Systematic Evaluation of Time-Frequency Parameters from Surface Electrocardiograms for Monitoring Amiodarone Effects in Atrial Fibrillation

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Abstract

Determination of spectral parameters from surface electrocardiograms (ECG) during atrial fibrillation (AF) may prove useful for understanding underlying pathomechanisms and selecting optimal treatment. Dominant fibrillatory frequency is the most commonly used parameter today, but bandwidth (BW) and an index of temporal frequency stability (IS) have also been described. However, no study has systematically evaluated the influence of parameter settings on interindividual differences and distinguishing antiarrhythmic drug effects.

This study included 20 patients with persistent AF. ECG recordings were taken before and after amiodarone administration. The atrial fibrillatory component was extracted from ECG by Principal Component Analysis techniques, and the spectral properties were obtained from the Welch´s periodogram and the time-frequency transform. The following parameters were evaluated: BW, instantaneous main frequency and IS. Several parameter settings were studied in order to determine the values that maximize interindividual differences and allow monitoring of drug effects.

Baseline frequency measured 6.54±0.53Hz (range 5.7 to 7.4Hz) and was reduced to 5.64±0.54 Hz (range 4.8 to 6.5Hz) by amiodarone (p<0.0001). Using Receiver Operating Characteristic analysis with a temporal resolution of 1s in the time-frequency distribution, BW obtained from a threshold at 50% of main peak amplitude and IS based on consecutive frequency differences between 0.5 and 0.9Hz resulted in both maximal interindividual parameter differences and differentiation of baseline and amiodarone recordings.

1. Introduction

Spectral analysis of fibrillatory waves of surface electrocardiograms has been shown to provide useful information in understanding underlying mechanisms of atrial fibrillation (AF) [1]. Clinical and experimental studies have revealed a close inverse relation between atrial refractory periods and the rate of electrical atrial activation [2]. Subsequently, the dominant frequency of fibrillatory waves has been suggested to be an important indicator of different aspects like effectiveness of therapies or state of AF.

Earlier investigations have led to the development of several techniques focused on the analysis of the surface ECG of AF. The signal processing employed in extracting the atrial activation is getting more and more elaborated prompted by the results in these investigations. These studies have two aims: (1) development of methods for estimating or extracting the isolated atrial signal, based on different strategies [3] and the second one being the (2) development of different techniques of for atrial signal analysis and characterization [4]. Regarding thisthe latter, some parameters derived from analysis of the surface ECG analysis have been recently introduced and have shown to correlate well with usual clinical parametersAF course and outcome. So far, these measurements have dominant fibrillatory frequency has been suggested to predict spontaneous and pharmacological conversion of AF to sinus rhythm and AF recurrence following cardioversion [5]. The influence of antiarrhythmic drugs, especially amiodarone and flecainide, has been advocated to can be evaluated by changes in dominant frequency and spectral profiles means of surface ECG obtained by time-frequency analysis [6].

The advantage of ECG parameters is the non-invasive, simple and rapid approach whereas many of the clinical parameters can only be measured invasively.

In this study we investigate the following parameters: the instantaneous main frequency of the fibrillatory wave (imf), the bandwidth (BW) of the principal peak and the Index of Stability (IS) of the principal frequency. These measurements have been calculated from time-frequency transforms and the Welch's periodogram using several temporal resolutions and different thresholds thresholds

for evaluating different definitions of them.

The aim of this study is to propose an optimized definition of parameters obtained from surface ECG exhibiting sufficient interindividual differences and allowing containing prognostic information. Evaluation of different alternatives of calculating each value was made and its use in distinguishing between signals was checked.

A systematic analysis of the parameters was performed in order to study the behaviour of this measurement and to define an optimal definition of these parameters.

To take the effect of antiarrhythmic drugs into account we studied ECG parameters of patients before and after administration of amiodarone. The purpose was to select optimum measurements of parameters and compare monitoring of changes in atrial activation changes after antiarrhythmic drug initiation.

2. Methods

This observational study includes 20 consecutive patients of persistent AF ($\geq$ 30 days, range 2 months to 8 years), 14 of whom were males and 6 were females. All patients provided written informed consent before study participation. The clinical characteristics of the study population are summarized in Table 1.

Table 1. Clinical characteristics of the study population (n=20)

Age (years)	66±9
Male/Female	14/6
AF duration (months)	30±32
Lone AF/Hypertension/Coronary artery disease/Dilated cardiomyopathy/Valvular heart disease	2/8/4/3/3
LAD (mm)	47±4
LVEF (%)	47±18
Digitalis/Beta-blocker/Calcium channel blocker*	11/6/5

* more than one possible

Amiodarone was initiated on an inpatient basis under continuous ECG monitoring with a loading dose of 1200 mg/day for 7 days, followed by 200 mg/day. Patients received concomitantly either oral anticoagulation therapy to maintain an international normalized ratio between 2.5 and 3.5 or weight-adapted low molecular weight heparin following exclusion of left atrial thrombus formation by transesophageal echocardiography.

A two-minute ECG recording was performed before amiodarone was given and three days following drug initiation with the subject relaxed in a supine position after a 5-minute equilibration period. In each patient a high-gain, high-resolution electrocardiogram (Predictor, Dr. Kaiser Medizintechnik GmbH, Bad Hersfeld, Germany) was recorded. Electrodes were applied in an optimum lead positioning.

Signals were analog-to-digital converted at 2000 Hz, a 12 bit resolution and a frequency response at 0.05-300Hz.

Atrial component was obtained using an algorithm based on Principal Component Analysis concepts [7]. Then, atrial signal was downsampled from 2000Hz to 50Hz and time-frequency analysis was performed using the Choi-Williams transform with consecutives windows of about 2s (5 cycles of the maximum f-wave's period) and without overlapping.

The frequency of the main peak and the Index of Stability were calculated from the Choi-Williams distribution (CWD, see Figure 1) [8], for several temporary resolutions so that these spectral parameters were obtained at different time intervals. The chosen time resolutions were 0.1s, 0.25, 0.5s and 1s between each sample. All parameters obtained from the CWD were computed for each temporary resolution.
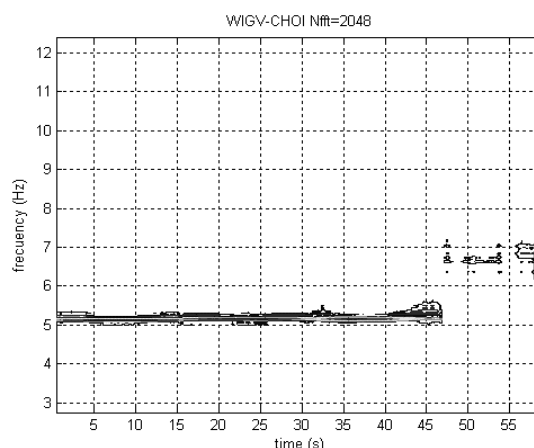

Figure 1. Example of the Choi-Williams distribution of the atrial fibrillatory signal

The instantaneous main frequency was defined as the frequency of the main peak at each time unit of the CWD. The mean value of the main frequency was similar independently of the time resolution employed. However, significant variations in the instantaneous frequency were observed. In order to establish an objective parameter to assess these frequency variations, we employed an Index of Stability of the main frequency (IS).

First, the stability (st) at each time unit i is defined as a function that returns 1 if the frequency variation within a certain time interval (n time units) does not exceed a determined threshold (th). Otherwise, the function returns 0:

$$st(i) = \begin{cases} 1 & if \quad |f_i - f_{i-1}| \leq th \\ 0 & otherwise \end{cases} \quad (1)$$

Then the IS is defined as the percentage of time where the variation of the instantaneous main frequency remained below th [6].

$$IndexofStability(th) = \frac{\sum_1^N st(i,th)}{N} \cdot 100 \qquad (2)$$

where N is the number of samples.

The Index of Stability (IS) has been computed by adjusting the threshold between 0.1Hz and 2Hz in steps of 0.1Hz. The criterion employed to assess the variability among patients was the difference between the largest value and the smallest one that could be reached among patients in every case:

$$MaximunRange = p_{95\%}(IS_{i,th}) - p_{5\%}(IS_{i,th}) \qquad (3)$$

where p is the percentile function that assured that the possible outliers had not influences and the range would be the most representative among different patients. This choice was made in order to get a broad range for the calculated parameters that could reflect with the greatest margin of variation the changes in the signal properties.
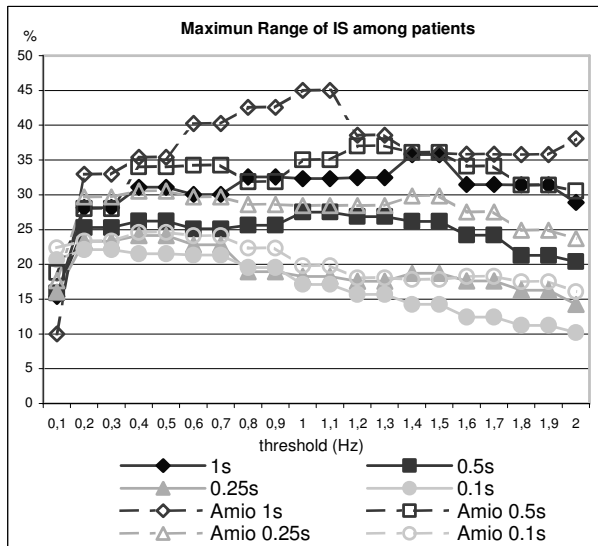

Figure 2. Maximum range of IS among patients before and after amiodarone administration for four different time resolutions

Bandwidth is defined as the difference between the upper and lower cut-off frequencies in the band of the peak. Cut-off frequencies are defined as the frequencies where the spectral amplitude was above a certain threshold. The spectral power density was computed from the Welch's Periodogram with an overlapping window of 8192 points. Several threshold settings were evaluated, ranging from 40% to 90% of the maximum amplitude (Ap), in 10% steps.

All values for imf, IS and BW have been obtained before and after amiodarone treatment.

3.   Results

Instantaneous main frequency (imf)

Baseline frequency measured 6.54±0.53 Hz (range 7.4 to 5.7) and was reduced to 5.64±0.54 Hz (range 6.5 to 4.8) by amiodarone (p<0.0001 all resolutions).

This parameter was calculated for four different resolutions. Results were very similar and highly correlated in all cases (Coefficient of Pearson correlation was always higher than 0.993). An arbitrary resolution of one second was then chosen for further analysis.

Index of Stability (IS)

Higher ranges of IS among patients and higher differences between amiodarone and baseline signals were observed at threshold settings between 0.5 and 1.2 Hz for 1s resolution. IS values were always higher after amiodarone administration than before (Figure 2).

Furthermore, Receiver Operating Characteristic (ROC) curves were constructed in order to identify the best threshold for classifying signals as baseline recordings or recordings after amiodarone administration (Figure 3).
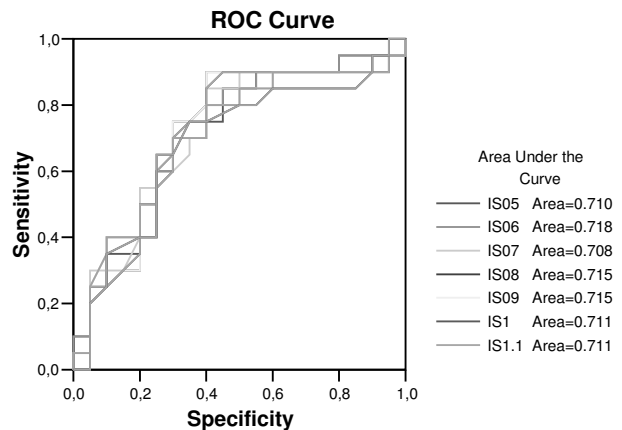

Figure 3. ROC curve for different IS with thresholds from 0.5Hz to 1.1Hz with temporary resolution of 1s

Bandwidth (BW)

Table 2 summarizes results regarding different bandwidth definitions and their influence on inter-patients range at baseline and after amiodarone as well as on differentiating baseline from amiodarone recordings.

Table 2. Maximum range of bandwidth values before and after amiodarone administration for different percentage of Ap

%Ap	50	60	70	80	90
Baseline	1,46	1,34	1,46	0,73	0,49
Amiodarone	1,22	0,98	0,98	0,85	0,61
P (T-test)	<0,001	0,005	0,026	NS	NS

Bandwidth at 50% of Ap provided the highest range among patients before and after drug administration. In addition, this value exhibited the most significant differences between signals of the same patient.

A summary of parameters that show the highest variability among patients and that better reflect amiodarone effects is provided in table 3.

Table 3. Summary of proposed parameter definitions and their statistical significance for studying amiodarone effects

Parameter definition	t-test
imf (resolution from 0.1 to 1s)	$p \leq 0.001$
Bw (50% Ap)	$p \leq 0.001$
IS (1s resolution and $0.5 \leq th \leq 0.9$)	$p \leq 0.012$

4. Discussion and conclusions

In the present report a time resolution of one second has been shown to be sufficient in order to study the main frequency of f-waves during AF. The increment of temporary resolution (less than one second) provides redundant information. However, it is necessary to take into account that other parameters that also change in the time domain could be influenced by the chosen time resolution. Regarding this, the IS shows an important relation with time resolution. An increase in time resolution leads to an increase of IS at the same thresholds. Hence, the optimal threshold setting for defining IS depends on the time resolution.The proper definition of the parameters under study is crucial in order to understand the relation between their properties and their interpretation.

Main frequency was the most important indicator for studying amiodarone effects. Our results confirm previous studies, but highlight also that other parameters can reflect drug effects.

In conclusion, main frequency, bandwidth and index of stability allow differentiation of interindividual differences in AF characteristics and monitoring of antiarrhythmic drug effects, but depend on temporal resolution and parameter definitions. Spectral analysis of fibrillatory waves may contribute to better AF characterization and enhance clinical management.

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