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ORIGINAL ARTICLE

Electrocardiographic Predictors of Silent Atrial Fibrillation in Cryptogenic Stroke

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Background Prolonged screening for the presence of atrial fibrillation (AF) is recommended after cryptogenic stroke (CS) and different electrocardiographic markers of atrial cardiopathy have been proposed as tools to identify patients at high-risk for AF.

Aim The aim of this study was to evaluate the relationship between different electrocardiographic parameters and in-hospital AF occurrence after acute CS.

Method In total, 222 patients with CS underwent 12-lead resting electrocardiogram (ECG) at admission and 7-day in-hospital ECG monitoring in order to evaluate the possible occurrence of silent AF. At admission, the following indices were evaluated: maximum and minimum P-wave duration (P max and P min), P-wave dispersion (PWD), P-wave index, P-wave axis, atrial size. Patients were dichotomised into two groups according to the detection of AF during 7-day in-hospital ECG monitoring and a logistic regression model was constructed to determine the predictors of AF.

Results Atrial fibrillation was detected in 44 patients. Those in the AF group had a significantly higher PWD, P-wave index, PR interval, and greater frequency of abnormal P-wave axis than those in the no AF group. The following variables were found to be the main predictors for AF: age (odds ratio [OR] 1.41 for 5 years, 95% confidence interval [CI] 1.15–1.72), PWD (OR 1.92 for 10 ms, 95% CI 1.45–2.55), abnormal P-wave axis (OR 3.31, 95% CI 1.49–7.35).

Conclusions In CS, high PWD and abnormal P-wave axis are independent predictors of AF, representing useful tools to identify patients at high-risk of AF.

Keywords Atrial fibrillation • P wave dispersion • P wave axis • P wave index • Cryptogenic stroke

Background

About one-third of ischaemic strokes occur without a well-defined aetiology and are classified as cryptogenic [1]. The detection of atrial fibrillation (AF) in patients with cryptogenic stroke (CS) is particularly important because it provides evidence of the mechanism of stroke and generally leads to a change in antithrombotic strategy from antiplatelet to anticoagulation [2]. For this reason, most guidelines recommend prolonged screening for the presence of AF in CS, even if, in common clinical practice, it is really difficult and expensive to perform an appropriate electrocardiographic monitoring with

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resulting underdiagnosis of AF and missed anticoagulant treatment opportunities for secondary stroke prevention [3]. Recently, we proposed that a 12-lead resting electrocardiogram (ECG) may represent a simple, fast, and inexpensive tool providing valuable prognostic information about the risk of silent AF, thereby helping to identify the candidates who should undergo prolonged ECG screening for AF [4,5].

Indeed, in patients with CS, some electrocardiographic parameters may reflect the presence of atrial cardiopathy that represents a substrate for the occurrence of AF [6]. In this view, the aim of this study was to evaluate the relationship between some parameters of 12-lead resting ECG and in-hospital AF occurrence after acute CS.

Methods

We enrolled 222 patients (108 males, 114 females; mean age 70.39 ± 13.05 years), admitted consecutively to the Stroke Unit of Siena University Hospital for ischaemic CS. Neurological status at admission was assessed with National Institute of Health Stroke Scale score (NIHSSs); three severity levels were defined: mild (NIHSSs <8), moderate (NIHSSs: 8–16), severe (NIHSSs >16). All patients underwent neuroimaging examination (brain computed tomography [CT] with angio-CT scan and/or brain magnetic resonance imaging), extracranial and transcranial arterial ultrasound examination, transthoracic echocardiography, 12-lead resting ECG at admission, and 7-day in-hospital ECG monitoring (by means of ECG wireless telemetry). Angio-CT scan included aortic arch, and extra- and intracranial artery examination. Patients with AF at admission or previous clinical paroxysmal or persistent/permanent AF were excluded. During 7-day ECG monitoring, AF was considered when normal sinus rhythm was replaced with irregular tachycardia lasting >5 minutes with no visible P wave or with unorganised F wavelets. In order to confirm the diagnosis of AF, a 12-lead ECG was performed when the duration of arrhythmias allowed it. ECGs were evaluated by a cardiologist (M.A., F.G., G.M.).

Left atrial size was evaluated by means of the following methods: left atrial area measured in four-chamber apical view and left atrial volume according to the area–length technique [7]. Strokes were classified as cryptogenic according to the trial of ORG 10172 in acute stroke treatment (TOAST) criteria [8], also excluding patients with more than one potential cause. The study was approved by the ethics committee of the University Hospital of Siena, Siena, Italy. Written informed consent was obtained from all patients.

P-Wave Duration and P-Wave Dispersion

Simultaneous 12-lead ECG (25 mm/second and 10 mV/cm) was recorded by means of a commercially available imaging system (Esaote P 8000 Power, Esaote s.p.a., Genoa, Italy) in all patients in the supine position (during spontaneous breathing) at the time of admission. Paper-printed ECGs were scanned and digitised in order to achieve greater precision in detecting and measuring P waves [9]; on-screen measurement of P-wave durations were made by a single observer (M.A.), who had no knowledge of AF occurrence on the 7-day ECG, by means of Adobe Photoshop CC 2017. P-wave duration was measured from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to isoelectric line in all simultaneous 12 leads. The following indices were derived from measurements of each ECG: maximum P-wave duration (P max), minimum P-wave duration (P min), P-wave dispersion (PWD), defined as the difference between P max and P min, and the P-wave index (the SD of P-wave duration across all 12 leads). Normal PWD values were <40 ms [10,11].

P-Wave Axis

P-wave axis was determined by measuring the positive or negative P-wave deflections on all six limb leads and then calculating the net direction of electric activity using the hexaxial reference system. Automated analysis of ECG data was conducted including selective averaging to obtain representative durations and amplitudes of ECG components to calculate the frontal P-wave axis (by means of ESAOTE P 8000 Power). An abnormal PWA was defined as any value outside 0–75° [12].

Statistical Analysis

All results are presented as mean ± SD. Normal distribution of quantitative variables was preliminarily tested using the Lilliefors test to select parametric or non-parametric inferential statistical methods. Homoscedasticity was tested using Fisher's F-test for normal distribution. Patients were dichotomised into two groups according to the detection of AF during 7-day in-hospital ECG monitoring.

A Mann–Whitney test was performed to compare age, PWD, P max, P min, P mean, P-wave index, PR interval, and atrial size, in both groups. A *t*-test was performed to compare P-wave index in both groups. A χ^2 test was performed to evaluate statistical association between categorical variables (sex, P-wave axis, cardiovascular risk factors, NIHSSs) evaluated in both groups of patients.

Logistic regression model was constructed to determine the predictors of AF. The following variables were entered initially: age, atrial size, all ECG parameters (PWD, P max, P min, P-wave index, PR interval, P-wave axis). The statistical criterion for considering retention of a variable in the model was $p < 0.05$. Akaike's information criterion was used to select the best subset of predictor variables and corresponding odds ratios (ORs) were obtained.

A p-value <0.05 was considered statistically significant.

Statistical analysis was performed using R Statistical Software (version 3.3.2 for Windows; R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical Variables

During the first 7 days from stroke symptom onset, AF was detected in 44 of 222 patients enrolled. The demographic characteristics of both groups of patients (AF group and no-AF group) are depicted in Table 1. The patients with AF were older than the patients without AF (76.95 ± 7.59 vs 68.77 ± 13.65 years, p = 0.0004). Severity levels of neurological deficit and CHA_2DS_2VASc score were higher in patients with AF; in particular, in AF group the percentage of patients with severe deficit (NIHSSs >16) was significantly higher than in no-AF group, whereas the percentage of patients with mild deficit (NIHSSs < 8) was significantly lower than that in no-AF group (Table 1). There were no differences between patients with and without AF concerning sex and other cardiovascular risk factors (Table 1).

ECG Parameters

With regard to ECG parameters, patients in the AF group had significantly higher values for P max, PWD, P-wave index, and PR interval compared with those in the no-AF group (Table 1). An abnormal P-wave axis was detected more frequently in patients with AF than in patients without AF (Table 1). Atrial size was slightly higher in patients with AF, but this difference was not statistically significant.

Logistic Regression and Multivariable Model

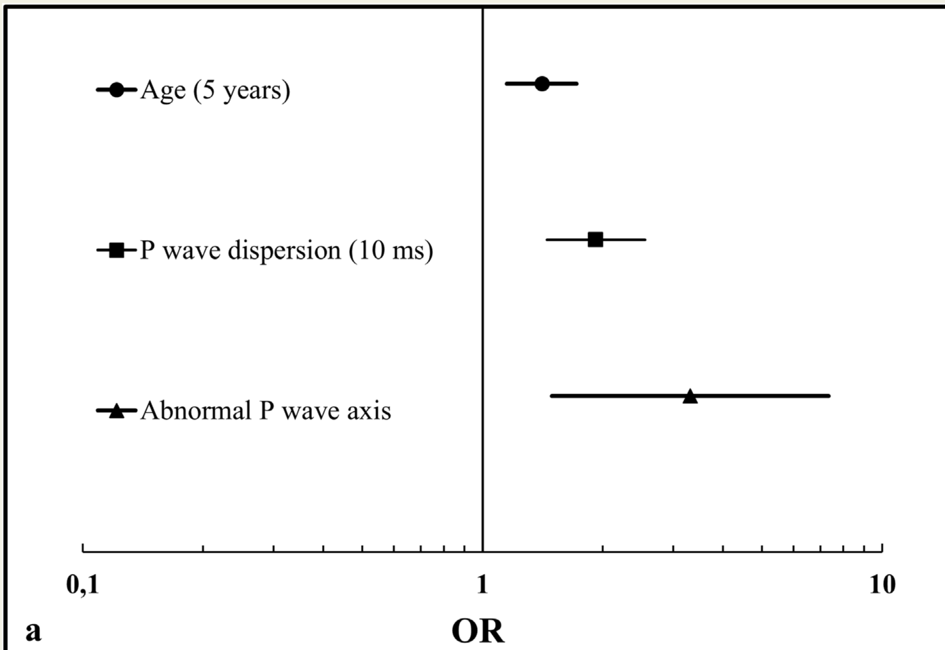
A logistic regression model was constructed to determine the predictors of AF. At first, we considered the following variables: age, atrial size, all ECG parameters (PWD, P max, P min, P-wave index, PR interval, P-wave axis). Akaike's information criterion showed that the best subset of predictor variables for AF included the following: age (OR 1.41 for 5 years, 95% confidence interval [CI] 1.15–1.72), PWD (OR 1.92 for 10 ms, 95% CI 1.45–2.55), abnormal P-wave axis (OR 3.31 for abnormal axis, 95% CI 1.49–7.35) (Figure 1).

Table 1 Characteristics of patients with cryptogenic stroke with and without silent atrial fibrillation (AF) detection.

	Patients with cryptogenic stroke (n = 222)		P-value
	AF (n = 44)	No AF (n = 178)	
Age (yr)	78 (71–82)	72 (59–79)	0.0004
Sex (F:M)	25:19	89:89	0.5
NIHSSs at admission			<0.0001
NIHSS score <8	15 (34)	111 (62)	
NIHSSs 8–16	6 (14)	43 (24)	
NIHSS >16	23 (52)	24 (13)	
CHA_2DS_2VASc score	5 ± 1.2	4.4 ± 1.4	0.01
Cardiovascular risk factors			
Hypertension	24 (55)	105 (59)	0.61
Diabetes mellitus	6 (14)	38 (21)	0.3
Hypercholesterolaemia	12 (27)	72 (40)	0.12
Previous CAD	6 (14)	13 (7)	0.22
Previous stroke	1 (2)	14 (8)	0.31
Smoking	15 (34)	58 (33)	0.86
BMI (kg/m^2)	25.3 ± 6	26.3 ± 4	0.5
Left atrial size (area, cm^2)	17 (16–21)	16 (15–20)	0.1
Left atrial size (volume, mL)	46 (40–61)	49 (40–55)	0.7
Mitral valve disease	12 (27)	52 (29)	0.85
Aortic valve disease	13 (29)	60 (33)	0.72
Hypokinetic/akinetic left ventricle	3 (7)	6 (3)	0.38
ECG parameters			
P-wave max (ms)	130 (120–142)	121 (120–135)	<0.05
P-wave min (ms)	80 (62–90)	80 (70–91)	0.44
P-wave dispersion (ms)	54 (46–69)	42 (40–54)	<0.0001
P-wave mean (ms)	102 (92–121)	105 (95–114)	0.95
P-wave index (ms)	18 ± 4	15 ± 4.5	<0.0001
Abnormal P-wave axis	13 (30)	20 (11)	0.004
PR interval (ms)	177 (160–200)	160 (148–180)	0.01

Data are expressed as median (range), mean ± SD or n (%).

Abbreviations: F, female; M, male; NIHSSs, National Institute of Health Stroke Scale score; CAD, coronary artery disease; BMI, body mass index; ECG, electrocardiogram.



	OR	95%CI
Age	1.41	1.15 – 1.72
Abnormal P wave axis	3.31	1.49 – 7-35
P wave dispersion	1.92	1.45 – 2.55
P wave max	1.01	0.99 – 1.03
PR interval	1	0.99 – 1.01
Atrial size	1	0.93 – 1.07
Smoking	1.52	0.54 – 4.14
C reactive protein	1.06	0.92 -1.22

b

Figure 1 Multivariate analysis of predictors of atrial fibrillation (AF). (A) Forest plot of significant predictors of atrial fibrillation (according to Akaike's information criterion). (B) Results of multivariate analysis of predictors of AF. Abbreviation: CI, confidence interval.

Discussion

The novel finding of our study is that increased PWD and abnormal P-wave axis are independent predictors of silent AF in the first 7 days after CS.

This result suggests that in patients with CS a simple 12-lead resting ECG at admission can be a useful and an inexpensive tool in order to predict AF and identify the subgroup of patients who have to undergo prolonged ECG screening. In a previous study [13], P-wave axis was found to be associated with an increased risk of AF in a community population. Notably, the results of the Atherosclerosis Risk in Communities Study (ARIC) showed that abnormal P-wave axis was associated with ischaemic stroke, predisposing patients to cardiac thromboembolism, regardless of AF occurrence, even if in this study the authors were unable to account for silent AF [13].

Instead, with regard to the association between PWD and the risk of silent AF in CS, the results of previous studies are conflicting. Kocer et al. [14] found no difference in PWD values in patients with acute non-cardio-embolic stroke in comparison with a control group, while in our previous study [9] we observed higher PWD values in CS, as well as in cardio-embolic strokes, suggesting that PWD could be a marker of silent AF episodes in these patients. Furthermore, two other studies showed a link between PWD and AF occurrence after stroke [15,16]; however, unlike our study, in the first study [15], Dogan et al. did not report the exact aetiology of stroke and the reason for the decision to perform a 24-hour Holter-ECG, whereas in the second study [16], Elansary et al. evaluated a small sample size (only 60 patients) that included patients with a previous documented history of episodes of AF before ECG monitoring, without reporting the minimum duration of AF episodes and without excluding thrombotic aetiology.

In contrast to these studies, our population consisted of patients with CS and no previous story of AF.

However, the incidence of newly diagnosed AF in our CS cohort (19.8%) appears higher in comparison with other previous studies in CS; in particular, in the CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF) study [17], AF had been detected in only 8.9% of patients with CS within the first 6 months of ECG monitoring. This discrepancy may be explained by the different characteristics of our cohort of patients. Our patients were older and with more severe neurological deficit, as evidenced by higher NIHSS scores and longer durations of hospitalisation. Furthermore, they were evaluated during the acute phase of stroke (the first 7 days) and classified as CS according to the TOAST classification, excluding a possible cardio-embolic mechanism based on ECG, transthoracic echocardiography, and previous history of cardiac disease but without a previous prolonged ECG monitoring; instead, the patients of CRYSTAL AF received a diagnosis of stroke or transient ischaemic attack within the previous 90 days from symptom onset and all patients underwent $\geq$24 hours of ECG monitoring prior to study entry.

Our results did not show significant differences in atrial size or mean P-wave duration between both groups. The presence of high P-wave dispersion values may also correlate with AF risk independently of the increase of atrial size, as reported in previous studies [18–20]; indeed, the increase in PWD with normal left atrium size represents an atrial electrical heterogeneity index, suggesting the presence of atrial microarchitecture change and site-dependent conduction delay that favours AF occurrence.

Our findings suggest the importance of ECG monitoring for 7-day Holter (or telemetry) in the acute phase of CS in order to detect the occurrence of AF, especially in patients with increased PWD or abnormal P-wave axis.

The opportunity to predict AF in these patients by means of these simple electrocardiographic markers is particularly important because it provides clues to the possible mechanism of stroke, thus contributing to the choice of the most appropriate therapy for secondary stroke prevention.

Conclusions

In CS, increased PWD and abnormal P-wave axis are independent predictors of AF, resulting in useful and inexpensive tools with which to identify the subset of patients who should undergo prolonged screening for AF. A more accurate detection of AF in these patients could be beneficial in order to choose the most appropriate therapy for secondary stroke prevention.

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Conflict of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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