

**Research Article** 

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# Extended Electrocardiographic Poincare Analysis (EPA) for Better Identification of Patients with Paroxysmal Atrial Fibrillation

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## Abstract

**Background:** Atrial fibrillation (AF) – be it permanent or paroxysmal – is the most frequent and most effectively treatable cause of stroke. However, when paroxysmal, even electrocardiography for 24 hours (24h-ECG) misses AF in more than 50% of cases. We assessed whether extended Poincaré analysis of ECG R-R intervals (EPA) can help to identify electrocardiographic remodeling suggestive of paroxysmal AF (PAF).

**Methods:** Twenty-nine patients with previously diagnosed PAF were re-assessed by 24h-ECG using conventional analysis and EPA based on a previously trained algorithm considering among other ratios of R-R interval duration, number of premature atrial complexes, approximate entropy, and standard deviation of Poincaré plots-axes. 24h-ECG from 21 healthy subjects without a history of AF served as negative, and 9 patients with permanent AF as positive controls.

**Results:** PAF during 24h-ECG was detected in 4 out of 29 (14%) patients with a history of PAF by conventional analysis. EPA classified ECGs of these and 22 additional patients with a history of PAF, i.e. a total 90%, as suggestive of PAF. All patients with permanent AF were identified by both tools. EPA additionally classified the ECG in 4 out of 21 control subjects as suggestive of PAF.

**Conclusions:** Extended Poincaré analysis in patients with a history of PAF is more sensitive to electrocardiographic abnormalities than is conventional 24h- ECG analysis. These findings warrant prospective studies of EPA in patients with a high likelihood of PAF, i.e. with stroke of undetermined origin.

**Keywords:** Atrial fibrillation; Poincaré analysis; Atrial remodeling; Ischemic stroke; Prevention

**Abbreviations:** AF: Atrial Fibrillation; EPA: Extended Poincaré Analysis; PAF: Paroxysmal Atrial Fibrillation; SD: Standard Deviation; MIT: Massachusetts Institute of Technology

# Introduction

One fifth of all strokes are caused by atrial fibrillation (AF) [1,2]. Oral anticoagulation is highly efficacious for both primary and secondary prevention of stroke in patients with AF [3], and thus detection of AF is essential. However, as in up to one third of cases AF is intermittent, appropriate diagnosis - and thus treatment - is frequently missed [4]. Even when suspected, diagnosis of paroxysmal AF (PAF) is estimated to be missed in more than 50% of patients [5,6]. Relative to standard ECG, 24h-ECG doubles the detection rate of PAF but still misses about one third of cases later identified by ambulatory 7-day ECG and up to 44% of cases detected by long-term event recorders [7]. The number of patients needed to screen to detect one case of PAF has been calculated to be 20 [8].

In patients having survived cerebral infarctions the cause of stroke remains undetermined in up to 40 % of cases despite extensive diagnostic work-up [9-11]. Because of the high frequency of PAF and the poor sensitivity of 24h-ECG, a substantial number of these patients are likely to have undetected PAF. These patients fail to receive effective preventive therapy although they carry as a high a risk of cardiogenic stroke as those with permanent AF [12,13].

Because limited time and resources do not allow monitoring all patients with cryptogenic stroke beyond a 24h-ECG, measures are needed to identify patients with an increased risk for paroxysmal AF. Since even short-duration AF can induce electrical and contractile atrial remodeling, previous episodes of PAF may increase the variability of the atrial electrical wavelength also in the absence of fibrillation, i.e. during sinus rhythm [14,15]. This phenomenon may manifest as increased R-R interval dynamics on ECG. Combined with an adequate analysis tool, it could help to identify patients with an increased likelihood of PAF who would profit from extended ECG monitoring.

Here we tested whether patients with previously diagnosed PAF show abnormalities of R-R dynamics during sinus rhythm. Assessment was based on automated extended Poincaré analysis (EPA) trained on an independent set of ECG from patients with PAF.

# Methods

# Patients

We enrolled 38 patients from our cardiologic department (mean age 68 years, range 44 to 85 years; 14 females). Twenty-nine had an established diagnosis of paroxysmal or persistent AF, identified as self-terminating episodes of AF on past conventional ECG analyses (< 1 year before start of the study, minimum of two ECGs). Fifteen of these

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patients had recurrences of AF after cardioversion in the past. Nine patients had a diagnosis of permanent atrial fibrillation and served as positive controls.

As negative controls, 21 volunteers (mean age 62 years, range 53 to 81 years; 11 females) without a diagnosis of arrhythmia or structural heart disease were included. These had undergone previous Holter ECG analyses and showed no episodes of AF. Twenty-six patients (68%) and 12 control subjects (55%) were treated with \_-blockers for blood pressure control. Patients with pacemakers and patients treated with antiarrhythmic drugs (sodium or potassium channel blockers or amiodarone) were excluded. Clinical characteristics of patients are listed in table 1.

Additionally, a 66 year old male patient with an infraction of the right cerebral artery of undetermined cause from our stroke-unit was screened. Standard 12- lead ECG on admission was unrevealing, so were transesophageal echocardiography and laboratory analyses. Extracranial and transcranial doppler/duplex sonography showed bilateral low grade atherosclerosis of the carotid arteries without hemodynamic relevance. No history of heart disease or arrhythmia and prior ischemic cardiovascular events was noted.

## Electrocardiographic recording

All patients were assessed by standard 12-lead ECG. Additionally, patients underwent a 24h-ECG with 6-channel recorders (H12+; Mortara Instruments). The median ECG recording time was 19.5 hours (SD  $\pm$  2.5, range 15.3 to 22.9 hours). Data were edited and cleaned from artefacts using the Pathfinder Software (Vers. V8.257, Reynolds). Channel 2 of the ECG recording was used to generate R-R lists with the same software. The results were analyzed, Interpreted, and additionally revised visually by two experienced cardiologists using the H-SCRIBE

Clinical characteristics of the study population			
	PAF Group (29)	Chronic AF Group (9)	Control Group (21)
Age	67 (± 9.8)	69 (± 9.6)	62 (± 15.3)
Gender male/female	18/11	6/3	10/11
Sinus bradycardia	1 (3%)		
Hypertensive crisis	2 (7%)		
Coronary 1 vessel disease	3 (10%)		3 (14%)
Coronary 2 vessel disease	1 (3%)		1 (5%)
Coronary 3 vessel disease	3 (10%)		
Ischemic cardiomyophathy		1 (11%)	
Unselected chronic heart disease	1 (3%)		2 (10%)
Diabetes mellitus	1 (3%)		
Sinus tachycardia		1 (11%)	
Orthostatic disorder		1 (11%)	
Medication			
Beta-blocking-agents	22 (76%)	4 (44%)	12(57%)
Calcium-channel- blockers	1 (3%)	1 (11%)	
ACE inhibitor	3 (10%)		
AT1 inhibitor	3 (10%)		
Digitalis	2 (7%)	1 (11%)	
No medication			3 (14%)

 Table 1: Clinical characteristics of patients. PAF = paroxysmal atrial fibrillation;

 Chronic AF = chronic atrial fibrillation; ACE = angiotensin-converting enzyme; AT1 inhibitor = angiotensin II type 1 receptor antagonist.

software (version 4.0; Mortara Instruments). The cardiologists were blinded to the patient's medical history and the results of any other ECG recordings of the patient. The detection criteria require >1:1 AV conduction for a minimum of 24 ventricular cycles.

#### **Extended Poincaré analysis (EPA)**

Onset of atrial fibrillation is often preceded by premature atrial complexes, atrial tachycardia, and other ectopic activities. While the origin of these phenomena is manifold, most of them cause changes in ventricular response due to alterations in atrioventricular nodal conduction [16]. Non-linear algorithms can reveal abnormalities in cardiac regulation not detected by traditional single or linear measures of heart rate variability [17]. We used a combination of published linear and non linear parameters for EPA [18-24]. We then trained the resulting algorithm to discriminate between AF, PAF and sinus rhythm using the MIT data set "Atrial Fibrillation" [http://www.physionet.org/ physiobank/database/nsrdb/] which contains data from 4 patients with permanent atrial fibrillation (40 hours), 19 patients with PAF (189 hours), and 18 control patients without arrhythmias (385 hours). The following parameters were considered for classification.

First, principle component analysis [18] was used to calculate the standard deviation (SD) of the minor axis (SD1), and of the major axis (SD2) of the Poincaré plots, and the ratio SD1/SD2 [20]. Dynamics of R-R interval fluctuations were assessed by creating R-R difference plots. Instead of plotting an R-R interval against its previous one, the differences between two consecutive R-R intervals were plotted and normalized by dividing them with the mean of the two corresponding R-R intervals [(Ri-Ri+1)/(Ri+Ri+1); (Figure 1)]. Krstacic et al. have shown that the ratio between the shortest and longest interval of maximal six consecutive R-R intervals might be a predictive parameter for PAF [19]. Since premature atrial complexes are known to play a major role in triggering AF, the number of these complexes was included in the analysis. As proposed by Thong et al., the number of complexes that trigger the risk for PAF depend on the preceding normal beats, the type of the premature atrial complexes (normal complexes with sinus node reset or abnormal complexes: interpolated, full compensatory pause, delayed sinus node reset) and also on the rhythm of the subsequent beats [21]. Thus, not all detected atrial premature complexes were rated equally, and only premature atrial complexes without sinus nodal reset were included in the analysis. Finally, regularity was analysed by calculating the approximate entropy of R-R interval data, which is a measure of complexity in time series analysis of ECG data [25].

Based on the MIT data sets, these mathematical parameters were weighted in an iterative procedure to establish cut off values, to predefine increasing risk of AF and to maximise the discriminating accuracy between the three groups. Each ECG data segment of one hour duration was classified using the following categories (Figure 2):

- Risk level 0: Sinus rhythm
- Risk level 1: Increased R-R interval dynamics, being at risk of paroxysmal atrial fibrillation
- Risk level 2: Indication of present atrial fibrillation

After establishing classification criteria, all 40 hours (100%) of permanent AF of the MIT data set were classified as present fibrillation (risk level 2). In the PAFpatient group 153 of 189 hours (81%) were classified as being at risk of paroxysmal AF or having present episodes of fibrillation (level 1 or 2). All 105 hours including episodes of fibrillation were classified as risk level 2 by algorithm. Thus, 48 hours without fibrillating episodes were correctly rated as being at risk of paroxysmal



Figure 1: Examples of Poincaré plots based on one hour ECG recordings. The R-R interval fluctuation is one calculated parameter used to rate the AF risk. The plot in the healthy subject (A) shows a baseball bat like structure. The calculated risk level is 0. The disseminated clusters in a patient with a history of PAF (B) indicate increased R-R interval dynamics (risk level 1). In patients with chronic AF (C) widely scattered R-R intervals indicate a maximum of variability. The calculated level is 2.

AF. All 385 hours (100%) of the control group were classified as risk level 0.

After fragmentation into one hour segments, the 24h-ECG data from our patient cohort were submitted to the automated time-series analyses of R-R interval dynamics and classified according to the criteria established before (Figure 2).

## Statistical analysis

Comparison between groups was performed by use of one-way analysis of variance for continuous variables that are described as mean  $\pm$  SD and the chi-square test, with statistical significance set at p < 0.05.

# Results

In all 29 patients with a history of PAF the initial standard 12-lead ECG showed normal sinus rhythm.

24h-ECG identified 17/560 (3%) hours of fibrillation (range: 18 seconds to 5 hours) in 4/29 (14%) of patients. All of these episodes were classified as level 2 (indication of present atrial fibrillation) by EPA.

From a total of 560 recorded hours in the 29 PAF-patients, 275 hours were classified as risk-level 1-2 in 26 patients (26/29 or 90% of patients; 275/560 or 49% of hours). Thus, EPA classified 22 more PAF-patients (and 258 hours) as at risk for PAF than did conventional analysis (p < 0.001). On 24h-ECG, the 26 identified patients did not differ in atrial premature complexes and maximum or minimum heart rate, compared to the three not identified patients.

All 9 cases of permanent AF were identified by the conventional ECG-analysis as well as by R-R interval analysis (174/174 or 100% of hours). ECG recordings were classified as level 2 by EPA.

Among the 21 control subjects (392 hours in total) none showed episodes of fibrillation on conventional analysis. By R-R interval analysis, however, 4 were classified as having risk grade 1 for AF (13/392 or 3% of hours graded as level 1).

Overall, EPA predicted PAF with a sensitivity of 89.7% (26 of 29) and a specificity of 81.0% (17 of 21), whereas conventional long-term ECG analysis had a sensitivity and specificity of 13.8% (4 of 29) and 100% (21 of 21). The sensitivity of the EPA of detecting hours at risk for AF outside episodes of fibrillation in PAF patients was 47.5% (258 of 543

hours; conventional long-term ECG: 0.0%) with a specificity of 96.7% (379 of 392 hours). The positive and negative predictive values of the EPA algorithm in the screened population were 89.7% (35/39 subjects) and 85.5% (17/20 subjects). Positive and negative predictive values of the conventional Holter-ECG analysis were 100% (13/13 subjects) and 45.6% (21/46 subjects). Figure 3 displays a graphical representation of the results.

The exemplary stroke patient with no history of arrhythmia showed risk grade > 1 in 62 of 68 hours in total (91%). Six hours were classified as normal sinus rhythm (level 0; 9%), and 2 of 68 hours were classified as present AF (level 2; 3%). The conventional Holter-ECG analysis identified a continuous sinus rhythm in the 66 hours, and confirmed two episodes of AF (40 and 33 minutes) in the hours graded as level 2 (Figure 4).

AF load between episodes of high risk for PAF (risk level 1) and low risk for PAF (risk level 0) prior to and after EPA analysis were not different. These findings support the hypothesis, that EPA rather detect more general changes in atrial function and structure than simply appear around episodes of fibrillation.

# Discussion

We tested whether ECG in patients with a history of PAF shows abnormalities during sinus rhythm that, e. g. when detected in patients with cryptogenic stroke, would help to identify individuals with probable PAF. The results of the present study indicate that such abnormalities can be identified. In patients with a history of PAF 24h-ECG detected AF in only 14% of cases. EPA detected abnormalities suggestive of PAF in 90% of patients with previous PAF, with an improved negative predictive value of 85.5% versus 45.6% (conventional ECG analysis).

Although EPA does not confirm the diagnosis of PAF, which is defined as a selfterminated sequence of AF, it demonstrates that analyzing ECG data outside episodes of fibrillation offers an additional diagnostic clue to identify patients with PAF. While conventional 24h-ECG has a yield of probably less than 50% for PAF, it nevertheless constitutes the present standard in organized stroke care [26-28]. If the patients in our study with a history of PAF had not been previously diagnosed but the 24h-ECG had been part of a stroke work-up, only 4 out of 29 would have been correctly diagnosed by conventional analysis

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**Figure 4:** Example of a long-term ECG-recording of a stroke patient with an acute cerebral infarction of undetermined cause. A total of 68 hours was recorded, whereof 6 hours were classified as risk level 0 (sinus rhythm), 2 hours as risk level 2 (risk of atrial fibrillation) and 60 hours of risk level 1 (indication risk for AF). Above, showcases of the heart rhythm of hour 19 (risk level 1, A) and hour 38 (risk level 2, B) are displayed. Given that only 2 hours of the ECG showed AF, a conventional Holter-ECG would likely have missed the diagnosis of paroxysmal AF, i.e. when monitored during the first 37 hours. Conversely, EPA graded 60 of 66 hours of sinus rhythm as having a risk for AF, along with classifying the 2 hours of AF correctly as level 2.

and treated accordingly. In addition to these four patients, EPA would have indicated that in another 22 patients R-R dynamics were highly suggestive of PAF and could have prompted extended monitoring in order to pick up episodes of PAF.

In organized stroke care ECG signals are often monitored continuously, but without automatic data analysis or storage. Such data would be amenable to EPA and allow automatic analysis of the full length of time a patients is monitored by ECG. Figure 4 gives an example of continuously monitored ECG in a patient with cryptogenic stroke. There was no AF during the first 24 hours but EPA was suggestive of PAF throughout during this time. It was only after 37 hours that an AF episode occurred.

Dynamics of cardiac excitation in PAF often change because even short periods of AF alter atrial function and structure [14,15]. Concomitant structural changes in the atrioventricular node additionally affect cardiac excitation [29,30]. Both mechanisms can increase ectopic activity and thereby enhance R-R interval dynamics outside periods of fibrillation. However, EPA provided false negative results in 10% of patients with an established history of PAF. Although these false negative results show that the premise of electrical remodeling due to PAF and its detection by ECG does not hold in all cases, this false negative rate is considerably less than that of conventional ECG analysis (86%). Conversely, EPA provided false positive results (grade one risk) in 4 out of 21 individuals without a known history of paroxysmal atrial fibrillation. These false positive results caution that analysis of R-R interval dynamics is complex. Grade one risk in controls without arrhythmia may reflect noise or artefacts in ECG recording as well as low-grade pathology or signs of remodeling due to undetected PAF, other paroxysmal arrhythmias or occult structural heart disease. However, all correctly identified hours with episodes of atrial fibrillation (in chronic AF patients as well as in patients with PAF) were graded as risk level two. Thus, using "level 2" would have allowed a clear distinction between individuals without and with present episodes of fibrillation, even if appearing only for seconds.

EPA also detects atrial extra systoles, and the number of these supraventricular ectopic complexes was included in the risk analysis. Although premature atrial complexes are a rather non-specific marker of an underlying heart disease, some authors have hypothesized that these complexes are the main single predictor of the presence of PAF and should be regarded as a masked type of paroxysmal atrial fibrillation [31-33]. In the current study, the number of atrial premature complexes did not differ between identified and not identified PAF-patients. However, this study did not assess whether manual determination of atrial extra systoles is similarly sensitive as EPA for the detection of a "risk for AF". From a practical point such manual analysis would be more than difficult to install in managed stroke care.

A limitation of this study is the exclusion of patients with class I-III antiarrhythmics because here possible interferences with cardiac electric excitation and, consequently, heart rate dynamics exist. The

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sensitivity and specificity of our procedure in these patients still has to be assessed.

In conclusion, EPA may allow identifying patients with a high likelihood for atrial fibrillation. An abnormal result from EPA should not be interpreted as "presence of AF" or "risk for stroke", but as an indication for further cardiological evaluation by serial long-term ECG, event-recording ECG or an insertable cardiac monitor. Even if the underlying pathomechanisms remain nonspecific, the method might offer a sufficient predictive power in a selected group of patients, e. g. stroke patients. EPA might help to focus extended and costly long-term ECG recordings in these patients. Prospective studies are needed to determine the reliability, validity, and finally sensitivity and negative predictive value of automated EPA to identify patients who later show PAF on extended ECG monitoring – and those who will not.

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