Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG

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Abstract

**Objective:** Automatic analysis of the frequency content of the fibrillatory baseline on the surface ECG accurately reflects the average rate of atrial fibrillation (AF). This frequency measurement correlates with the behavior of AF and predicts the response to administration of ibutilide, a new antiarrhythmic drug. Neither the temporal pattern of fibrillatory frequency in spontaneous paroxysmal or persistent AF, nor its response to chronic antiarrhythmic medication has been studied so far. **Methods and Results:** Holter ECG recordings were made in 20 patients during AF. One minute ECG segments were selected for analysis. The frequency content of the fibrillatory baseline was then quantified using digital signal processing. After high-pass filtering, the QRST complexes were subtracted using a template matching algorithm. The resulting fibrillatory baseline signal was subjected to Fourier transformation, displayed as a frequency power spectrum and the peak frequency (f) was determined. In 11 patients (7 male, 4 female, age 62±10 years) 31 paroxysmal AF episodes were analyzed. Duration ranged from 1 min to 665 min (115±175 min). Initial mean peak f measured 5.1±0.7 Hz (range 3.9 to 6.9 Hz). There was a positive correlation between f and AF duration ($R=0.53$, $p=0.002$). AF of less than 15 min duration ($n=13$) showed a lower f (4.8±0.6 Hz) when compared with longer lasting episodes ($n=18$, 5.3±0.7 Hz, $p=0.03$). In short AF episodes f was constant, whereas in longer-lasting episodes f increased to 5.8±0.5 Hz ($p<0.001$) within 5 min. In 9 patients (9 male, age 58±8 years) with persistent AF oral antiarrhythmic drugs (amiodarone $n=5$, sotalol $n=3$, flecainide $n=1$) were given prior to electrical cardioversion for prophylaxis of AF recurrence. Frequency measurements were obtained at baseline and 3 to 5 days after initiation of drug administration. At baseline mean f measured 6.9±0.4 Hz. Frequency was reduced by antiarrhythmic drugs to 5.8±0.4 Hz ($p<0.001$). **Conclusions:** (1) The duration of paroxysmal AF episodes can be predicted using spectral analysis of ECG recordings of AF episodes. (2) An increase in fibrillatory frequency is associated with AF persistence. (3) This technique can be used to monitor the response to antiarrhythmic medication.

Keywords: Atrial fibrillation; Arrhythmia (mechanisms); Antiarrhythmic agents; ECG; Spectral analysis

1. Introduction

Recently, our group [1] and others [2,3] have shown that analysis of the frequency content of the fibrillatory baseline on the surface ECG accurately reflects the average rate of atrial fibrillation (AF) recorded directly from the endocardium. The clinical utility of this technique has been explored by correlating fibrillatory frequency with the behavior of the arrhythmia, its response to ibutilide [1] and to predict AF recurrence after successful external cardioversion [4]. Low frequency fibrillation more likely terminates spontaneously or responds to antiarrhythmic therapy, while high frequency fibrillation is more often persistent, drug refractory and more likely recurs early after external cardioversion.

However, neither the temporal pattern of fibrillatory frequency in spontaneous paroxysmal or persistent AF, nor...
its response to chronic antiarrhythmic medication has been studied so far.

The aim of this study was threefold: (1) to evaluate the frequency spectrum in human paroxysmal and persistent AF from Holter ECG recordings, (2) to correlate peak frequency with the duration of paroxysmal AF episodes, and (3) to evaluate the capability of this test to monitor changes in atrial rate due to chronic antiarrhythmic medication.

2. Methods

The subjects of this study were 20 patients referred to our institution for treatment of AF. None of these patients were taking antiarrhythmic drugs at the time of the initial study. All patients had transthoracic echocardiograms within 3 months of the study. The left ventricular ejection fraction was normal in all patients and mean left atrial diameter was 43 ± 6 mm.

Two groups of patients undergoing Holter ECG recordings were enrolled in the study; those with paroxysmal AF and patients with persistent AF.

2.1. Patients with paroxysmal AF

Paroxysmal AF episodes were defined as showing no visible P-waves and exhibiting an irregular ventricular response interrupted by episodes of normal sinus rhythm. Episodes lasting longer than 1 min were selected for analysis if they had both onset and spontaneous termination during 24-h Holter ECG and were preceded by at least 60 min of sinus rhythm.

Eleven patients were included into this group. There were 7 male and 4 female, and their age was 62 ± 10 years. Three patients had coronary artery disease, 3 had essential hypertension, and the remaining 5 had no overt heart disease. Left ventricular ejection fraction was normal in all patients and mean left atrial diameter was 43 ± 6 mm.

In all episodes the first minute of AF was selected for analysis. In order to assess temporal pattern of AF frequency repeated measurements were performed. In all episodes lasting longer than 2 min the last minute before spontaneous termination was analyzed. In episodes lasting longer than 15 min measurements were made every 5 min for the first 15 min.

2.2. Patients with persistent AF

Persistent AF was defined as AF throughout the whole 24-h Holter ECG recording, not interrupted by any other supraventricular rhythm. The 9 subjects of this group were male, and their age was 56 ± 8 years. The underlying disease included coronary artery disease in 2 patients, essential hypertension in 2 patients and dilated cardiomyopathy in 3 patients. The remaining 2 patients had no structural heart disease. In this group, left ventricular ejection fraction and left atrial diameter measured 52 ± 13% and 46 ± 5 mm. The duration of the arrhythmia ranged between 3 months and 2 years (1.4 ± 1.1 years).

Patients with persistent AF had 24-h Holter ECG recordings performed both prior to and 3 to 5 days after initiation of antiarrhythmic drugs. These included amiodarone (n = 5, loading dose 600 to 1200 mg/d), sotalol (n = 3, dose 240 to 480 mg/d) and flecainide (n = 1, dose 200 mg/d)

Temporal pattern of AF frequency was explored by repeated measurements every 4 hours (8 AM, 12 AM, 4 PM, 8 PM, Midnight, 4 AM).

2.3. Data acquisition and signal processing

Holter ECG recordings of standard lead MCL1 were displayed using Pathfinder 700 (Reynolds Medical, Edinburgh, UK). One minute ECG-segments selected for analysis were digitized at a sampling rate of 1000 Hz with a resolution of 12 bits. The frequency content of the fibrillatory baseline was then quantified using digital signal processing. After high-pass filtering, the QRST complexes were subtracted using a template matching algorithm. The resulting fibrillatory baseline signal was subjected to Fourier transformation, displayed as a frequency power spectrum and peak frequency was determined in the 3 to 12 Hz range (Fig. 1). The algorithm has been described in detail previously [1–3].

It has been shown that the right atrium is responsible for the major contribution to the fibrillatory activity on the precordial leads [1,2]. However, this contribution is not restricted to the right atrium. Holm et al. [2] noted that some structures of the left atrium had a similar distance to the surface ECG lead V1 as parts of the right atrium. Furthermore, their [2] and our initial study [1] revealed a good correlation between fibrillatory frequency of the right and the left atrium with a mean difference of about 0.5 Hz.

2.4. Data analysis

The initial fibrillatory peak frequency was correlated with the duration of paroxysmal AF episodes using linear regression analysis. This frequency measurement was compared for paroxysms lasting <15 min and those where the arrhythmia persisted for longer than 15 min using Student’s t-test for unpaired data. In short AF episodes, peak frequencies obtained after AF initiation were compared to those obtained just prior to AF termination using Student’s t-test for paired data. In longer-lasting AF episodes, the measurements obtained within the first 15 min and prior to termination were compared using analysis of variance for repeated measurements.

In persistent AF, mean frequency and coefficients of variation were calculated from the 6 recordings obtained before and after antiarrhythmic medication. Variability of
AF frequency was assessed using analysis of variance for repeated measurements. The response to chronic antiarrhythmic medication was analyzed by comparing mean frequency to the baseline measurement. For this analysis Student’s t-test for paired data was used.

All results are presented as mean±one standard deviation. A p value <0.05 was considered statistically significant.

3. Results

3.1. Frequency spectrum in paroxysmal atrial fibrillation

Seventy-nine paroxysmal AF episodes were observed. Of those, 31 episodes fulfilled the predefined requirements and were selected for analysis. Duration ranged from 1 min to 665 min (115±175 min).

Frequency spectra derived from Holter recordings were characterized by a single sharp peak (Fig. 1). Mean peak frequency of the first AF minute measured 5.1±0.7 Hz (range 3.9 to 6.9 Hz). There was a positive correlation between this measurement and paroxysmal AF duration (R=0.53, p=0.002; Fig. 2). AF of less than 15 min duration (n=13) had a lower frequency (4.8±0.6 Hz) when compared with longer lasting episodes (n=18, 5.3±0.6 Hz, p=0.03).

In AF lasting less than 15 min there was no significant shift in peak frequency when comparing the first with the last minute of the episode 5±5 min later (4.8±0.6 Hz vs. 5.2±0.8 Hz, p=ns). In AF episodes lasting longer than 15 min (mean duration 194±195 min) there was an increase in AF frequency to 5.8±0.5 Hz, 5.8±0.5 Hz and 5.9±0.7 Hz at min 5, 10 and 15, respectively (p<0.001; Fig. 3).

In 7 patients, peak frequency of 19 consecutive AF episodes were compared. There was no difference in peak frequency between the initial and subsequent episodes (5.0±0.7 Hz vs. 4.9±0.6 Hz, p=ns). Within-patient variation of consecutive peaks in paroxysmal AF episodes ranged from 0 to 2.9 Hz.

3.2. Frequency spectrum in persistent atrial fibrillation and its response to chronic antiarrhythmic medication

As with paroxysmal AF episodes, frequency spectra derived from Holter recordings in persistent AF were characterized by a single sharp peak. Fibrillatory frequencies obtained over 24 h before and after antiarrhythmic medication are depicted in Fig. 4. At baseline, mean frequency of the 6 recordings of each patient was 6.9±0.5 Hz (range 6.4 to 7.7 Hz) and coefficient of variation was 4.6±1.7% (range 2 to 8%). This fibrillatory frequency was higher when compared to the paroxysmal AF episodes (p<0.001).

After antiarrhythmic medication, mean frequency was
5.8±0.4 Hz (range 5.1 to 6.4 Hz, \( p<0.001 \) vs. baseline) and coefficient of variation was 4.6±1.2% (range 2 to 6%, \( p=ns \) vs. baseline). Peak frequency was reduced in all patients by 1.0±0.4 Hz (range 0.5 to 1.6 Hz) without termination of AF.

In both groups neither underlying heart disease nor left
Fig. 4. A: AF frequency during 24 h obtained every 4 h. Presented are the values before and after antiarrhythmic drug (AAD) administration. Note the stability of AF frequency before and after antiarrhythmic drug administration. Also note the reduction in AF frequency during all measurements. B: Mean AF frequency before and after antiarrhythmic drug administration in all patients (Amio=Amiodarone, Flec=Flecainide, Sot=Sotalol).

atrial diameter revealed significant correlations with both fibrillatory frequency and its temporal pattern.

4. Discussion

4.1. Main findings

This study applied a signal processing technique measuring the peak frequency of the fibrillatory baseline from Holter ECG recordings in patients with both paroxysmal and persistent AF. This frequency measurement correlated with the duration of paroxysmal AF episodes. AF that terminated spontaneously within 15 min had a lower frequency than AF that persisted longer. Furthermore, patients with paroxysmal AF exhibited a lower frequency than those with persistent AF. In short AF episodes frequency exhibited no significant shift, whereas in longer-lasting AF episodes frequency increased within 5 min. In contrast, peak frequency was constant over the duration of the 24-h Holter recording in persistent AF. The spectral analysis technique was used to investigate the effects of antiarrhythmic drugs on the fibrillatory frequency in persistent AF. Peak frequency was consistently reduced by antiarrhythmic medication.

4.2. AF frequency and arrhythmia complexity

Konings and colleagues classified AF in patients with the Wolff-Parkinson-White syndrome undergoing cardiac surgery by using high-density mapping of the right atrial free wall [7]. They categorized the arrhythmia based on the number and complexity of activation wavefronts within the 3.6 cm diameter region being studied. There was a clear correlation between AF frequency and complexity of the arrhythmia. Type I AF, characterized by a single uniform wavefront, exhibited a mean frequency of 5.7 Hz; Type II AF, defined as showing one non-uniform or two simultaneous wavefronts and even more complex type III fibrillatory frequency, measured 6.6 Hz and 7.4 Hz, respectively. This frequency measurement has been shown to reflect local atrial refractoriness [8].

Several experimental and clinical studies have shown an association between the cycle length of AF recorded on the intracardiac electrogram and the behavior of the arrhythmia. Asano et al. induced atrial fibrillation with rapid pacing in 30 patients undergoing electrophysiologic study [9]. Those patients where AF terminated spontaneously had an average fibrillatory frequency of 5.7 Hz, significantly lower than the 6.4 Hz recorded in the group of patients where the arrhythmia persisted. Similar observations were made by Boahene et al. who measured the fibrillatory cycle length from the right atrium in 55 patients with Wolff-Parkinson-White syndrome [10]. These investigators also found that patients with sustained AF had shorter mean AA intervals compared to patients with non-sustained AF. In both experimental models of AF and in clinical studies, persistent rapid atrial rates have been shown to produce a marked, progressive shortening of the atrial refractory period [11,12]. The decrease in refractoriness is accompanied by a comparable increase in the fibrillation frequency [8,11]. Capucci et al. induced AF in 25 patients with a history of paroxysmal AF. As with this study, the authors found a different behavior of atrial rates...
between sustained and self-terminating AF episodes. In both studies long-lasting fibrillation was associated with an increase in fibrillatory frequency within 5 min after AF onset. Electrical remodeling is felt to contribute to the self-perpetuating nature of AF and may play a major role in the natural history of the arrhythmia [13].

To the best of our knowledge this study is the first to characterize the behavior of atrial rates in spontaneous paroxysmal AF episodes in humans. There was a direct relationship between the duration of paroxysmal AF episodes and the peak frequency recorded on the ECG. Furthermore, patients with paroxysmal AF had a lower frequency than those with persistent AF. Those observations suggest that patients with a low fibrillatory frequency have longer atrial wavelengths and a smaller number of activation wavefronts while those with a high fibrillatory frequency have shorter wavelengths and a larger number of wavelets. In other words, spectral analysis of the ECG may be useful for quantifying the AF complexity in patients with both paroxysmal and persistent AF.

### 4.3. AF frequency during antiarrhythmic drug administration

Several studies have investigated the impact of antiarrhythmic drug administration on atrial rates in patients with AF. Procainamide [10,14–16], propafenone [10], disopyramide [9], cibenzoline [17], sotalol [2] and ibutilide [1,16] have all been shown to reduce the average frequency of fibrillatory activity. The magnitude of slowing appears to correlate with the drug effect. Boahene et al. noted that procainamide- and propafenone-induced slowing of atrial cycle length was greater in patients who were successfully converted from AF to sinus rhythms [10]. Similarly, the baseline fibrillatory rate was predictive of conversion to sinus rhythm with ibutilide, whether recorded directly from the atrial endocardium [16] or derived from the surface ECG [1]. The current study extends these observations to examine the effects of chronic oral antiarrhythmic administration on fibrillatory frequency. The reduction of AF ratio is consistent with earlier reports and suggests that this technique may be useful for assessment of the antiarrhythmic drug efficacy.

### 4.4. Study limitations and clinical implications

The correlation between fibrillatory frequency, the probability of spontaneous termination, and the response to antiarrhythmic drugs were evaluated in a small, heterogeneous cohort of patients with AF. A larger sample is needed to confirm the present findings and to determine the role of this technique in the management of AF.

Although fibrillatory frequency shows a good correlation with AF duration it is not the only electrophysiologic parameter determining AF sustenance or termination. Conduction velocity, dispersion of refractoriness and anisotropy may also contribute but were not evaluated in this study.

Furthermore, our observation that fibrillatory frequency increases within 5 min after AF onset and decreases prior termination in long-lasting episodes is most interesting and deserves further investigation.

Results of the present study show a clear relationship between fibrillatory rate and the behavior of the atrial arrhythmia. Low frequency fibrillation is more likely to terminate, while high frequency fibrillation is more often persistent. The magnitude of frequency slowing by antiarrhythmic drugs can be quantified using spectral analysis of the ECG. Continued study will help to confirm the accuracy of this non-invasive test for the prediction of spontaneous conversion or the response to antiarrhythmic drug administration prior to external cardioversion. Prospective trials are currently underway in order to assess the clinical value of this technique for estimation of time to recurrence after internal or external cardioversion.

### References


