (17%) had an ejection fraction <50%. Mean indexed left atrial volume was 29.5 ± 18.6 ml/m^2 and six patients (17%) had marked left atrial enlargement,

defined as left atrial volume index >34 ml/m^2. Mitral regurgitation was present in 7 patients (19%), mild in 5 of them (14%) and moderate degree in 2 patients (6%).

No one of the patients had aortic atheromatosis or carotid artery pathology.All patients were in sinus rhythm at the moment of their baseline ECG registration. Mean NIH Stroke scale was 5.3 ± 2.4.

Telemonitoring was performed for a median time of 22 days, ranging from 13 to 36 days. During this time period we detected AF episodes lasting up to 30 sec in 7 patients of the study group (19%). Longer AF episodes were present in 3 other patients (8%) – Fig. 1. Combining all AF episodes registered during telemonitoring, more than one fourth (27%) of our group of cryptogenic stroke patients turned out to suffer from this rhythm disorder. The mean time from initiation of telemonitoring to AF detection was 10 days, ranging from 2 to 29 days.
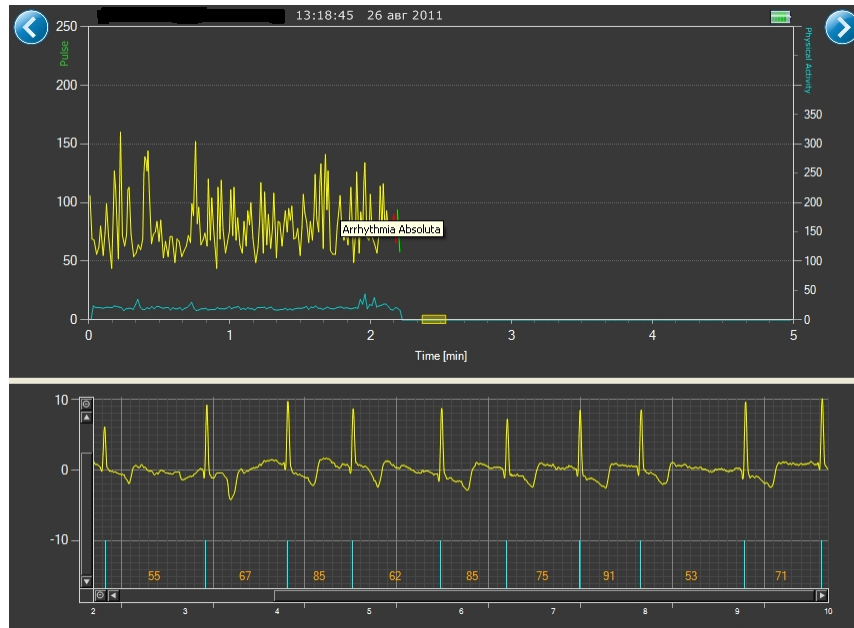

Fig. 1. AF episode lasting 2 minutes. Upper panel - heart rate variation (yellow line) during a five-minute monitoring period, showing typical absolute arrhythmia in AF and corresponding physical activity (blue line). Lower panel - single-channel ECG made on patient's demand which verifies the arrhythmia.

Four of the patients had symptomatic AF episodes with symptoms coinciding with previous history of undocumented arrhythmia. The other six (60% of the group with AF) had asymptomatic runs of absolute arrhythmia.

Therapy was modified in all of the 10 persons with AF detected during telemonitoring. Anticoagulants (either vitamin K antagonists - Sintrom, or novel anticoagulants such as the thrombin inhibitor dabigatran or factor Xa antagonists rivaroxaban) were included in the therapy.

3.2 Discussion

In the present study we hypothesized that AF is underdiagnozed as an etiologic factor in cryptogenic stroke / TIA patients with standard diagnostic methods and we applied longer-period ECG monitoring with ambulatory noninvasive telemedicine device. Telemonitoring for a median period of 22 days yielded an AF detection rate of 27% (10 patients). AF episodes were of short duration (<30 sec) in 7 of these patients and asymptomatic in 6 of them.

There are few published trials evaluating the merit of telemonitoring in stroke / TIA patients. EMBRACE [22] is a randomized trial to determine the diagnostic yield of 30 days of home-based cardiac monitoring vs repeat Holter monitoring to detect paroxysmal AF in 572 patients with an ischemic stroke or TIA deemed cryptogenic after a standard diagnostic workup, including an initial negative result on Holter monitoring. The investigators use an event-triggered loop recorder programmed to record AF episodes (Accuheart, Cardiac Bio-Systems), which has a maximum recording capacity of 30 minutes. The primary outcome is detection of one or more episodes of AF or atrial flutter lasting 30 seconds or more. Significantly more patients are found to have newly detected AF in the 30-day monitoring group (16%) vs those who use repeat Holter monitoring (3%), p <0.001, which translates into a number needed to screen to identify one additional patient with atrial fibrillation of eight. Most events are detected within two weeks of monitoring, but incremental events are detected out to four weeks.

Another study evaluated 56 consecutive patients with cryptogenic TIA/stroke using Mobile Cardiac Outpatient Telemetry (MCOT) for up to 21 days [23]. The median MCOT monitoring duration was 21 (range 5–21) days resulting in an AF detection rate of 23%. AF was first detected after a median of 7 (range 2–19) days of monitoring. Twenty-seven asymptomatic AF episodes were detected in the 13 patients, of which 85% were <30 seconds.

In a comparison between 24/48-hour and 7-day Holter ECG monitoring in 224 stroke / TIA patients without previously known paroxysmal AF, the detection rate with prolonged Holter monitoring (12.5%) was significantly higher than for 24-hour (4.8%, p =0.015) or 48-hour monitoring interval (6.4%, p =0.023) [24].

It is already established that short periods of ECG monitoring, as provided by Holter ECG, yielded a low rate of AF detection after stroke or TIA. In a systematic review of Holter studies 24 to 72 hours of monitoring resulted in new AF detection in 4.6% of consecutive ischemic stroke patients [25].

Prolonged ECG monitoring using telemedicine devices although not routinely implemented has already proved its value to increase significantly the detection rate of previously undocumented AF. In our study AF was detected in 27% of the study group which is a very similar result to the one in the telemonitoring study by Tayal et al [23]. In the EMBRACE study [22] the diagnostic yield of telemonitoring was somewhat lower probably due to the prerequisite for a negative initial Holter result as an inclusion criterion. It is possible that part of the AF episodes that we have detected during telemonitoring could have been detected prior to telemonitoring if we have used an initial Holter ECG.

Another reason for the lower rate of AF detection during telemonitoring in EMBRACE [22] could be the fact that the primary outcome in that study was the detection of AF or atrial flutter lasting 30 seconds or more, while in the design of our study, as well as in that of Tayal et al [23] AF episodes of shorter duration (<30 sec) were also considered significant.

There isn't really consensus on the optimal or appropriate cutoff of duration of AF. Regarding previous published literature, it does seem that short-duration events may be a marker for patients who have longer-duration events at other times. There's a growing belief that even short episodes may be a valid stroke risk factor. Recent data collected in patients with implanted devices [26] and by Holter ECG in epidemiological studies [27] reinforce the assumption that even short episodes of "silent" AF convey an increased risk for stroke. Another study showed that brief bursts of AF detected by Holter (mean monitoring time 22.6 hours; bursts often <30 seconds) were associated with the presence of acute and chronic brain infarcts on brain imaging, especially cortical lesions consistent with embolism [28]. And AF, irrespective of its type, is associated with higher in-hospital mortality both in cardioembolic and atherothrombotic stroke patients [29,30].

This line of consideration reflects the current concept that AF begets AF, based most probably on the fact that this rhythm disorder is a progressive condition, beginning with paroxysmal AF, and over time, progressing to persistent and permanent AF, so there may well be a role for early detection.

In our study group 60% of patients with positive findings during telemonitoring had asymptomatic episodes of AF. In the overall population of patients suffering from this arrhythmia it has been estimated that at least one third of cases do not have any obvious symptoms or degradation of quality of life [31]. This fact has important clinical implications and together with the result from the present and previous studies gives us the reason to recommend telemonitoring as a standard of care in cryptogenic stroke / TIA patients.

Limitation of the present study is the relatively small study group. Beside that several patients in our study group had prior history of undiagnosed arrhythmia and those with pertinent comorbidities (atrial septum aneurysm, carotid atherosclerosis) were excluded – that means that the rate of AF is likely lower in general cryptogenic stroke population.

4. CONCLUSION

Telemonitoring after cryptogenic stroke or TIA detects AF episodes in one in every four patients. The important therapeutic implication of this finding (initiation of anticoagulation as a secondary prophylaxis for stroke and systemic embolism) could serve as a ground for recommending the routine application of prolonged ECG monitoring in this patient group.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

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