Automatic detection of paroxysmal atrial fibrillation in patients with ischaemic stroke: better than routine diagnostic workup?

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Background and purpose: Prolonged electrocardiogram (ECG) monitoring after ischaemic stroke increases the diagnostic yield of paroxysmal atrial fibrillation (pAF). In order to facilitate the additional workload involved in ECG analysis due to prolonged monitoring times, we investigated the effectiveness of pAF detection with an automated software algorithm (SA) in comparison to the routine staff-based analysis (RA) during standard stroke-unit care. Therefore, patients with acute ischaemic stroke or transitory ischaemic attack presenting with sinus rhythmus on the admission ECG and no history of atrial fibrillation were prospectively included.

Methods: A 24-h Holter ECG assessment was performed using either RA based on a computer-aided evaluation and subsequent review by a cardiologist or a commercially available automated SA. In the case of discordant results concerning the occurrence of pAF between the two methods, the data underwent an independent external rating.

Results: Of 809 prospectively enrolled patients, 580 patients fulfilled the inclusion criteria. pAF was ultimately diagnosed in 3.3% of the cohort (19 patients). SA and RA correctly diagnosed pAF in 17 patients resulting in a comparable diagnostic effectiveness of the analysis methods (sensitivity: SA 89.5% vs. RA 89.5%; specificity: SA 99.3% vs. RA 99.1%; κ, 0.686; P < 0.001; 95% confidence interval, 0.525–0.847). RA revealed clinically relevant ECG abnormalities in an additional seven patients.

Conclusions: Although it should not completely replace RA, SA-based evaluation of Holter ECG reaches a high diagnostic effectiveness for the detection of pAF and can be used for a rapid and resource-saving analysis of ECG data to deal with prolonged monitoring times.

Introduction

Atrial fibrillation (AF) remains one of the most common causes of ischaemic stroke and carries a 2.5-fold higher risk of future ischaemic stroke [1]. The detection of paroxysmal AF (pAF) can be challenging due to its short duration, frequently asymptomatic presentation and occurrence in a cluster [2]. Although current guidelines recommend electrocardiogram (ECG) monitoring for at least 24 h after a stroke [3], recently published studies report higher detection rates (up to one quarter of patients with ischaemic stroke) with prolonged AF detection times and sequential cardiac monitoring methods [1]. A prolongation of the Holter monitoring times might easily be achieved in routine practice and could lead to a higher detection rate of pAF and subsequent prescription of oral anticoagulation, resulting in a reduction of risk of recurrent stroke [4]. Nevertheless, an extension of the monitoring time would require additional staff-based...
capacities for ECG analysis that might be difficult to implement within the routine diagnostic workup, especially in primary and secondary hospitals, and could be challenging in terms of cost-effective patient care. In this scenario, an automated computer ECG analysis strategy utilizing a software algorithm (SA) might facilitate and accelerate the analysis of increased ECG data due to prolonged detection times in a human-resource-preserving manner. In addition, SA might be used to extend Holter ECG times beyond the routinely used 24 h to increase the detection rate of pAF.

Here we assessed whether an automated SA is able to reach the diagnostic effectiveness of the commonly used routine staff-based analysis (RA) with respect to pAF detection in 24-h Holter ECG, obtained during routine diagnostic workup of patients with ischaemic stroke in a tertiary hospital.

**Methods**

**Study design**

This study was conducted at the board-certified stroke unit of the Department of Neurology, University of Mainz. All patients with symptoms of acute ischaemic stroke or transitory ischaemic attack were prospectively included between August 2012 and July 2013. Patients presenting with sinus rhythmus on the admission ECG and no history of AF were eligible. The detailed patient selection procedure is depicted in Fig. 1. Ultimately, 580 patients fulfilled the inclusion criteria and completed 24-h Holter ECG (Spacelabs, LifecardCF digital Holter®, Snoqualmie, WA, USA) during their hospital stay. The study was approved by the local Ethics Committee (Landesa¨rztekammer Rheinland Pfalz).

**Definition of atrial fibrillation**

According to the 2010 European Society of Cardiology guideline on AF [5], we defined AF as showing absolutely irregular RR intervals without any repetitive ECG pattern, lacking a distinct p-wave on surface ECG and showing an atrial cycle length of <200 ms (>300 beats/min). Only episodes lasting at least 30 s and not atrial flutter were included.

**Data analysis**

The RA used Pathfinder digital® software (version PA 8.602, Spacelabs, Snoqualmie, WA, USA) to identify episodes of suspected arrhythmia (e.g. pAF). A senior cardiologist performed a rating of the ECG data especially with regard to the occurrence of pAF and other relevant arrhythmias, which were documented within a structured report. Automated SA analyzed the same copied ECG dataset with the commercially available software SRAclinic® (Apoplex Medical Technologies GmbH, Pirmasens, Germany). Based on a time-series analysis of multiple mathematical parameters, the software creates a report indicating whether pAF is present, including an extended Poincaré analysis [2,6]. In the case of pAF diagnosis by SA or a mismatch between the RA and SA report concerning the occurrence of pAF, the ECG data were analyzed in a dedicated core laboratory (M.W.-K. and R.W.) with experience in cardiac electrophysiology and conduct of randomized trials [7,8]. The diagnostic workup of ECG data is depicted in Fig. 2. All investigators responsible for the rating of ECG data were blinded to the results of other methods, arrhythmias detected by telemetry on the stroke unit and the clinical data of the patients.

**Statistics**

Data are presented as means (±SD) or numbers with percentages, if not otherwise indicated. For univariate analysis, the Mann–Whitney U-test, Student’s t-test, chi-square test or Fisher’s exact test were used as appropriate. Inter-rater reliability analysis used κ statistics to determine consistency between RA and SA. Agreement was quantified as fair (κ, 0.21–0.40),
moderate (κ, 0.41–0.60), substantial (κ, 0.61–0.80) or almost perfect (κ, 0.81–0.99) [9]. P < 0.05 was considered as significant. Statistical analysis was performed using SPSS (version 23, IBM, Armonk, NY, USA).

Results

During the study period, a total of 809 patients were admitted to the stroke unit, 693 of whom were identified as having had a stroke or transitory ischaemic attack. Because of AF documented by 12-channel ECG (98 patients, 14.1%) and technical reasons (15 patients, 2.2%), the analysis of the Holter ECG (SA vs. RA) was performed in a total of 580 patients (mean age, 69.3 ± 12.6 years; male, 54.4%). Holter ECG was typically performed within the first 72 h after admission (mean, 28.5 ± 25.6 h) and in all cases during the hospital stay that was due to the qualifying event (stroke/transitory ischaemic attack).

After external validation, pAF could be detected during Holter ECG monitoring in 19 of 580 (3.3%) enrolled patients. The occurrence of pAF was associated with a history of diabetes mellitus [pAF, 9 (47.4%) vs. no AF, 137 (24.4%), P = 0.023] and greater age [pAF (mean), 81.6 ± 7.7 vs. no AF, 69.3 ± 12.6, P < 0.001]. For details see Table 1.

The RA detected pAF in 22 patients (five false-positive and two false-negative results) leading to a sensitivity of 89.5% and a specificity of 99.1%. Similarly, SA was able to detect pAF in a total of 21 patients (four false-positive and two false-negative results), resulting in a sensitivity of 89.5% and a specificity of 99.3% (Table 2). The inter-rater reliability for the two methods (RA vs. SA) was found to be substantial (κ, 0.686; P < 0.001; 95% confidence interval, 0.525–0.847) [9]. For details see Table 3.

In two patients, the Holter ECG recording was interrupted because of insufficient ECG data due to low signal quality. However, the diagnosis of pAF was suspected based on the Poincaré plot and was corroborated after validation. These two patients were therefore included in the ‘pAF detected by SA’ group in the final data analysis.

In addition to pAF, RA was able to detect seven clinically relevant ECG abnormalities (e.g. sinoatrial blockades) leading to further cardiological diagnostics and pacemaker implantation in two cases. These

Table 1 Baseline characteristics of the study population

| Variable                  | No AF  | pAF   | P-value |
|---------------------------|--------|-------|---------|
| n                         | 561    | 19    |         |
| Male sex                  | 305 (54.4) | 11 (57.9) | 0.761   |
| Age (years)               | 69.3 ± 12.6 | 81.6 ± 7.7 | <0.001  |
| History of stroke/TIA     | 114 (20.3) | 1 (5.3)  | 0.144   |
| Arterial hypertension     | 444 (79.1) | 18 (94.7) | 0.144   |
| Diabetes mellitus         | 137 (24.4) | 9 (47.4)  | 0.023   |
| Coronary artery disease   | 96 (17.1)  | 6 (31.6)  | 0.103   |
| Hyperlipidemia            | 144 (25.7) | 6 (31.6)  | 0.563   |
| Current tobacco use       | 139 (24.8) | 2 (10.5)  | 0.184   |
| NIH-SS at admission       | 2 (1–5)   | 3 (2–11) | 0.101   |
| Qualifying event          |         |       | 0.711   |
| Stroke                    | 422 (75.2) | 15 (79.0) |         |
| TIA                       | 139 (24.8) | 4 (21.1)  |         |

Data are presented as n (%) except for age [mean (±SD)] and National Institute of Health Stroke Scale (NIH-SS) [mean (range)]. AF, atrial fibrillation; pAF, paroxysmal AF; TIA, transitory ischaemic attack.

Table 2 Detection rates of paroxysmal atrial fibrillation and test effectiveness of different analysis procedures

|            | RA          | SA          |
|------------|-------------|-------------|
| Correctly detected cases | 17 (89.4) | 17 (89.4) |
| False positive      | 5           | 4           |
| False negative      | 2           | 2           |
| Sensitivity         | 89.5        | 89.5        |
| Specificity         | 99.1        | 99.3        |

Data are presented as n (%). RA, routine analysis; SA, software algorithm.
clinically relevant arrhythmias were not identified during stroke-unit telemetry or after reviewing the report of the SA.

**Discussion**

Within our patient cohort, SA-based analysis of 24-h Holter ECG data after acute ischaemic stroke was comparable to current routine ECG analysis in a tertiary hospital with regard to the detection of pAF. Concerning the diagnostic effectiveness of the two analysis methods (SA vs. RA), the accuracy of the diagnosis after an external blinded validation was high and yielded a sensitivity of 89.5% and specificity of at least 99.1% for each method (Table 2).

The detection of pAF in patients presenting with ischaemic stroke is of major clinical importance, as it changes the secondary preventive therapy from antiplatelet drugs to oral anticoagulation [10], leading to a 60–70% reduction of recurrent strokes in patients with AF compared to placebo [11]. Because of this remarkable secondary preventive effect, recent studies [1,6,7,12,13] and randomized trials [8,14] achieved higher detection rates of pAF by simply prolonging monitoring times. Nevertheless, the analysis of prolonged monitoring data is costly in terms of time and resources, and therefore difficult to implement in clinical practice. In this regard, the SA might offer a cost-effective and rapid option for the analysis of increased ECG data to improve the diagnostic yield of pAF after cerebral ischaemia. However, competent ECG readers must still verify positive SA diagnoses and a major limitation of solely SA analysis is the potential to overlook clinically relevant arrhythmias. This is reflected by the detection of seven such arrhythmias by RA resulting in further cardiological diagnostics and pacemaker implantation in two cases. Therefore, we would recommend using the SA approach as a complementary analysis tool to facilitate the prolongation of Holter ECG monitoring for patients with stroke in order to detect pAF.

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**Table 3** Agreement between routine analysis (RA) and software algorithm (SA)

|       | SA   | RA  |
|-------|------|-----|
|       | No AF| pAF |
| RA    |      |     |
| No AF | 552  | 6   |
| pAF   | 7    | 15  |

AF, atrial fibrillation; pAF, paroxysmal AF. \( \kappa = 0.686; P < 0.001; 95\% \) confidence interval, 0.525–0.847.
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