International Journal of Cardiology 153 (2011) 165–172

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Novel non-invasive P wave analysis for the prediction of paroxysmal atrial fibrillation recurrences in patients without structural heart disease
A prospective pilot study

Vassilios Vassilikos [a], George Dakos [a], Yiannis S. Chatzizisis [a,*], Ioanna Chouvarda [b], Charalambos Karvounis [a], Charles Maynard [c], Nicos Maglaveras [b], Stylianos Paraskevaidis [a], George Stavropoulos [a], Charalambos I. Styliadis [a], Sotirios Mochlas [a], Ioannis Styliadis [a]

[a] 1st Cardiology Department, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
[b] Medical Informatics Laboratory, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
[c] Department of Health Services, University of Washington, Seattle, WA, United States

ARTICLE INFO

Article history:
Received 21 March 2010
Received in revised form 1 July 2010
Accepted 8 August 2010
Available online 15 September 2010

Keywords:
Paroxysmal atrial fibrillation
P wave
Wavelet analysis

ABSTRACT

Objectives: The pathogenetic mechanisms responsible for the initiation and recurrence of PAF are not fully elucidated and vary among individuals. We evaluated the ability of a novel non-invasive approach based on P wave wavelet analysis to predict symptomatic paroxysmal atrial fibrillation (PAF) recurrences in individuals without structural heart disease.

Methods: We studied 50 patients (24 males, mean age 54.9 ± 9.8 years) presented to our emergency department with a symptomatic episode of PAF. The patients were followed-up for 12.1 ± 0.1 months and classified into two groups according to the number of PAF episodes: Group A (<5 PAF, $n = 33$), Group B (≥5 PAF, $n = 17$). A third Group of 50 healthy individuals without history of PAF was used as control. Study groups underwent echocardiography and orthogonal ECG-based wavelet analyses of P waves at baseline and follow-up. Maximum and mean P wave energies were calculated in each subject at each orthogonal lead using the Morlet wavelet analysis.

Results: Larger P wave energies at X lead and relatively larger left atrium were independently associated with >5 PAF episodes vs. <5 PAF episodes. No difference in P wave duration was detected between Groups A and B ($p > 0.1$), whereas Group A and B patients had longer P waves at Z lead compared to Group C (86.4 ± 13 vs. 71.5 ± 15 msec, $p < 0.001$).

Conclusions: P wave wavelet analysis can reliably predict the generation and recurrence of PAF within a year. P wave wavelet analysis could contribute to the early identification of patients at risk for increased number of PAF recurrences.

1. Introduction

Paroxysmal atrial fibrillation (PAF) is the most common sustained cardiac arrhythmia in clinical practice, and the number of patients affected worldwide is increasing [1–3]. Even though PAF is self-limited, the rapid, ineffective atrial activity with the irregular ventricular response may lead to serious complications, including decreased exercise capacity and quality of life, thromboembolic events, congestive heart failure, and tachycardia-induced cardiomyopathy [4,5]. Furthermore, PAF recurrences are associated with increased cardiovascular morbidity and mortality [6,7]. The pathogenetic mechanisms responsible for PAF initiation and recurrences are still under investigation. Electrical and structural remodeling of the heart, focal triggers in the pulmonary veins, abnormalities in intracellular calcium handling and genetic predisposition appear to play a major role [8]. Understanding of the pathophysiological mechanisms underlying PAF and assessment of atrial electrophysiological properties using easily available non-invasive diagnostic tools are essential for further improvement of patient-tailored treatment strategies.

Studies have shown that P wave duration measured either on the traditional surface ECG or in the signal-averaged ECG could serve as a reasonable non-invasive marker of atrial conduction disturbances [9–11]. These studies have shown that P wave prolongation is associated with PAF recurrences. Other investigations have underscored the importance of P wave morphology in the prediction of PAF recurrences [3]. In addition to P wave duration and morphology analysis, our group has introduced the Morlet wavelet analysis of P

* Corresponding author. 1st Cardiology Department, AHEPA University Hospital, Aristotle University Medical School, 1 Stylponos Kyriakidi Street, Thessaloniki, 54636, Greece. Tel./fax: +30 2310 994837.
E-mail address: joc@med.auth.gr (Y.S. Chatzizisis).

0167-5273/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2010.08.029

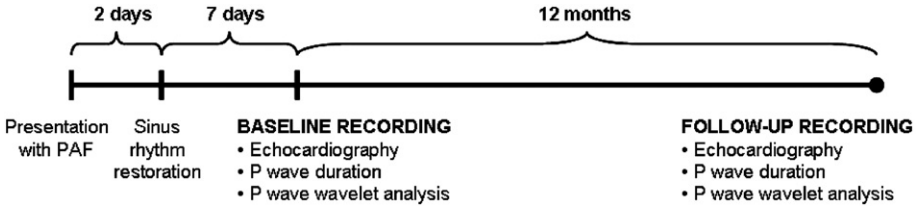

Fig. 1. Study protocol.

waves that is a novel technique of orthogonal ECG analysis based on the combination of time-domain and frequency-domain. This technique has been found useful in the detection of small signal components hidden in large ECG waves [12]. Furthermore, it appears to be superior to signal-averaged ECG in its ability to reveal dynamic changes occurring during the whole cardiac cycle [13], as well as to identify coronary heart disease patients who are prone to PAF post coronary aorta by-pass grafting surgery [14]. In this setting, P wave wavelet analysis could potentially be useful in understanding the impact of electrical atrial activation and remodeling on PAF recurrences.

The purpose of our study was to evaluate the potential of a novel non-invasive approach based on the Morlet wavelet analysis of P waves to predict symptomatic PAF recurrences in subjects without clinically and echocardiographically evident structural heart disease.

2. Methods

2.1. Study population

We studied 50 randomly selected patients (24 males, mean age 54.9 ± 9.8 years) presented to our emergency department with an episode of symptomatic PAF from January 2006 to January 2009. Of them, 14 patients had a first episode and 36 had a recurrent episode of PAF. Patients with structural heart disease, hyperthyroidism, alcohol abuse and pulmonary disease were excluded from the study. To minimize the effect of atrial enlargement in our results, individuals with left atrial diameter more than 4 cm at baseline were also excluded.

Patients were followed-up for 12.1 ± 0.1 months (from 11.5 to 12.7 months) and classified into two groups according to the number of PAF recurrences per year: Group A with less than five recurrences per year ($n = 33$, 16 males, mean age 53.4 ± 11 years, 3 ± 2 recurrences per year) and Group B with more than five recurrences per year ($n = 17$, 8 males, mean age 58.3 ± 7 years, 15 ± 6 recurrences per year). A third Group (Group C) of 50 individuals (19 males, mean age 56 ± 9 years), age- and gender-matched to Groups A and B, without any history of PAF or structural heart disease was used as the control group. Detailed demographic and clinical characteristics of the study groups are presented in Table 1. Although Group A and Group B patients did not differ in terms of the time in AF, Group B patients had more PAF episodes in their medical record, these episodes were longer and the time in sinus rhythm until last PAF episode was longer compared to Group A patients (Table S1, Online Data Supplement).

All study subjects underwent transthoracic echocardiography and ECG analyses as described below at baseline and follow-up (Fig. 1). The baseline recordings were performed 7 days after sinus rhythm restoration to minimize the potential effect of stunning and immediate post-conversion electrical instability in our results. Sinus rhythm was restored at 23 ± 16 h (from 1 h to 58 h) from the estimated time of onset of PAF. Termination of PAF was achieved spontaneously in 34 (70%) patients, with loading dose of propaphenone per os in 10 (18%) patients, with loading dose of amiodarone intravenously in 3 (6%) patients, with ibutilide intravenously in 1 (2%) patient and with β-blockers intravenously in 2 (4%) patients. The follow-up study was performed at 12.1 ± 0.1 months (from 11.5 to 12.7 months) from the baseline.

The Institutional Medical Ethics Committee approved the research protocol and all patients gave written informed consent for their participation in the study.

2.2. Echocardiography

All study subjects underwent transthoracic echocardiography at baseline and follow-up. Left atrial diameter was calculated in the apical four-chamber view at the longitudinal and transversal axis, in end-diastole (longitudinal atrial diameter in diastole: Lald, transversal atrial diameter in diastole: Latd) and in end-systole (longitudinal atrial diameter in systole: Lals, transversal atrial diameter in systole: Lats).

2.3. Orthogonal ECG

Orthogonal ECG recordings were obtained from all study subjects at baseline and follow-up with the application of a three-channel digital recorder (Galix Biomedical Instrumentation, Inc. USA) [14]. The recordings were performed for 10 m with the study subjects at rest. The ECGs were digitized with a sampling frequency of 1000 Hz. Thirty consecutive P waves were selected from each subject's ECG and pre-processed with amplitude normalization, baseline correction and application of a denoising wavelet filter [15].

.2.3.1. P wave duration

P wave duration was assessed at baseline and follow-up in the orthogonal ECG. P wave start and end were manually identified in each cardiac cycle by two experienced electrophysiologists using a cursor on a high-resolution computer screen.. The inter-observer agreement and intra-observer agreement of the P wave measurements were significantly high ($r = 0.96$, $p < 0.001$ and $r = 0.92$, $p < 0.001$, respectively).

.2.3.2. P wave wavelet analysis

Continuous wavelet transform using the Morlet mother wavelet (*See* Appendix) was applied for the P wave analysis in the X, Y and Z orthogonal leads, as well as in the vector magnitude using a customized software [15] (Fig. 2a). The vector magnitude was calculated from the formula $\sqrt{(X^2 + Y^2 + Z^2)}$. The "Mean" and "Maximum" ("Max") energy (mV^2) of P waves were calculated in each orthogonal lead (i.e. X, Y, Z), as well as in the

Table 1
Baseline demographic and clinical characteristics of the study subject.

	Group A (<5 episodes/year)	Group B (>5 episodes/year)	Group C (control)	*p*
N	33	17	50	–
Age (years)	53.4 ± 11.0	57.9 ± 7.0	56.0 ± 9.0	$p > 0.05$
Male sex (%)	16(48)	8(47)	19(38)	$p > 0.05$
Hypertension (%)	15(45)	8(47)	20(40)	$p > 0.05$
Diabetes mellitus (%)	1(3)	1(5.8)	2(4)	$p > 0.05$
Dyslipidemia (%)	5(15)	2(12)	5(10)	$p > 0.05$
Smoking (%)	5(15)	2(12)	5(10)	$p > 0.05$
Alcohol (%)	1(3)	1(6)	1(2)	$p > 0.05$
Statins (%)	4(12)	2(12)	5(10)	$p > 0.05$
ACEIs/ARBs (%)	9(27)	5(29)	15(30)	$p > 0.05$
Calcium antagonists (%)	7(21)	5(29)	12(24)	$p > 0.05$
β-blockers (%)	11(33)	9(53)	6(12)	$p > 0.05^{A\ vs.B}$ **$0.02^{A\ vs.\ C}$** **$< 0.001^{B\ vs.\ C}$**
Propafenone (%)	9(27)	7(41)	0	$p > 0.05^{A\ vs.\ B}$ **$< 0.001^{A\ vs.\ C}$** **$< 0.001^{B\ vs.\ C}$**
Amiodarone (%)	5(15)	7(41)	0	$p > 0.05^{A\ vs.\ B}$ **$0.005^{A\ vs.\ C}$** **$< 0.001^{B\ vs.\ C}$**

Values are presented as mean ± SD or absolute number and percentages. ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers. β-blockers, propafenone and amiodarone correspond to treatment at baseline and during the follow-up.

vector magnitude in three frequency bands which were defined on the basis of P wave duration [i.e. high band (1): 200–160 Hz, medium band (2): 150–100 Hz, and low band (3): 90–50 Hz]. As shown in a representative example in Fig. 2b the "Mean" P wave energy in a given frequency band corresponded to the area under the spectral curve of P wave at that band, whereas the "Maximum (Max)" energy corresponded to the global maximum energy of the spectral curve of P wave at that band. Totally, 24 P wave energy variables were calculated for each subject (i.e. Mean and Max energy of P wave in three orthogonal leads and in the vector magnitude in each of the three frequency bands). The terminology that was used to describe these energy variables was Mean or Max{band}{orthogonal lead}, e.g. Mean1X corresponded to the "Mean" energy of P wave in the high band 1 (200–160 Hz) at X orthogonal lead (Fig. 2b).

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as absolute numbers and percentages. Using the student's *t*-test, we compared echocardiographic and P wavelet analysis variables in those subjects with and without recurrence of PAF. Similar comparisons were made for those subjects with at least one but less than five PAF recurrences per year and those with more than five PAF recurrences per year. Given the many comparisons of data, $p<0.001$ was chosen as the alpha level. Multivariate logistic regression was performed to determine the association of demographic, echocardiographic, and P wavelet analysis variables with PAF. We performed two separate analyses comparing a) any number of PAF recurrences vs. no PAF, and b) less than five PAF recurrences vs. more than five PAF recurrences. Variables with $p<0.10$ in bivariate analysis were allowed to enter in a stepwise fashion, with $p<0.05$ required for entry. A predicted probability of PAF recurrence was obtained from the logistic model and was then assessed using the c statistic or area under the receiver operating characteristic (ROC) curve. The statistical package SPSS (version 17.0, Chicago, IL, USA) was used for all analyses.

3. Results

There were no differences in the demographic parameters across the study groups (Table 1). All measurements in the study were done after sinus rhythm restoration. Of note, there was no difference in terms of medication with antiarrhythmic drugs between Groups A and B at baseline and during the follow-up (Table 1). The echocardiographic variables, P wave duration and P wave energies at baseline in PAF patients with self-terminated episodes ($n=34$ out of 50 patients, 70%) and in those with drug-terminated episodes ($n=16$ out of 50, 30%) were comparable.

3.1. Echocardiographic parameters among study groups

All PAF patients and controls had normal left atrial size and the rest echocardiographic parameters at baseline and follow-up (Table 2). There was no difference in the size of left atrium and left ventricle

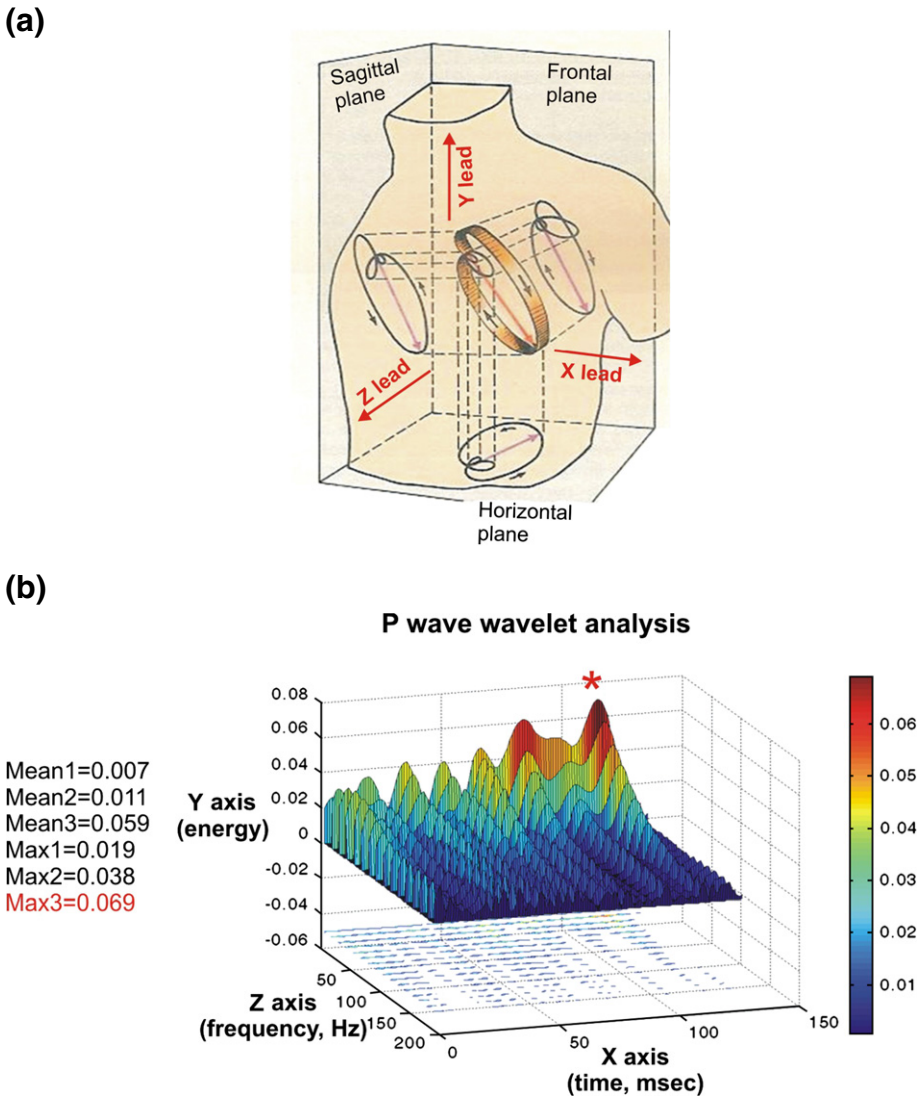

Fig. 2. a. Schematic representation of orthogonal leads, b. Representative figure of P wave wavelet transformation at X orthogonal lead. Time (P wave duration, msec) is shown at X axis, frequency (Hz) at Z axis and P wave energy values (mV^2) at Y axis. Mean1, Mean2 and Mean3 represent the mean energy of P wave (i.e. total area under the spectral curve) in the 1st (high, 160–200 Hz), 2nd (medium, 100–150 Hz) and 3rd (low, 50–90 Hz) frequency band, respectively. Max1, Max2 and Max3 represent the maximum energy of P wave (i.e. global maximum of the spectral curve) in the 1st, 2nd and 3rd frequency band, respectively. The red asterisk denotes the maximum energy of P wave which occurred at the 3rd frequency band (low band, 50–90 Hz).

Table 2
Echocardiographic parameters of the study subjects at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
Lald (cm)	4.98 ± 0.7	5.33 ± 0.3	0.055	5.09 ± 0.6	4.69 ± 0.6	**0.012**
Latd (cm)	2.91 ± 0.5	3.32 ± 0.7	0.026	3.04 ± 0.6	3.14 ± 0.5	0.510
Lals (cm)	4.24 ± 0.6	4.69 ± 0.5	**0.011**	4.39 ± 0.6	4.18 ± 0.6	0.170
Lats (cm)	2.36 ± 0.5	2.54 ± 0.6	0.193	2.39 ± 0.5	2.59 ± 0.5	0.130
LVDD (mm)	49.5 ± 4	49.3 ± 5	0.937	49.4 ± 4	46.5 ± 5	**0.019**
LVSD (mm)	28.5 ± 7	28.4 ± 10	0.207	28.4 ± 7	28.1 ± 7	0.380
EF (%)	66 ± 3	66 ± 3	0.656	66 ± 3	65 ± 5	0.160

Values are presented as mean ± SD. Lald: left atrial longitudinal diameter in end-diastole, Latd: left atrial transverse diameter in end-diastole, Lals: left atrial longitudinal diameter in end-systole, Lats: left atrial transverse diameter in end-systole, LVDD: left ventricular diastolic dimension, LVSD: left ventricular systolic dimension, EF: ejection fraction.

Table 3
P wave duration at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
PdurX (msec)	70 ± 8	71 ± 18	0.801	70.4 ± 12	70.7 ± 12	0.870
PdurY (msec)	81.6 ± 13	88.1 ± 14	0.117	83.8 ± 14	80 ± 12	0.130
PdurZ (msec)	85.8 ± 13	87.7 ± 13	0.630	86.4 ± 13	71.5 ± 15	<**0.001**
PdurVM (msec)	88.4 ± 14	91.2 ± 11	0.425	89.3 ± 13	81.8 ± 15	**0.008**

Pdur: P wave duration, X: X lead, Y: Y lead, Z: Z lead, VM: vector magnitude.

between baseline and follow-up for all study groups (follow-up data are not shown).

Patients with any number of PAF episodes (Groups A and B) had larger left atrial longitudinal diameter and left ventricular diameter in end-diastole compared to healthy controls at baseline and follow-up (lald; $p=0.012$; LVDD; $p=0.019$; Table 2), whereas the rest of the echocardiographic parameters were comparable.

Both at baseline and follow-up, Group B patients with more than five PAF recurrences per year had larger left atrial longitudinal diameter in end-systole compared to Group A patients with fewer than five PAF recurrences per year (lals; $p=0.011$, Table 2), whereas the rest of the echocardiographic parameters were comparable.

3.2. P wave duration among study groups

Patients with any number of PAF recurrences per year (Groups A and B) had significantly longer P waves at Z orthogonal lead compared to healthy controls (86.4 ± 13 vs. 71.5 ± 15 msec, $p<0.001$; Table 3), confirming the role of P wave duration in the prediction of PAF recurrences. There was no difference in P wave duration between Group A and B patients (Table 3).

3.3. Mean and maximum P wave energy values among study groups

The differences in P wave energy values among the study groups are shown in Table 4. Compared to controls, patients with PAF recurrences (Groups A and B) had significantly lower baseline Mean and Max energy values in the low frequency band in the X orthogonal lead (Mean3X, Max3X; $p<0.003$; Table 4). In the Z lead, patients with any number of PAF recurrences had higher baseline Mean and Max P wave energy values in the high (200–160 Hz), medium (150–100 Hz) and low (50–90 Hz) frequency band compared to healthy controls (Mean1Z, Mean2Z, Mean3Z, Max1Z, Max2Z; $p<0.01$). These differences in energy values along the X and Z lead remained significant during the follow-up

Table 4
Mean and maximum P wave energy values at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
Mean1X	1.55 ± 1	2.07 ± 0.9	0.081	1.73 ± 0.9	2.16 ± 1.2	0.059
Mean2X	3.18 ± 1.9	4.31 ± 2.1	0.077	3.56 ± 2.1	4.68 ± 2.6	0.020
Mean3X	14.1 ± 7.3	17.7 ± 17.2	0.309	15.3 ± 11.6	24.2 ± 15.7	**0.002**
Max1X	8.96 ± 2.9	11.1 ± 2.5	**0.013**	9.7 ± 2.9	10.8 ± 3.2	0.090
Max2X	12.3 ± 3.3	14.5 ± 3.5	0.041	13.1 ± 3.5	15 ± 4.3	0.020
Max3X	22.5 ± 5.9	27.7 ± 6.9	**0.014**	24.3 ± 6.7	29.3 ± 9.5	**0.003**
Mean1Y	2.25 ± 1.3	2.59 ± 1.8	0.503	2.36 ± 1.5	2.35 ± 1.4	0.960
Mean2Y	4.86 ± 2.9	5.67 ± 4.2	0.481	5.14 ± 3.4	5.34 ± 3.3	0.760
Mean3Y	27.8 ± 15.1	23.2 ± 17.2	0.337	26.2 ± 15.8	30.9 ± 23.1	0.240
Max1Y	10.5 ± 3.3	10.8 ± 4	0.721	10.6 ± 3.5	10.7 ± 3	0.890
Max2Y	14.6 ± 4.8	15.2 ± 6.7	0.772	14.8 ± 5.5	15.2 ± 4.3	0.690
Max3Y	29.7 ± 9	26.2 ± 10.2	0.223	28.5 ± 9.5	31.6 ± 10.3	0.120
Mean1Z	3.02 ± 2.2	3.58 ± 1.8	0.376	3.2 ± 2.1	2.09 ± 1.1	**0.001**
Mean2Z	7.39 ± 6.5	7.82 ± 4.3	0.808	7.54 ± 5.8	4.84 ± 2.9	**0.005**
Mean3Z	35.1 ± 21.9	44.6 ± 27.3	0.224	38.3 ± 24.1	27.9 ± 15.9	**0.012**
Max1Z	12.1 ± 3.9	13.2 ± 3.4	0.310	12.5 ± 3.8	10.5 ± 3	**0.005**
Max2Z	17.5 ± 5.8	18.5 ± 5.2	0.545	17.8 ± 5.6	15.2 ± 4.8	**0.013**
Max3Z	34.5 ± 10.4	38.7 ± 11.5	0.203	36 ± 10.8	31.4 ± 9.9	0.031
Mean1VM	2.26 ± 0.5	2.73 ± 1.5	0.222	2.42 ± 0.9	2.11 ± 09	0.100
Mean2VM	4.4 ± 1.6	4.06 ± 2.1	0.532	4.29 ± 1.8	4.22 ± 1.9	0.090
Mean3VM	17.9 ± 6.9	16.9 ± 11.9	0.747	17.6 ± 8.8	19.8 ± 12.9	0.320
Max1VM	9.7 ± 1.4	10.7 ± 3.1	0.235	10 ± 2.1	9.88 ± 2.1	0.720
Max2VM	13.6 ± 2.8	14.9 ± 4.9	0.334	14 ± 3.7	13.5 ± 3.4	0.460
Max3VM	25.8 ± 5.9	26.8 ± 9.8	0.666	26.1 ± 7.4	26.1 ± 6.8	0.960

Mean1, 2 and 3: mean energy value in the 1st, 2nd and 3rd frequency band, respectively, Max 1, 2 and 3: maximum energy value in the 1st, 2nd and 3rd frequency band, respectively, X: X lead, Y: Y lead, Z: Z lead, VM: vector magnitude. Energies are expressed in μV^2.

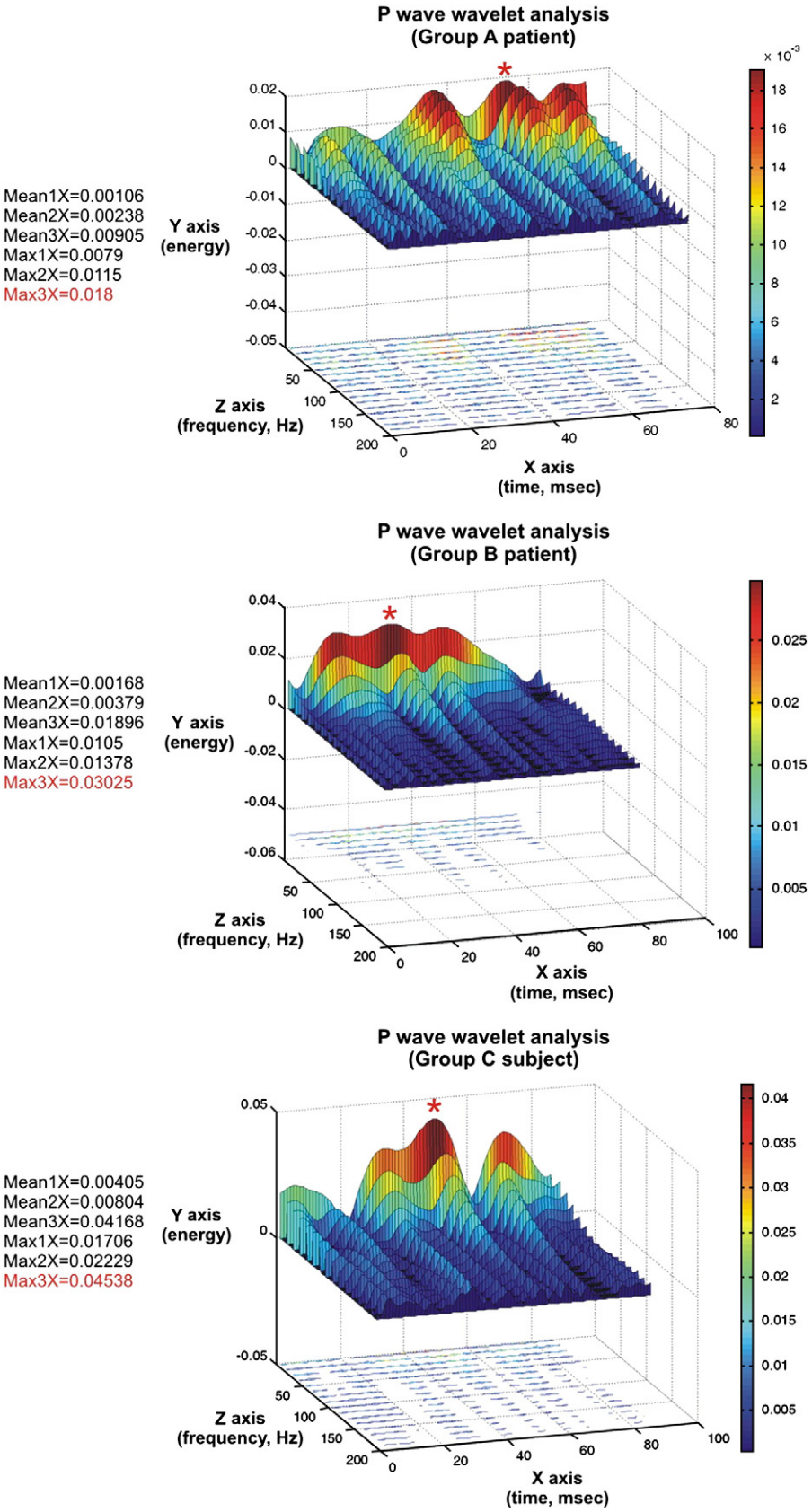

Fig. 3. P wave wavelet representations at X orthogonal lead. a) A patient with less than five PAF recurrences per year, b) A patient with more than five PAF recurrences per year, and c) A normal subject with no history of PAF. Time (P wave duration, msec) is shown at X axis, frequency (Hz) at Z axis and P wave energy values (mV^2) at Y axis. Mean1, Mean2 and Mean3 represent the mean energy of P wave in the 1st (high, 160–200 Hz), 2nd (medium, 100–150 Hz) and 3rd (low, 50–90 Hz) frequency band, respectively. Max1, Max2 and Max3 represent the maximum energy of P wave in the 1st, 2nd and 3rd frequency band, respectively. The red asterisks denote the maximum energy values of P wave. Note that the Max1X and Max3X are greater in the Group B patient compared to Group A patient.

(follow-up data are not shown). No significant differences in Mean and Max energy values were observed between patients with PAF recurrences and controls along the Y axis at baseline and follow-up.

Compared to Group A, Group B patients had significantly higher baseline maximum energy values in the high and low frequency band along the X axis (Max1X, Max3X; $p<0.02$; Table 4). These differences remained significant during the follow-up (follow-up data are not shown). The differences in the P wave energy values between Groups A, B and C are depicted in the representations of P wave wavelet analysis of Fig. 3.

3.4. Independent predictors of PAF recurrences

To identify the best predictors of increased PAF recurrences we applied stepwise logistic regression which revealed that increased P wave duration along the Z axis (PdurZ) and reduced baseline Mean energy of P wave in the low frequency band in X axis (Mean3X) were the best predictors of PAF recurrences (Table 5). Of note, the area under the receiver operating characteristics (ROC) curve for the combination of those best predictors was markedly significant (area under the curve: 0.85; $p<0.001$; Fig. 4a), suggesting that these two ECG parameters could be used to identify patients at risk to develop any number of PAF recurrences during a year of follow-up.

Application of logistic regression analysis between Groups A and B showed that the relatively larger left atrial longitudinal diameter during systole (lals) and the increased baseline Max P wave energy in the high frequency band in X axis (Max1X) were the best predictors for more than five vs. less than five PAF recurrences per year (Table 6). The area under the ROC curve for the combination of those best predictors was markedly significant (area under the curve: 0.80; $p=0.001$; Fig. 4b), suggesting that these echocardiographic and ECG parameters could be used to identify patients at risk to develop many vs. fewer PAF episodes during a year.

4. Discussion

In this prospective pilot study we utilized a novel P wave wavelet analysis in patients with PAF without clinically and echocardiographically evident structural heart disease. We demonstrated for the first time that certain P wave energy parameters derived from this P wave wavelet analysis can independently predict the occurrence and recurrence of PAF episodes during a year of follow-up. We further confirmed the implication of increased left atrial size and prolonged inter-atrial conduction (i.e. P wave duration) in PAF recurrences.

To date there have been proposed several non-invasive approaches for the prediction of PAF recurrences. P wave duration is generally accepted as the most reliable non-invasive measure of atrial conduction and its prolongation has been associated with paroxysmal PAF [16]. However, patients with PAF without structural heart disease may not have any impressive P wave prolongation, thus suggesting that global conduction slowing is not an obligatory requirement for the development of PAF [3]. In the absence of significant P wave prolongation in PAF patients without structural heart disease, the morphology of P wave has become an alternative non-invasive source

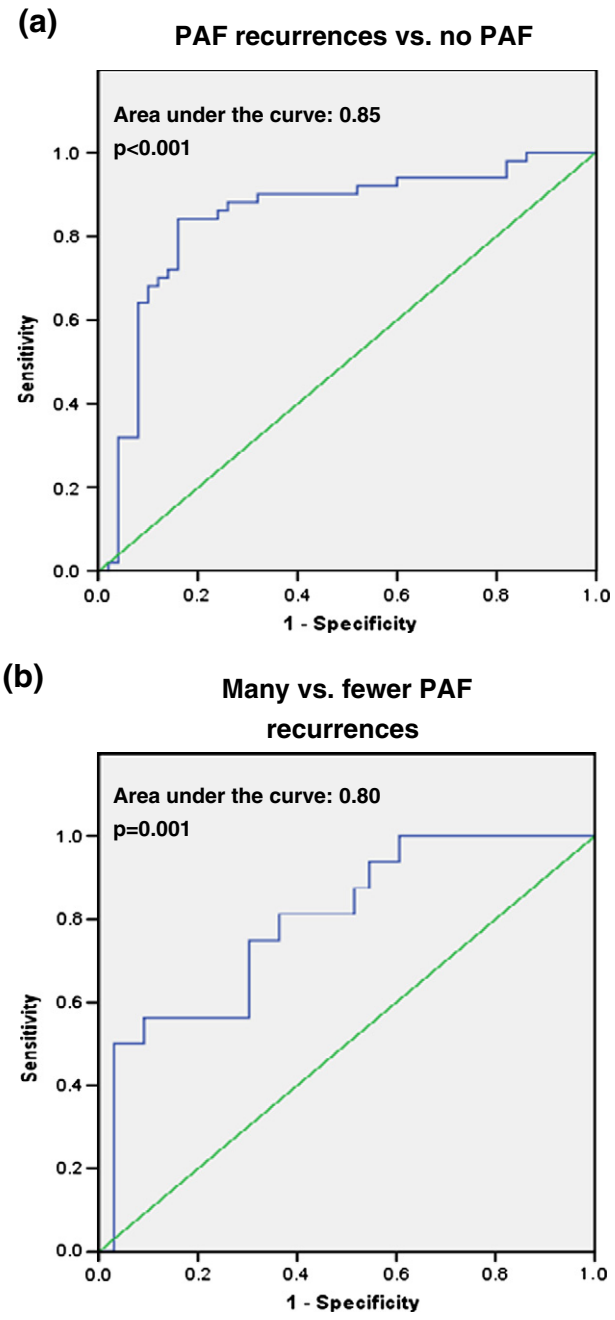

Fig. 4. Receiver operating characteristic (ROC) curves: a. Patients with any number of PAF recurrences vs. healthy controls without PAF for the parameters Mean3X and PdurZ, and b. Patients with more than five vs. patients with less than five PAF recurrences for the parameters lals and Max1X.

Table 5
Logistic regression analysis for patients any number of PAF recurrences per year (Groups A and B) vs. healthy controls without history of PAF (Group C).

		B	SE	p
Step 1	PdurZ	76.892	17.563	<0.001
	Constant	−6.073	1.409	<0.001
Step 2	Mean3X	−66.93	22.567	**0.003**
	PdurZ	84.114	18.775	<**0.001**
	Constant	−5.361	1.460	<0.001

Mean3X: mean P wave energy at the 3rd frequency band in the X orthogonal lead, PdurZ: P wave duration in the Z lead.

Table 6
Logistic regression analysis for PAF patients with more than five recurrences per year (Group B) vs. patients with less than five recurrences per year (Group A).

		B	SE	p
Step 1	Max1X	293.710	126.888	0.021
	Constant	−3.675	1.342	0.006
Step 2	Lals	1.551	0.678	**0.022**
	Max1X	308.018	139.925	**0.028**
	Constant	−10.80	3.651	0.003

Max1X: maximum P wave energy at the 1st frequency band in the X orthogonal lead, Lals: left atrial longitudinal diameter in end-systole.

of information concerning spatial propagation of atrial activation and its role in PAF recurrences [3]. However, the predicting ability of P wave morphology in PAF has not been confirmed. Our group has proposed a novel approach of P wave analysis based on the application of Morlet wavelets [14]. Morlet wavelet analysis is a non-invasive, easily applicable and inexpensive technique which can reveal dynamic, spectro-temporal ECG changes within certain frequency bands during the cardiac cycle. This technique differs from classical time-domain or Fourier analysis techniques in that it unmasks non-stationarities hidden in the ECG's constituent waves, thereby revealing the changes that occur in the generation and propagation of the electrical signal in the atria. Of note, the Morlet wavelets extend beyond the P wave analysis and can be used for the analysis of QRS or ST complexes to potentially investigate conduction abnormalities in a wide range of cardiovascular disorders, including hypertrophic cardiomyopathy and ischemic heart disease.

In the current study we demonstrated that patients with an increased number of PAF episodes in a year had significantly larger P wave energies in the X orthogonal lead at baseline. The clinical importance of that novel finding is based on the fact that P wave energy at X lead can be used to identify the subpopulation of PAF patients without structural heart disease who have the potential to develop increased PAF recurrences. In this setting, early pharmacological or invasive therapeutic approaches may be applied to avert future PAF events.

The pathogenesis of PAF initiation and recurrence remains a complex issue. Interplay of geometrical and electrophysiological properties of the atria which generate anisotropic (inhomogeneous) intra- and inter-atrial electrical conduction, especially in the horizontal orthogonal lead (X lead), may play a key role as indicated from the P wave wavelet analysis of the current study. The implication of anisotropic P wave conduction in the pathogenesis of PAF has been also suggested from prior studies conducted from our group in coronary aorta by-pass grafting surgery patients [14]. However, further clinical and experimental studies are warranted to elucidate the molecular and electrophysiologic characteristics of atria responsible for the anisotropic excitation patterns and their role in PAF generation and recurrences.

Intriguingly, we found that patients with many PAF recurrences had relatively larger left atrium, but still within the normal range, compared to patients with fewer PAF episodes. The rationale of enrolling PAF patients without clinically and echocardiographically evident structural heart disease or abnormally dilated left atrium (<4 cm) in our study was to minimize the influence of atrial remodeling in PAF recurrences. To adjust however for the effect of that minimal left atrial enlargement in PAF recurrences we performed logistic regression which revealed that P wave energy values in certain frequency bands and axes, as well as increased left atrial diameter were independent predictors of increased AF recurrences. The association of relatively increased left atrium with PAF recurrences is consistent with other studies and indicates the pathogenetic implication of left atrial size in PAF [17–19].

With regard to P wave duration, we showed that there was no difference in P wave length between patients with many vs. fewer PAF episodes. This finding is also in line with other studies which demonstrated that P wave prolongation does not always occur in lone PAF [3]. In contrast, we demonstrated that patients with any number of PAF recurrences had longer P waves, and therefore slower signal propagation, in Z orthogonal lead compared with healthy controls. Other studies have also shown that prolonged P wave duration is an independent predictor of new PAF events [3,8]. These results suggest that although the velocity of P wave conduction in the anteroposterior direction (Z axis) may play a key role in the generation of PAF recurrences it does not appear to be essential in the prediction of the frequency of these recurrences. Notably, in our study the P wave was measured on the orthogonal ECG. Although P wave duration on surface ECG could be of value, the P wave duration on the orthogonal ECG appears to be more sensitive in identifying AF recurrences.

4.1. Limitations

The major limitation within the current prospective study pertains to the small study population, especially in the groups of patients with more than five or less than five PAF episodes per year. However, the studied subjects were representative enough and all the groups were matched and homogeneous in terms of confounding factors, such as co-morbidities and medications. Our study is a pilot study which serves as a proof of concept by providing a novel clinical observation that P wave wavelet analysis may enable the prediction and pathophysiologic investigation of PAF recurrences in patients without structural heart disease. Further clinical studies in larger cohorts are warranted to confirm the importance of our findings.

The PAF episodes recorded in our study were all symptomatic bringing the patients to the hospital. Occurrence of asymptomatic episodes could not be excluded. Although we did not monitor our patients for asymptomatic episodes, such episodes could likely occur in both low and high frequency AF patients [20]. The effect of such asymptomatic episodes in atrial remodeling, P wave energies and subsequent symptomatic AF recurrences is not known.

The manual identification of P waves was a minor clinical and rate-limiting step in our P wave analysis process. Even though the time delay due to that manual intervention was not substantial we are currently working towards refining our software tool so that it can automatically identify the P waves.

5. Conclusions

Our study shows for the first time that Morlet wavelet analysis of P waves, which can be applied easily and inexpensively, can reliably predict the frequency of symptomatic PAF episodes in patients without clinically and echocardiographically evident structural heart disease. P wave wavelet analysis could advance our understanding of the electrophysiological mechanisms underlying PAF generation and recurrences and may enable the identification of high-risk patients for increased PAF recurrences, thereby creating the perspective of early application of non-invasive and invasive therapeutic strategies to avert future PAF events.

6. Conflicts of interest

None.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [22].

Appendix A. Supplementary data

Supplementary materials related to this article can be found online at doi:10.1016/j.ijcard.2010.08.029.

Appendix B

Wavelet transform of a time-series $f(t)$ is expressed as:

$$W(u,\alpha) = \frac{1}{\sqrt{\alpha}} \int f(t) \cdot \varphi\left(\frac{t-u}{\alpha}\right)^{*} dt,$$

where $\varphi(t)$ is the Morlet mother wavelet [21], expressed as:

$$\varphi(t) = \frac{1}{\sqrt{2\pi}\sigma} e^{-j\omega t} e^{-t^2/2\sigma^2}.$$

The outcome of the transform is a function $W(u,\alpha)$ of two variables, time and scale. Changing the scaling parameter α, results in a function with different frequency content and time spanning, and therefore each scale value corresponds to a function with a specific central frequency f which can be used instead of α for simplicity. $W(u,\alpha)$ constitutes a measure of the similarity between the mother wavelet and the base function scaled by α, in terms of common frequency content. The wavelet coefficient thus refer to this similarity at the specific frequency and time area, i.e. if the signal has a strong component at a specific frequency and time area, then due to its similarity with a scaled version of the mother wavelet, the wavelet components in that region will have high values.

Following the continuous wavelet analysis, three frequency bands were defined: Band 1: high band (160–200 Hz), Band 2: medium band (100–150 Hz) and Band 3: low band (50–90 Hz). Two energy parameters were calculated in each band in order to express the overall time-frequency characteristics:

a) "Max" corresponding to the maximum energy of P wave which was associated with the maximum energy of the P wave in a specific time-frequency area:

$$Max_i = \max\{W_{abs}(t,f)\}, \qquad t_i \le t < t_{i+1},\ f_i \le f < f_{i+1}$$

where f_i and f_{i+1} define the frequency band.

b) "Mean" corresponding to the mean energy of P wave which was associated with the total energy of the P wave in a specific time-frequency area:

$$Mean_i = \sqrt{\frac{\sum_{t=t_i}^{t_{i+1}} \sum_{f=f_j}^{f_{j+1}} |W(t,f)|^2}{num}}$$

where num is the total number of samples summed.

References

[1] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982;306:1018–22.

[2] Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the cardiovascular health study). Am J Cardiol 1994;74:236–41.

[3] Platonov PG. Atrial conduction and atrial fibrillation: what can we learn from surface ECG? Cardiol J 2008;15:402–7.

[4] Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med 2006:448.e1–448.e19.

[5] Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a veterans affairs cooperative studies program substudy. J Am Coll Cardiol 2006;48:721–30.

[6] Stewart S, Hart CL, Hole DJ, Mc Murray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.

[7] Benjamin EJ, Wolf PA, Agustino D, Silbershatz RB, Kannel H, Levy D WB. Impact of atrial fibrillation on the risk of death: the Framingham heart study. Circulation 1998;98:946–52.

[8] Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled research perspectives in atrial fibrillation. Europace 2009;11:860–85.

[9] Darbar D, Hardy A, Haines JL, Roden DM. Prolonged signal-averaged P-wave duration as an intermediate phenotype for familial atrial fibrillation. J Am Coll Cardiol 2008;51:1083–9.

[10] Aras D, Maden O, Ozdemir O, et al. Simple electrocardiographic markers for the prediction of paroxysmal atrial fibrillation in hyperthyroidism. Int J Cardiol 2005;99:59–64.

[11] Fukunami M, Yamada T, Ohmori M, et al. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. Circulation 1991;83:162–9.

[12] Morlet D, Peyrin F, Desseigne P, Touboul P, Rubel P. Wavelet analysis of high-resolution signal-averaged ECGs in postinfarction patients. J Electrocardiol 1993;26:311–20.

[13] Rubel V, J.Ph. Couderc, Morlet D, Fayn J, Peyrin F, Touboul P. Spectral Analysis of High-Resolution ECGs. In: Moss AJ, Stern S, editors. Non Invasive Electrocardiology. W.B.Saunders Company Ltd; 1996. p. 291–314.

[14] Vassilikos V, Dakos G, Chouvarda I, et al. Can P-wave wavelet analysis predict atrial fibrillation after coronary artery bypass grafting? Pacing Clin Electrophysiol 2003;26:305–9.

[15] Chouvarda I, Maglaveras N, Pappas C, Boufidou A. An integrated environment for ECG processing. Medinfo 1998;9:986–9.

[16] Stafford PJ, Turner I, Vincent R. Quantitative analysis of signal-averaged P waves in idiopathic paroxysmal atrial fibrillation. Am J Cardiol 1991;68:751–5.

[17] Thamilarasan M, Klein A. Factors relating to left atrial enlargement in atrial fibrillation: "chicken or the egg" hypothesis. Am Heart J 1999;137:381–3.

[18] Dittrich H, Pearce L, Asigner R, et al. Left atrial diameter in nonvalvular atrial fibrillation: an echocardiographic study. Stroke prevention in atrial fibrillation investigators. Am Heart J 1999;137:494–9.

[19] Pritchett A, Jacobsen S, Mahoney D, Rodeheffer R, Bailey K, Redfield M. Left atrial volume as an index of left atrial size: a population-based study. J Am Coll Cardiol 2003;41:1036–43.

[20] Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol 2004;43:47–52.

[21] Morlet D, Peyrin F, Desseigne P, et al. Time-scale analysis of high-resolution signal-averaged surface ECG using wavelet transformation. Proc IEEE 1992:393–6.

[22] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.