



Wavelet-based analysis of P waves identifies patients with lone atrial fibrillation: A cross-sectional pilot study

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ARTICLE INFO

Article history:

Received 20 February 2014

Accepted 31 March 2014

Available online 6 April 2014

Keywords:

Lone atrial fibrillation

Orthogonal ECG

Morlet wavelet

P wave analysis

Accumulating data suggest that lone atrial fibrillation (AF) has a multifactorial etiology [1–4]. The development of diagnostic tools to identify the individuals at risk to develop AF is important. P wave wavelet-based analysis is a novel non-invasive tool that can identify atrial conduction abnormalities [5,6]. The aim of this study was to investigate the hypothesis that P wave analysis with wavelets during sinus rhythm can identify patients without structural heart disease at risk to develop AF. Identification of these patients is important as it could advance our understanding of AF substrate characteristics guiding further therapeutic approaches.

Fig. 1 summarizes the study design. The study protocol was approved by the Institutional Medical Ethics Committee and all patients gave written informed consent. Detailed methods are provided in the online Supplement. The study population consisted of 47 consecutive patients (32 males, mean age 49.8 ± 7.4 years) without structural heart disease who presented to the emergency department with an episode of symptomatic lone AF of recent onset (≤ 48 h). Lone AF was defined as AF occurring in subjects ≤ 60 years without predisposing factors for AF, no history of AF ablation and no evidence of structural heart disease i.e. normal EKG during sinus rhythm and a normal echocardiogram. Forty five age- and gender-matched healthy individuals without history of AF, structural abnormalities or factors predisposing to AF were used as controls (31 males, mean age 49.5 ± 7.4 years).

The AF patients underwent pharmacological or spontaneous cardioversion to sinus rhythm 24 ± 17 h (from 1 h to 59 h) from the estimated time of onset of AF. After sinus rhythm restoration, the study subjects underwent transthoracic echocardiography and orthogonal ECG acquisition. Left ventricular dimensions were

obtained using 2D echocardiography, while left ventricular end-diastolic and end-systolic volumes, as well as left ventricular ejection fraction were calculated using the modified Simpson's biplane method.

The methodology used for the orthogonal ECG recordings was previously described [5–8]. Briefly, orthogonal ECG was obtained with a three-channel digital recorder that allowed acquisition of three bipolar orthogonal leads (i.e. horizontal lead on X axis, coronal lead on Y axis and sagittal lead on Z axis) (Supplemental Fig. 1). Thirty P waves were randomly selected in each orthogonal lead by two independent cardiologists and pre-processed [5–7]. P wave length was calculated manually.

In each study participant P waves were analyzed using the Morlet wavelets, as previously described [5–7]. The “Mean” and “Maximum” (“Max”) energies (μV^2) of P waves were calculated in each orthogonal lead in three frequency bands that were defined on the basis of the central frequency of the mother wavelet: high band (1) 200–161 Hz, medium band (2) 160–91 Hz and low band (3) 90–50 Hz. Supplemental Fig. 2 shows representative examples of maximum P wave energies in all three EKG leads. The “Mean” and “Max” energies represented the area under the spectral curve and the maximum of the spectral curve during the P wave, respectively. The terminology used to describe the energy variables was *Mean or Max {band}{orthogonal lead}*, e.g. Mean1X was the “Mean” energy of P wave in distal frequency band 1 (200–161 Hz) in the horizontal lead.

To localize the maximum P wave energies on the P waves, we plotted the maximum energies from each orthogonal lead in all three frequencies against the wave duration. The point in time (ms) in which the maximum energy occurred was defined as *Max{band}{orthogonal lead}loc* e.g. Max3Zloc represented the time point on P wave with the maximum P wave energy in the sagittal axis at the low band (Fig. 2). The detailed statistical methods used are provided in the online Supplement.

As shown on Supplemental Table 1 there were no significant differences in the demographic and echocardiographic characteristics across the study groups. Of note, the left atrial size was comparable between the study groups further confirming the non-structural nature of lone AF.

P wave in all three orthogonal leads was significantly longer in lone AF patients than their controls (Supplemental Table 2). Supplemental Table 3 shows the mean and maximum P wave energies on the three orthogonal leads across the three frequency bands. Mean and maximum P wave energies on the sagittal lead in the three frequency bands were significantly higher in AF patients compared to their controls (Supplemental Fig. 2). In contrast, mean and maximum P wave energies in the horizontal and coronal leads were comparable across the study groups.

Supplemental Table 4 shows the location of maximum energies along the P wave. Of note there were no differences in P wave duration, P wave energies and P wave energy peaking across genders, patients with first episode of AF vs. those with history of AF and patients with spontaneous- vs. drug-induced cardioversion.

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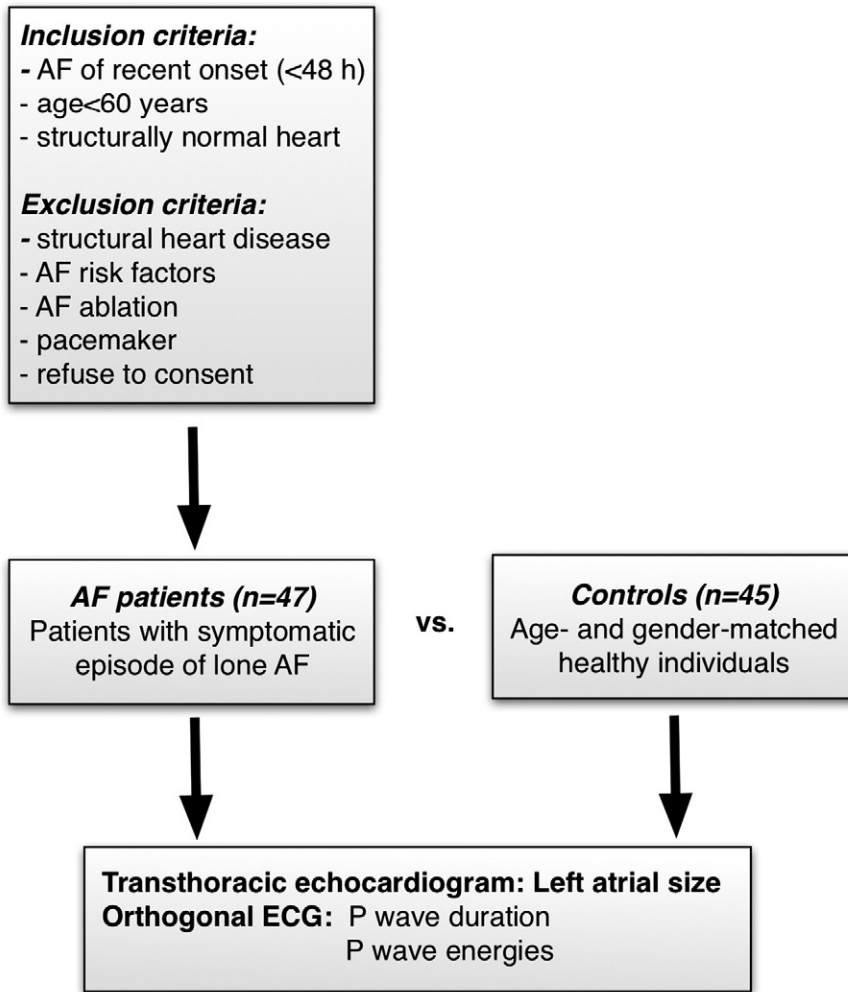


Fig. 1. Study design.

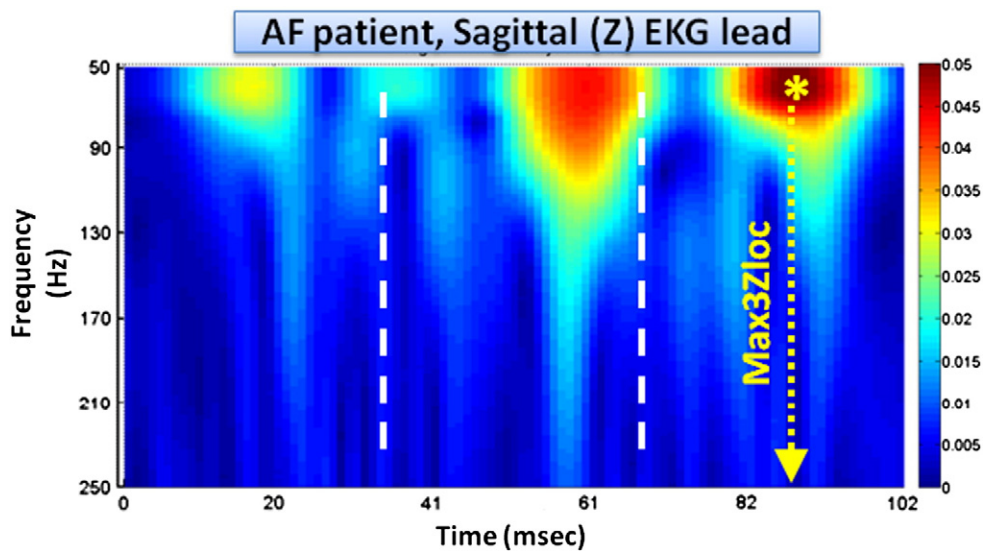


Fig. 2. Representative example showing the temporal variation of P wave energies in the sagittal plane during the duration of P wave. Maximum energy (asterisk) occurred in the low frequency band 87 s after the onset of P wave, representing the Max3Zloc as denoted by the dashed yellow line.

The absolute time interval between the onset of P wave and the maximum P wave energy in the low and medium frequency bands at the sagittal lead (Max3Zloc and Max2Zloc, respectively) were significantly higher in lone AF patients compared to controls (58.5 ± 18.5 vs. 35.4 ± 15.6 ms, $p < 0.001$; 56.46 ± 20.3 vs. 39 ± 17.4 ms, respectively). Fig. 3 shows the P wave wavelet transforms in Z lead of an individual with lone AF patient and a healthy control. Of note the maximum energies (asterisks) at the low frequency band peaked earlier in the control compared to the AF patient, suggesting a directional variation of atrial conduction velocities [4]. To adjust for the P wave duration, which was found greater in the lone AF group, the Max3Zloc was divided by the total duration of P wave and the results were expressed as percent of the total P wave time. There was a significant delay in the peak of P wave energy in the sagittal axis at the low band in the lone AF group compared to the healthy controls (64.9 ± 19 vs. $48.8 \pm 18\%$ of P wave duration, $p < 0.001$), whereas for the medium band the times were comparable (62.7 ± 21.6 vs. $54 \pm 22\%$ of P wave duration, $p = 0.343$). Plotting the Max3Zloc against the P wave duration

further showed that in the majority of patients with lone AF there was a delayed peak of energies in the sagittal plane at the low band during the atrial depolarization (Fig. 2). These findings suggest that the P wave prolongation and delayed energy peaking in the sagittal plane may be unique atrial depolarization characteristics of lone AF.

Logistic regression analysis showed that the P wave duration on the sagittal lead (PdurZ), maximum P wave energy in the low frequency band of the sagittal lead (Max3Z) and Max3Zloc were independently associated with the occurrence of lone AF (Supplemental Table 5). Optimal cut-off points were identified for each multivariate predictor of AF by plotting ROC curves as shown in Supplemental Fig. 3. The area under the receiver operating characteristic curve for each of these independent factors, as well as for their combination was high [area under the curve: 0.88 (0.81–0.95), sensitivity: 80.4%, specificity: 82.6% for the combined variable] (Fig. 4). Collectively, these findings suggest that the combination of PdurZ, Max3Z, and Max3Zloc can be used to differentiate lone AF from controls.

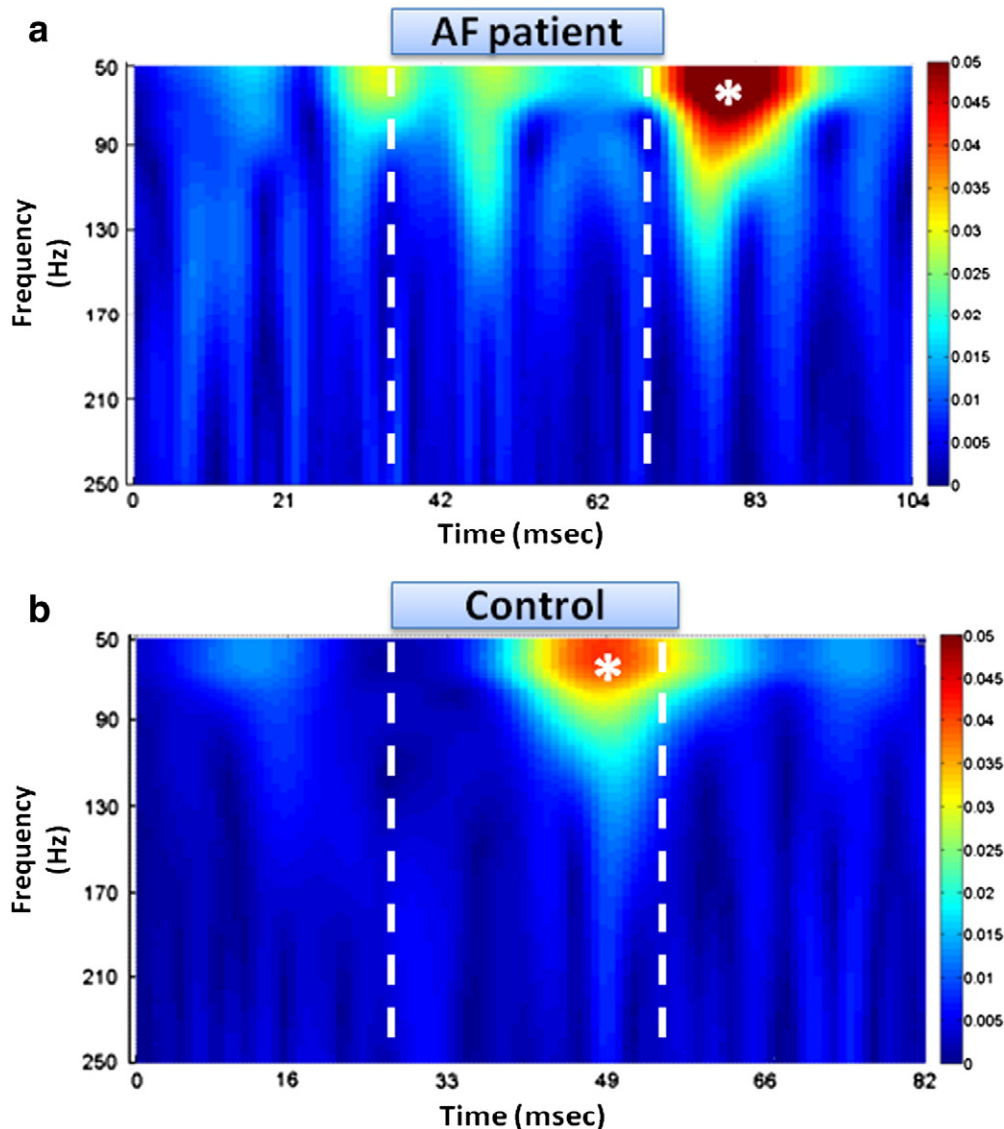
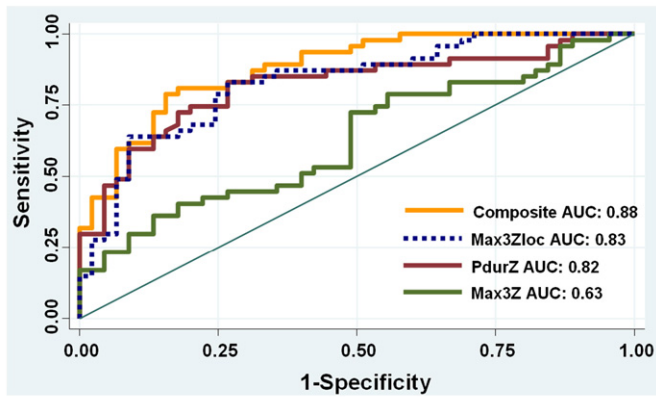


Fig. 3. Time–frequency representations of the Morlet wavelet transform on Z axis in a (a) lone AF patient and (b) a healthy control. The asterisks denote the maximum P wave energy in the low frequency band (50–90 Hz; Max3Z). Of note, Max3Z in this AF patient was higher ($60.01 \mu V^2$ vs. $40.46 \mu V^2$) and occurred later (third tertile) in the P wave compared to the control (second tertile, 80 ms vs. 48.5 ms). Also, P wave duration was longer in the AF patient compared to the control (102 ms vs. 82 ms).



Comparison of AUC	<i>p</i>
Composite vs. Max3Zloc	0.11
Composite vs. PdurZ	0.05
Composite vs. Max3Z	<0.001

Fig. 4. Receiver operating characteristic curves assessing the diagnostic accuracy of PdurZ, Max3Z and Max3Zloc for lone AF. Max3Z: max P wave energy at the low frequency band in the Z orthogonal lead, PdurZ: P wave duration in the Z lead, Max3Zloc: location of Max3Z.

In this pilot, cross-sectional study we utilized a novel, non-invasive P wave analysis technique based on the Morlet wavelet to extract P wave characteristics in patients with lone AF with clinically and echocardiographically normal heart. The study showed that patients with lone AF were characterized by a longer P wave duration, higher P wave energies in all frequency bands in the sagittal plane and a delayed peak of maximum P wave energy in the low frequency band in the sagittal lead compared with healthy controls, suggesting unique pathophysiologic conduction patterns in the anteroposterior left atrial axis [1,9,10]. The combination of these parameters was found signifi-

cantly sensitive and specific in the identification of patients at risk to develop lone AF.

Overall, this study provides novel evidence that P wave wavelet analysis may identify unique spatio-temporal features of atrial depolarization associated with lone AF. A combined approach based on P wave duration and P wave spatio-temporal energy characteristics could potentially help identify patients at risk to develop lone AF. These findings warrant to be further investigated in adequately powered and appropriately designed prospective studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2014.03.195>.

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<http://dx.doi.org/10.1016/j.ijcard.2014.03.195>

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