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P wave analysis with wavelets identifies hypertensive patients at risk of recurrence of atrial fibrillation: A case–control study and 1 year follow-up

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Abstract

Aims: Hypertension is a major risk factor for atrial fibrillation (AF); however, reliable non-invasive tools to assess AF risk in hypertensive patients are lacking. We sought to evaluate the efficacy of P wave wavelet analysis in predicting AF risk recurrence in a hypertensive cohort.

Methods: We studied 37 hypertensive patients who presented with an AF episode for the first time and 37 age- and sex-matched hypertensive controls without AF. P wave duration and energy variables were measured for each subject [i.e. mean and max P wave energy along horizontal (x), coronal (y) and sagittal (z) axes in low, intermediate and high frequency bands]. AF-free survival was assessed over a follow-up of 12.1 ± 0.4 months.

Results: P wave duration (Pdurz) and mean P wave energy in the intermediate frequency band across sagittal axis (mean2z) were independently associated with baseline AF status ($p = 0.008$ and $p = 0.001$, respectively). Based on optimal cut-off points, four groups were formed: Pdurz < 83.2 ms/mean2z < 6.2 μV^2 (n = 23), Pdurz < 83.2 ms/mean2z ≥ 6.2 μV^2 (n = 10), Pdurz ≥ 83.2 ms/mean2z < 6.2 μV^2 (n = 22) and Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2 (n = 19). AF-free survival decreased (Log Rank $p < 0.0001$) from low risk (Pdurz < 83.2 ms/mean2z < 6.2 μV^2) to high-risk group (Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2). Patients presenting with longer and higher energy P waves were at 18 times higher AF risk compared to those with neither (OR: 17.6, 95% CI: 3.7–84.3) even after adjustment for age, sex, hypertension duration, left atrial size, beta-blocker, ACEi/ARBs and statin therapy.

Conclusions: P wave temporal and energy characteristics extracted using wavelet analysis can potentially serve as screening tool to identify hypertensive patients at risk of AF recurrence.

Keywords: Atrial fibrillation; P wave wavelet analysis; Orthogonal ECG; Hypertension

Introduction

Hypertension is considered a major and independent risk factor for atrial fibrillation (AF) [1]. The proposed pathophysiological mechanisms linking hypertension with AF include left atrial enlargement [2] and renin-angiotensin system upregulation [3]. Nevertheless, the unique myocardial electrophysiological characteristics predisposing hypertensive patients to AF are still elusive.

Abbreviations: ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AF, atrial fibrillation; Band 1, high frequency band; Band 2, intermediate frequency band; Band 3, low frequency band; Pdur, P wave duration; ROC, receiver operating characteristics; SAECG, signal averaged ECG; X axis, horizontal; Y axis, coronal; Z axis, sagittal.

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It has been reported that slow electrical conduction or block and anisotropy within the atrial tissue underlie AF pathogenesis [4–7]. These defects are partly reflected in P wave prolongation and in distinct energy characteristics of its terminal part in signal averaged ECG (SAECG) studies [8]. Additionally, increased dispersion of P wave duration in 12-lead ECG has been reported as a marker of AF [9]. However, these small amplitude high frequency signals may be under-detected using SAECG especially if P wave morphology is not completely stable, i.e. if there are small beat to beat variations in their exact location, duration, frequency and amplitude. P wave patterns may also demonstrate spatial variability, another characteristic of AF, which would require an analysis using a three dimensional approach (i.e. axes x-y-z). Thus, in addition to the SAECG-based and classical time or frequency P wave analytics methods, metrics from the spectro-temporal space could be sought, to enable identification of the distribution of small time-scale, localized components at a broad range of frequencies.

Wavelet analysis is a sensitive method for the detection of electrical signals coinciding in time and frequency within the cardiac cycle, which would otherwise be masked using time-domain or frequency-domain methods. This principle has also been illustrated in the identification of ventricular late potentials [10]. Moreover, wavelet based P wave analysis is a non-invasive and inexpensive tool utilizing data derived from any ECG digital recording (e.g. standard Holter monitoring) which are further processed using dedicated software. This software module is available for use to all interested bodies and applications (e.g. telemonitoring, clinical trials). Earlier reports from our center support that P wave analysis can be applied for the prediction of paroxysmal AF recurrences in patients without structural heart disease [11], as well as in patients with hypertrophic cardiomyopathy at risk for paroxysmal AF [12]. More recently, we have demonstrated that wavelet analysis of QRS may predict response to cardiac resynchronization therapy [13].

The aims of the current study were to (i) assess whether P wave analysis with wavelets during sinus rhythm can accurately identify hypertensive patients with paroxysmal AF, and (ii) investigate prospectively whether certain P wave temporal and energy characteristics carry an independent predictive value over conventional AF risk factors for subsequent AF episodes.

Methods

Study population at the baseline

This study complies with the Declaration of Helsinki and the study protocol is shown in Fig. 1. The Institutional Medical Ethics Committee approved the research protocol and all patients gave written informed consent prior entering the study. We enrolled 37 consecutive patients (15 males, mean age ± SD 63.8 ± 7.3 years) with a history of hypertension who presented in the emergency department of our institution with their first symptomatic AF episode. The mean time ± SD elapsed between AF onset and patient admission was 5.8 ± 10.8 hours (range from 1 to 40 hours). Arrhythmia terminated spontaneously in 16 (43%) patients, with pharmacological cardioversion with amiodarone in 13 (35%) patients and with propafenone in 8 (22%) patients. Mean time ± SD until sinus rhythm restoration was 27.9 ±26 hours (range from 2 to 72 hours). An equal number (n =37) of age- and sex-matched hypertensive controls with no history of AF was also identified.

Echocardiography

All participants underwent transthoracic echocardiography at the baseline. In AF patients, echocardiography was performed at 10.5 ± 19 hours post-cardioversion. Left atrial diameter, left ventricular wall thickness, left ventricular end-diastolic and end-systolic diameter were assessed using 2D measurements from the parasternal long axis view. Left ventricular systolic and diastolic function was assessed using Simpson's biplane method and pulsed wave Doppler measurements of the mitral valve inflow respectively.

Electrocardiography and wavelet analysis

"Ten minutes long orthogonal ECG recordings were obtained from all study participants under resting conditions using Galix GBI-3SM three-channel digital recorder (Galix Biomedical Instrumentation, Inc. USA). The recordings were undertaken at a sampling rate of 1000/s using a pseudo-orthogonal lead configuration (Supplementary Table 1)." The X (horizontal) lead is positioned at the fourth inter-costal space from the right (negative) to the left (positive) mid-axillary line. The Y (coronal) lead is positioned from the superior aspect of the manubrium (negative) to proximal left leg (positive). The Z (sagittal) lead is positioned from the fourth inter-costal space on the left of the sternum (positive) to a position directly posterior to the left of the spine (negative) (Supplementary Fig. 1). In AF patients, P wave analysis recordings were obtained after sinus rhythm restoration. Antiarrhythmic drugs were discontinued for more than 5 half-lives and amiodarone for at least 2 months before the recordings.

All ECGs were digitized with a sampling frequency of 1 kHz. Thirty P waves were randomly selected from each subject's ECG recordings and pre-processed with amplitude normalization, baseline correction and filtering with a de-noising wavelet filter [14]. P wave onset and termination were manually identified for each cardiac cycle in each of the orthogonal ECG leads by two experienced electrophysiologists who were unaware of patients AF status.

Continuous wavelet transform using the Morlet basis function was applied for the P wave analysis at the horizontal, coronal and sagittal orthogonal axes using customized software [14]. The idea behind this analysis is the following: instead of transforming the signal into frequency components, as spectral analysis would do, a series of filtered versions of the signal is produced via the basis function, each one preserving temporal information and frequency information at a different range of frequencies, low or high. A time–frequency representation is formed and is further used to calculate specific features of the transformed ECG signal. Three time–frequency areas were defined, temporally confined by P wave duration, and in the frequency axis as high band (1): 200–161 Hz, intermediate band (2): 160–91 Hz, and low band (3): 90–50 Hz. Two parameters were calculated within each time–frequency area: (a) the "Max", maximum energy of the transformed P

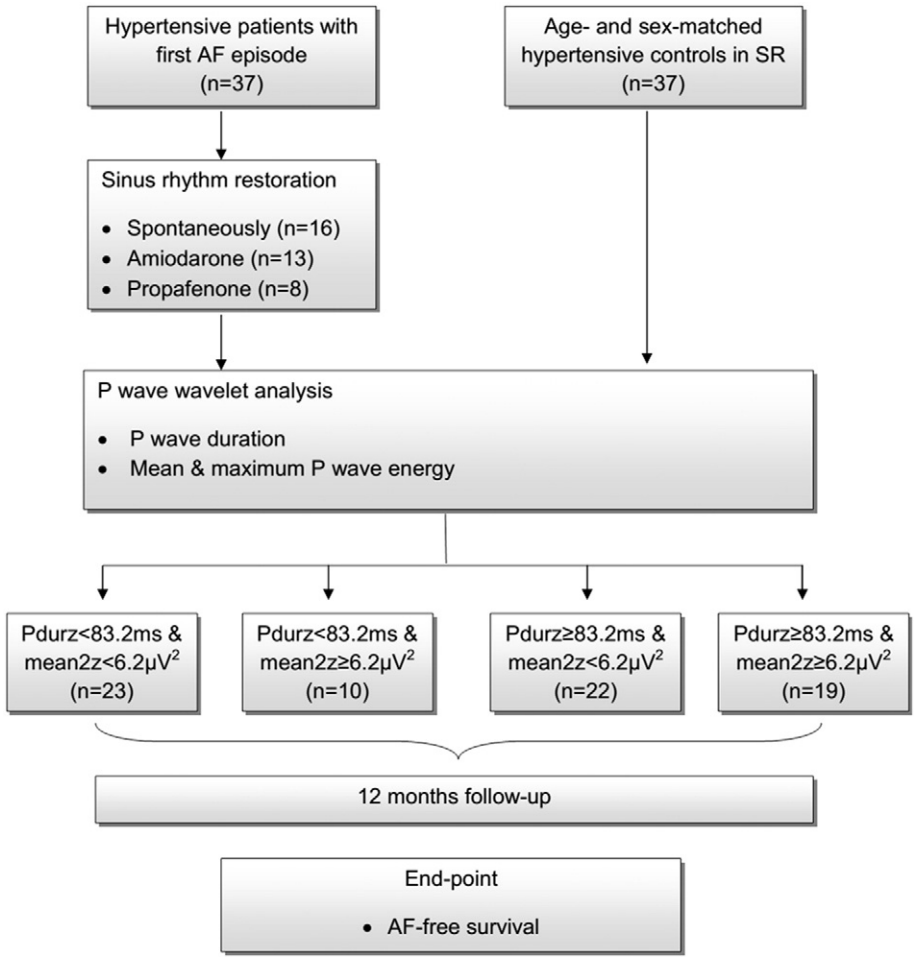


Fig.1. Study protocol.

wave in a given time–frequency area and (b) the "Mean", corresponding to the total energy of the transformed P wave in a given time–frequency area. For every study participant the "Mean" and "Maximum" ("Max") energy of the transformed P waves were calculated in each orthogonal lead, at three time–frequency areas. The terminology used to describe these wavelet variables is Mean or Max{band}{orthogonal lead}, e.g. Mean1x corresponds to the "Mean" energy of the transformed P wave in the high frequency band 1 (200–161 Hz) at horizontal orthogonal lead. In total, 18 transformed P wave energy variables were calculated for each subject (i.e. Mean and Max energy of the transformed P wave in three orthogonal leads in each of the three frequency bands).

Follow-up

P wave duration (Pdurz) and mean P wave energy in the intermediate frequency band at sagittal axis (mean2z) were independently associated with baseline AF status. Based on optimal cut-off values identified by ROC curve analysis, four groups of patients were formed: Pdurz < 83.2 ms/mean2z $< 6.2\ \mu V^2$ ($n = 23$), Pdurz < 83.2 ms/mean2z $\geq 6.2\ \mu V^2$ ($n = 10$), Pdurz ≥ 83.2 ms/mean2z $< 6.2\ \mu V^2$ ($n = 22$) and Pdurz ≥ 83.2 ms/mean2z $\geq 6.2\ \mu V^2$ ($n = 19$). In Fig. 2, P wave duration and time-scale representations of wavelet coefficients absolute values and wavelet energy in the intermediate frequency band at sagittal axis are displayed. Each set of panels corresponds to a representative case, one of each of the four patient groups identified. All study participants were prospectively followed-up for a mean ± SD of 12.1 ± 0.4 months. Our study's end-point was time to first AF episode.

AF recurrence assessment

All participants were instructed to check their pulse for two minutes twice a day using an electronic sphygmomanometer or a pulse oximeter irrespective of their symptomatic status. Previous studies using plethysmographic analysis of finger-tip pulse [15] or modified sphygmomanometer-based techniques [16] have been reported as both sensitive and specific in unmasking asymptomatic AF bouts. In the event of palpitations or lightheadedness extra pulse checks were performed. All participants were educated how to identify AF i.e. as an irregularly irregular rhythm. All patients were provided with a diary where the exact date and time of the first AF episode, duration and severity of associated symptoms should be documented.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) and categorical variables as absolute numbers and percentages. Variables were tested for normal

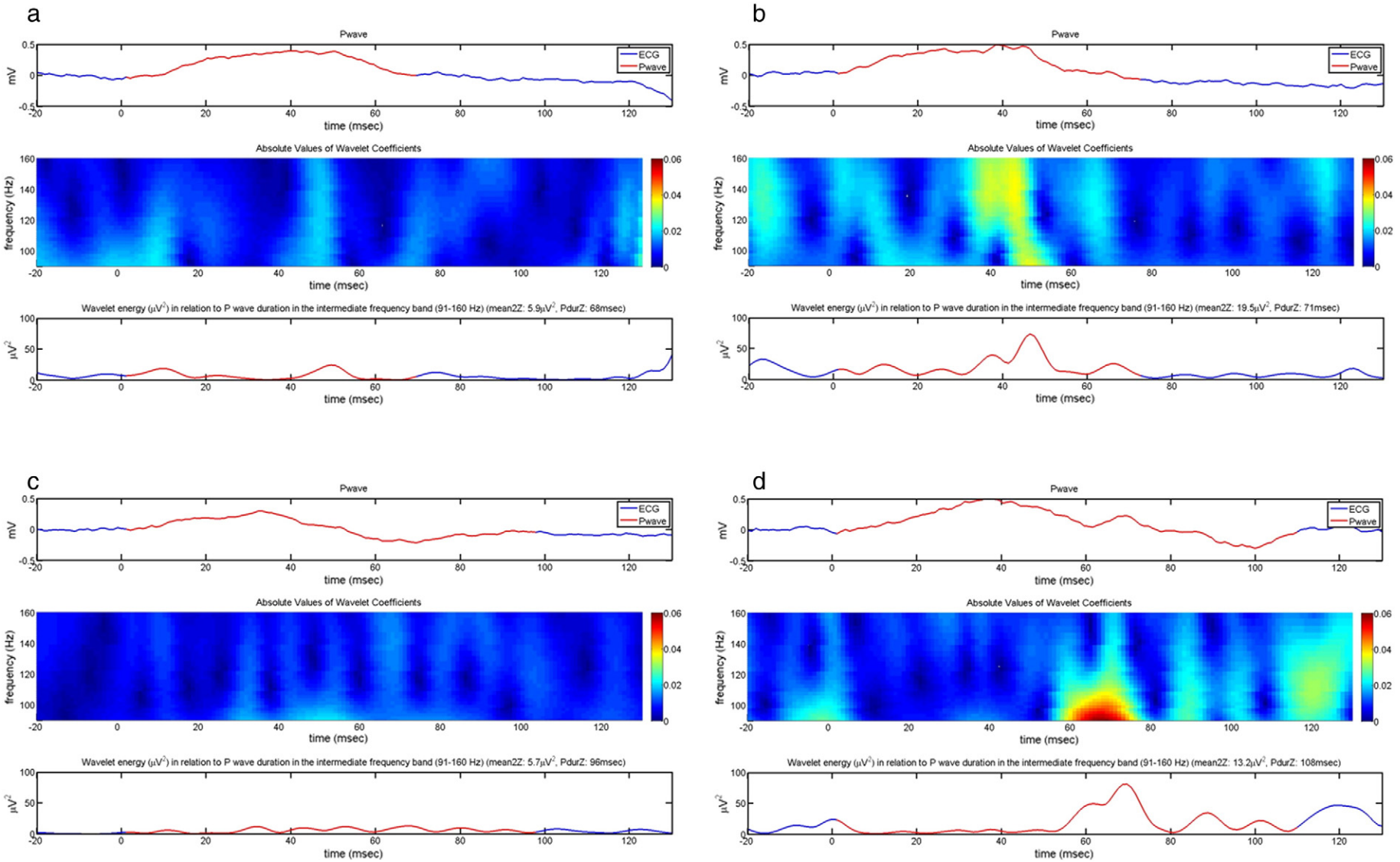


Fig. 2. Top panel: ECG tracing where P wave duration (ms) is denoted with red color. Middle panel: time–frequency graph illustrating P wave wavelet coefficients absolute values. Bottom panel: wavelet energy (μV^2) in relation to P wave duration (ms) in the intermediate frequency band (91–160 Hz) at sagittal axis. Each set of panels corresponds to a representative case, one of each of the four patient groups identified: **a.** Pdurz < 83.2 ms/mean2z < 6.2 μV^2, **b.** Pdurz < 83.2 ms/mean2z ≥ 6.2 μV^2, **c.** Pdurz ≥ 83.2 ms/mean2z < 6.2 μV^2 and **d.** Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2.

Table 1
Baseline demographics, clinical data and background medical therapy in the total population and stratified by AF status. Data are mean values ± SD or absolute figures (%).

	Total (n = 74)	AF+ (n = 37)	AF− (n = 37)	p
Age (years)	62.9 ± 7.9	63.8 ± 7.3	62.1 ± 8.4	0.364
Gender (male)	30 (40.5)	15 (40.5)	15 (40.5)	1.000
HTN (years)	9.3 ± 5.1	9.1 ± 4.9	9.5 ± 5.2	0.785
Diabetes mellitus	8 (10.8)	4 (10.8)	4 (10.8)	1.000
Dyslipidemia	27 (36.5)	14 (37.8)	13 (35.1)	0.809
Smoking	14 (18.9)	7 (18.9)	7 (18.9)	1.000
Alcohol (daily)	2 (2.7)	1 (2.7)	1 (2.7)	1.000
beta-Blockers	13 (17.6)	6 (16.2)	7 (18.9)	0.760
ACEi/ARBs	45 (60.8)	24 (64.9)	21 (56.8)	0.475
Statins	24 (32.4)	12 (32.4)	12 (32.4)	1.000
CCB	23 (31.1)	11 (29.7)	12 (32.4)	0.802
≥2 anti-HTN drugs	18 (24.3)	10 (27.0)	8 (21.6)	0.588
No anti-HTN drugs	11 (14.9)	6 (16.2)	5 (13.5)	0.744

ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers; HTN: hypertension.

distribution with the Kolmogorov–Smirnov test. Student's t-test for independent samples was used for the comparison of means of continuous variables with normal distribution and Mann–Whitney U-test was used for non-normally distributed continuous variables. Chi-square test was used for comparisons between proportions. Variables found to be significantly different between patients and controls with a p value < 0.01 were allowed to enter the multivariate model in a stepwise fashion. Forward Wald logistic regression analysis was applied to identify independent predictors of baseline AF status. Receiver operating characteristics (ROC) curves were employed to calculate optimal cut-off points and to assess the overall accuracy of each independent variable in distinguishing AF patients from controls. Kaplan–Meier analysis was applied to compare AF-free survival across patient groups. Cox regression analysis was performed to adjust survival curves for conventional AF risk factors. The statistical software SPSS (version 10.0.5, Chicago, IL, USA) was used for all analyses. A two-sided p value of 0.05 was considered to be statistically significant unless otherwise stated.

Table 2
Baseline echocardiographic parameters in the total population and stratified by AF status. Data are mean values ± SD.

	Total (n = 74)	AF+ (n = 37)	AF− (n = 37)	p
LAd (mm)	38.9 ± 4.4	39.4 ± 4.5	38.3 ± 4.4	0.278
LVEDD (mm)	50.0 ± 5.1	51.1 ± 5.9	48.9 ± 4.1	0.069
LVESD (mm)	28.2 ± 8.0	28.7 ± 8.5	27.7 ± 7.5	0.593
EF (%)	66.5 ± 6.6	67.5 ± 7.4	65.4 ± 5.7	0.172
IVSd (mm)	10.7 ± 2.2	10.5 ± 2.0	10.8 ± 2.0	0.555
PWd (mm)	9.6 ± 2.0	9.7 ± 2.0	9.5 ± 1.0	0.588
E/A	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.000

LAd = left atrial diameter measured in the parasternal long axis view at end-systole, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, IVSd = interventricular septum thickness at end-diastole, PWd = posterior wall thickness at end-diastole, EF = ejection fraction.

Table 3
Baseline P wave duration, mean and maximum P wave energy values measured at the three axes (horizontal, coronal, sagittal) in each frequency band (low, intermediate, high) in the total population and stratified by AF status. Data are mean values ± SD.

	Total (n = 74)	AF+ (n = 37)	AF− (n = 37)	p
Horizontal axis				
Pdurx (ms)	75.9 ± 14.3	78.2 ± 14.0	73.6 ± 14.5	0.178
Mean1x (μV^2)	2.2 ± 1.9	2.5 ± 2.4	2.0 ± 1.0	0.240
Mean2x (μV^2)	5.0 ± 3.6	5.4 ± 4.4	4.6 ± 2.5	0.295
Mean3x (μV^2)	27.7 ± 19.6	30.7 ± 22.9	24.8 ± 15.6	0.198
Max1x (μV^2)	10.5 ± 3.6	10.6 ± 4.0	10.5 ± 3.1	0.947
Max2x (μV^2)	14.8 ± 4.9	14.9 ± 5.1	14.7 ± 4.7	0.905
Max3x (μV^2)	30.0 ± 10.9	30.8 ± 11.4	29.3 ± 10.6	0.574
Coronal axis				
Pdury (ms)	89.0 ± 15.2	92.8 ± 18.0	85.2 ± 10.7	**0.031**
Mean1y (μV^2)	3.0 ± 2.3	3.5 ± 2.9	2.4 ± 1.3	**0.037**
Mean2y (μV^2)	6.5 ± 4.7	7.6 ± 5.9	5.3 ± 2.8	**0.032**
Mean3y (μV^2)	35.5 ± 35.7	45.9 ± 45.9	25.1 ± 16.0	**0.013**
Max1y (μV^2)	11.7 ± 3.9	12.5 ± 4.3	10.9 ± 3.3	0.070
Max2y (μV^2)	16.4 ± 5.5	17.6 ± 6.3	15.3 ± 4.3	0.064
Max3y (μV^2)	32.8 ± 12.7	36.4 ± 15.1	29.2 ± 8.7	0.013
Sagittal axis				
Pdurz (ms)	85.0 ± 18.0	93.7 ± 15.7	76.3 ± 15.8	**<0.001**
Mean1z (μV^2)	3.1 ± 2.1	4.1 ± 2.3	2.0 ± 0.9	**<0.001**
Mean2z (μV^2)	7.3 ± 5.2	10.1 ± 5.9	4.5 ± 2.2	**<0.001**
Mean3z (μV^2)	39.9 ± 40.0	57.7 ± 49.7	22.1 ± 11.3	**<0.001**
Max1z (μV^2)	12.0 ± 3.9	13.9 ± 4.3	10.2 ± 2.3	**<0.001**
Max2z (μV^2)	17.4 ± 6.0	20.3 ± 6.5	14.4 ± 3.7	**<0.001**
Max3z (μV^2)	35.3 ± 14.2	41.0 ± 16.6	29.6 ± 8.3	**<0.001**

Pdur = P wave duration, Mean1 = mean energy at the low (50–90 Hz) frequency band, Mean2 = mean energy at the intermediate (91–160 Hz) frequency band, Mean3 = mean energy at the high (161–200 Hz) frequency band, Max1 = max energy at the low (50–90 Hz) frequency band, Max2 = max energy at the intermediate (91–160 Hz) frequency band, Max3 = max energy at the high (161–200 Hz) frequency band, X = horizontal axis, Y = coronal axis, Z = sagittal axis.

Results

Clinical and echocardiographic characteristics at baseline

Baseline demographics, clinical characteristics and background medical therapy between patients and controls are shown in Table 1. Left atrial diameter, left ventricular size and wall thickness, left ventricular systolic and diastolic function are presented in Table 2. There was no statistically significant difference in any of the clinical or echocardiographic characteristics between AF and non-AF patients.

P wave duration and energy characteristics at baseline

P wave wavelet analysis was applied in the whole population and P wave duration, mean and maximum P wave energies were calculated in each of the three axes (horizontal, coronal, sagittal) in each frequency band (low, intermediate, high). The results from between-group comparisons are outlined in Table 3. None of the P wave temporal and wavelet energy characteristics measured in the horizontal axis was statistically different between AF and non-AF patients. Conversely, P wave duration and most of P wave energy variables measured in the coronal and sagittal axes were significantly different between AF and non-AF patients.

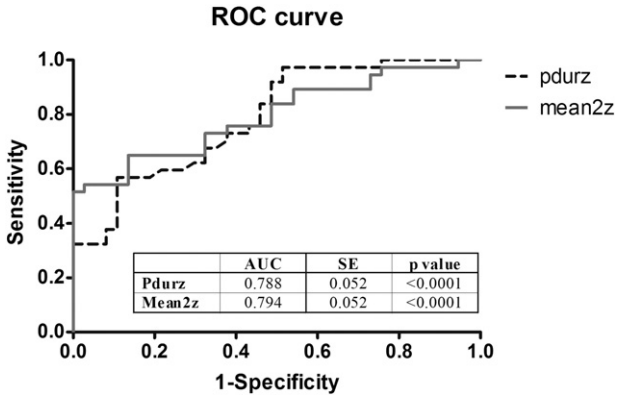


Fig. 3. ROC curve analysis showing the relationship between sensitivity and specificity of Pdurz and mean2z with respect to baseline AF status.

Independent predictors of baseline AF

Variables that were found to be significantly different between AF and non-AF patients with a p value < 0.01 were entered in multivariate analysis. Forward Wald logistic regression analysis revealed that Pdurz and mean2z were independently associated with baseline AF status (Supplementary Table 2). ROC curve analysis was employed to identify optimal cut-off values and to assess associated sensitivity, specificity and diagnostic accuracy (Fig. 3). A cut-off point for Pdurz at 83.2 ms identified AF patients with 73% sensitivity, 62.2% specificity and 67.6% accuracy. Setting the cut-off point for mean2z at 6.2 μV^2, AF patients were identified with a sensitivity of 65%, a specificity of 86.5% while test's overall accuracy was 75.8%.

AF-free survival

The whole cohort was stratified into four groups based on baseline Pdurz and mean2z values as follows: Pdurz < 83.2 ms/mean2z < 6.2 μV^2 (n = 23) (reference group), Pdurz < 83.2 ms/mean2z ≥ 6.2 μV^2 (n = 10), Pdurz ≥ 83.2 ms/mean2z < 6.2 μV^2 (n = 22) and Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2 (n = 19). During a mean ± SD follow-up of 12.1 ± 0.4 months, a total of 73 AF episodes were recorded in 24 patients. No AF episodes were observed in the control group during the whole study period. The mean time ± SD until the first AF episode was 154.3 ± 109.6 days (range from 5–334 days). AF-free survival was significantly different across patient categories (Log Rank p < 0.0001). Patients in Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2 group experienced the shortest AF-free survival compared to the other groups (Fig. 4). Similar results were obtained when only the patients presenting with an AF episode (n = 37) were studied. In this subgroup of patients, there was a strong trend (Log Rank p = 0.07) toward reduced AF-free survival among those combining both prolonged and higher energy P waves (n = 17) compared to those with P waves of shorter duration and/or lower energy (n = 20) (Supplementary Fig. 2). The observed difference in AF-free survival across patient categories persisted even after adjustment for conventional AF risk factors including age, sex, duration of hypertension, left atrial diameter, beta-blocker, ACEi/ARBs and statin therapy. Patients with the longest P wave duration and highest energy profile in the sagittal axis (i.e. Pdurz ≥ 83.2 ms/mean2z ≥ 6.2 μV^2) were at 18-times higher AF risk compared to the reference group (i.e. Pdurz < 83.2 ms/mean2z < 6.2 μV^2) (OR: 17.6, 95% CI: 3.7–84.3, p = 0.00032).

Discussion

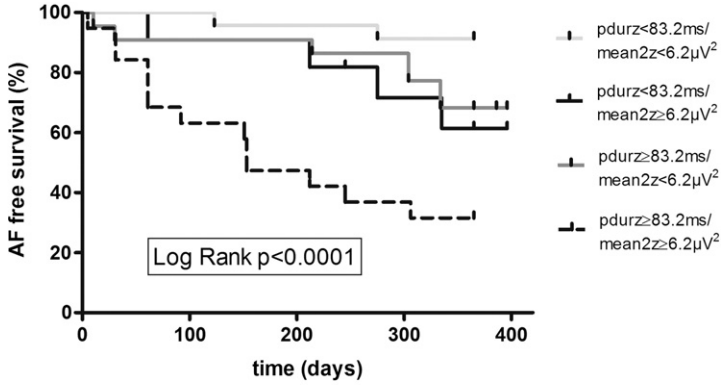
In the present study we have demonstrated that hypertensive patients with paroxysmal AF of recent onset are characterized by higher P wave energy values and prolonged P wave duration compared to a cohort of age- and sex-matched hypertensive controls. Moreover, individuals combing both a Pdurz ≥ 83.2 ms and a mean2z ≥ 6.2 μV^2 experienced the shortest AF-free survival during follow-up. This excess AF risk persists even after taking into account conventional disease modifiers including age, sex, left atrial diameter, duration of hypertension and background therapy with drugs with potentially anti-arrhythmic properties including beta-blockers, ACEi/ARBs and statins.

Despite the generally acknowledged role of P wave prolongation in the pathogenesis of AF, AF patients without structural heart disease may harbor local irregularities of atrial conduction without any significant P wave prolongation [17]. These discrepancies have been identified and were qualitatively referred to as differences in P wave morphology. The novelty in this study is that the electrophysiological derangements associated with AF, known as the AF substrate, can be unmasked and quantified as well, through identification of energy and temporal characteristics of wavelet components hidden within the large P waves of the surface ECG.

P wave duration and AF risk

Reentry is one of the pathophysiological mechanisms that is thought to underlie AF [4] therefore, detection of atrial conduction abnormalities facilitating reentrant circuits is critical. The prolongation of P wave duration assessed by SAECG was considered to be a sensitive surrogate marker for atrial conduction disorders suggesting slowed atrial conduction [18]. Furthermore, maximum P wave duration on surface ECG has been established as an independent predictor of AF in hypertensive patients [19]. Slowing of atrial conduction velocity leading to longer P waves was also reported in hypertensive patients in 30% of who sustained AF was induced [20].

In our study we have demonstrated that P wave duration at sagittal axis was significantly prolonged in hypertensive patients who presented with the first episode of AF compared to age- and sex-matched hypertensive controls. This finding reinforces the hypothesis that slow atrial conduction and block are essential electrophysiological elements of the AF substrate predisposing to reentry. Of note, P wave wavelet analysis was undertaken shortly after the first clinically evident AF episode. This is of particular importance as AF per se is known to promote further atrial remodeling thus forming a vicious cycle although the time needed for this



N° at risk					
Pdurz<83.2ms & mean2z<6.2μV²	23	23	22	21	21
Pdurz<83.2ms & mean2z>=6.2μV²	10	9	9	7	7
Pdurz>=83.2ms & mean2z<6.2μV²	22	20	20	19	16
Pdurz>=83.2ms & mean2z>=6.2μV²	19	12	9	7	6

Fig. 4. Kaplan–Meier analysis of AF-free survival across patient categories. In the table below, each row corresponds to one of the four study groups while each column depicts the number of participants at baseline and those remaining free from AF recurrence at 100, 200, 300 days and at the end of follow-up.

may vary among patients due to anatomical and arrhythmogenic substrate related individual characteristics. The fact that mean left atrial diameter both among AF and non-AF patients was <40 mm suggests that the observed atrial conduction abnormalities preceded any structural alterations associated with AF-induced atrial remodeling process. Our findings are consistent with those of earlier SAECG studies, where P wave duration was positively associated with AF risk independently of atrial size [8].

P wave energy and AF risk

Present data support the identification of AF substrate through mapping of complex fractionated atrial electrograms and low voltage regions during sinus rhythm [21]. Regional atrial voltage reduction due to fibrosis and an increased prevalence of complex fractionated atrial electrograms during sinus rhythm have been associated with AF in a wide spectrum of diseases, including hypertension [22]. Recordings from complex fractionated atrial electrograms regions demonstrated a higher mean voltage both during AF [21] and sinus rhythm [22] compared to signals corresponding to non-complex fractionated atrial electrograms sites. In our study, the higher P wave energy values in the sagittal axis among hypertensive patients with new onset AF may actually represent high amplitude signals stemming from complex fractionated atrial electrograms sites. These subtle fluctuations in P wave energy values unmasked by wavelet analysis provide incremental data compared to the standard ECG, which can only provide a rough estimation of P wave duration.

Clinical implications

AF-free survival was significantly decreased in patients with broad, high energy P waves compared to those with narrow, low energy P waves. The higher propensity to AF in patients with a longer P wave i.e. Pdurz ≥ 83.2 ms and higher P wave energies at the sagittal axis i.e. mean2z ≥ 6.2 μV^2 may reflect more diffuse conduction defects. Apparently, in the presence of more extensive electrophysiological derangements, AF threshold becomes significantly lowered. These patients may benefit from closer monitoring, more aggressive anti-arrhythmic drug therapy or early referral for AF ablation. Randomized controlled trials allocating hypertensive patients with paroxysmal AF to tight versus lenient monitoring and/or anti-arrhythmic therapy based on their baseline P wave duration and energy characteristics are needed before definite conclusions could be drawn.

Limitations

This is a pilot, single-center, hypothesis generating study recruiting a limited number of patients with a relatively short follow-up. A larger prospective clinical study would provide more robust evidence on the role of wavelets in AF. Patients with AF frequently have enlarged left atria with longer P wave duration and fractionation. Hence, we aimed to recruit patients presenting with an AF episode for the first time in order to avoid AF-induced alterations in left atrial anatomical and electrical substrate confounding our results. However, given the insidious clinical course of the disease, we cannot rule out the possibility of earlier episodes of subclinical AF that were self-terminated. The same caveat lies in the identification of AF recurrences which was limited by the participants' perception of symptoms and ability to identify rhythm abnormalities via self-monitoring. Baseline AF status was not included among the variables entered in the multivariate model as none of the controls developed AF during follow-up. Our control group included patients who were relatively young (mean age 62 years) and with non-dilated left atria (mean left atrium diameter of 38 mm). The annual risk of incident AF is therefore low and the follow-up period of 12 months is insufficient to detect events in this group of patients. In logistic regression

analysis seven wavelet parameters were included as independent variables in the model while in Cox regression analysis one wavelet and seven clinical parameters were considered as covariates. However, given the relatively small sized population of our study, the robustness of calculated beta values and odds ratios might be considerably affected. Among agents used for chemical cardioversion of AF, amiodarone has a very prolonged and often unpredictable half-life; therefore, it is difficult to rule out any potential drug effects on the reported P wave duration and amplitude.

Conclusions

Wavelet analysis is a non-invasive, inexpensive and easy to apply tool which can reveal subtle abnormalities in P wave temporal and energy characteristics, and thereby identify AF patients after successful cardioversion from an otherwise identical cohort of hypertensive patients with no history of AF. Hypertensive patients with more pronounced derangements in atrial impulse formation and propagation – reflected by P waves that are longer in duration and carrying a higher mean energy – experienced a significantly decreased AF-free survival during follow-up. Larger epidemiological studies including different patient populations and a longer follow-up are needed to establish the value of P wave wavelet analysis as a screening tool for paroxysmal AF.

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Conflicts of interest

None.

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