Türk Kardiyol Dern Arş 2001; 29: 481-487

Fourier Transformation Analysis of Atrial Fibrillation Intervals Following Ibutilide and Procainamide to Predict Successful Cardioversion

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BAŞARILI KARDİYOVERSİYONU ÖNGÖRMEDE İBÜTİLİD VE PROKAİNAMİD VERİLMESİNİ TAKİBEN ATRİAL FİBRİLASYON İNTERVALLERİNİN "FOURIER" TRANSFORMASYONU ANALİZİ

ÖZET

Atriyal fibrilasyon (AF) esnasında atriyum içi kayıtlarının fraksinasyon derecesi ve frekansı reentran yolların dalgaboyu ve büyüklüğü ile uyum gösterir. Atriyal fibrilasyonun ilaç ile sonlanma mekanizmalarını açıklamada spectral analizin yardımcı olabileceğini savunduk.

Sağ atriyumdan kaydedilen monofazik aksiyon potansiyellerinin frekans spekturumu, hızlı Fourier dönüşümü (FFT) ile incelendi. Atriyal fibrilasyonlu 24 hastada en yüksek, en düşük ve ilk 5 tepe frekansı ile frekans dağılımının genişliği, plasebo (grup C, n=7), ibutilid 1.6±0.4 mg (grup I, n=10) veya prokainamid 1240±221 mg (grup P, n=10) infüzyonu öncesi ve sonrası 5'er saniyelik zaman dilimleri halinde saptandı. Yaş (66±9, 68±6 ve 64±7), sol atrial çap (40±8, 44±5 ve 46±4 mm) ve sol ventrikül EF (44±11, 43±7 ve 40±11) gruplar arasında farklı değildi (sırası ile grup I, P ve C, p>0.05). Ibutilid and prokainamid AF tepe frekansını sırası ile 6.2±0.6 ve 6.5±1.1 Hz'den 4.3±0.3 ve 4.5±0.8 Hz'e indirdi (p<0.001). Plasebonun FFT üzerine etkisi olmadı. Ibutilid tepe frekanslarını her doz sonrası 30 saniye içinde anlamlı olarak azalttı. Grup I'da 3 hastada AF sonlandı. Kardiyoversiyon sağlanan hastalar sağlanmayanlarla karşılaştırıldığında bazal AF frekanslarının daha düşük olduğu izlendi (5.7±.3' e karşı 6.4±.6 Hz). İbutilid kardiyoversiyon öncesi AF frekansını 3.5±0.1 Hz'e indirdi. Sonuç olarak AF elektrogramların FFT analizi ilaçların atriyal doku üzerine olan etkilerinin değerlendirilmesinde faydalı bir metoddur. Ibutilid kardiyoversiyon öncesi AF frekansını kritik bir düzeye indirmektedir.

Anahtar kelimeler: *Atriyal fibrilasyon, monofazik aksiyon potansiyeli, hızlı Fourier dönüşümü*

Received: 20 April, accepted 5 June 2001
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This article was presented at XVI[th] Congress of the Turkish Society of Cardiology

Atrial fibrillation usually is the result of multiple simultaneous reentrant activation wavefronts [1,2]. Atrial wavelength (conduction velocity*refractory period) determines average size and the number of reentry pathways during AF at a given time [3,4]. Long wavelengths are associated with larger and fewer wavefronts, whereas short wavelengths result in a greater number of small circuits. An association between shorter wavelengths and persistent AF has been shown both in animal [5] and human clinical[6] studies. A high degree of fractionation and high frequency of AF corresponds a short wavelength and size of reentry pathways [7]. Fast Fourier Analysis (FFT) is a spectral analysing method and has been applied in a variety of studies eliminating the need of manual measurement of wave cycle length (CL) [8]. Ibutilide is a unique class III antiarrhythmic drug in that its action involves not only K+ current blockade but also slow inward Na+ current activation during the plateau phase of the action potential. It prolongs action potential duration and effective refractory period dose-dependently both in the atria and ventricles [9]. Procainamide suppresses maximal velocity in the action potential in a use-dependant manner and increases effective refractory period in most of the heart tissue.

In this study, intraatrial electrograms recorded by monophasic action potential (MAP) catheter in patients with atrial fibrillation were analyzed before and after ibutilide and/or procainamide administration. We hypothesized that analysis of the Fourier transformation of atrial electrograms during atrial fibrillation would show a correlation of the variance of the signal frequency and its spectral distribution with the organization of AF wavelets following ibutilide and procainamide and would predict the success of medication in converting atrial fibrillation.

METHODS

Study patients: The study patients consisted of 24 patients with atrial fibrillation referred for elective cardioversion. These patients had been participated in the previously published studies [10,11] and the inclusion/exclusion criteria had been revised by Stambler et al.[12] Briefly, patients received procainamide if they had previously received ibutilide, were unwilling to receive ibutilide or if they had an exclusion criteria for ibutilide which were cardiac surgery within the previous 30 days, serum potassium <4.0 mEq/L, serum creatinine >2.0 mg/dL, heart rate <60 bpm. Patients were also excluded if any of the following were present: AF duration <24h or >90 days, hemodynamic instability (systolic blood pressure <90 mmHg or diastolic blood pressure >105 mmHg), unstable angina pectoris or heart failure, acute myocardial infarction within the previous 30 days, inadequate anticoagulation, age<18 or >90 years, weight>300 lbs, history of torsade de pointes, corrected QT >440 msec on ECG, concurrent or within 5 half-lives before enrollment treatment with class I or III antiarrhythmic drugs.

Ten patients received ibutilide (group-I), 10 were given procainamide (group P) and 7 received placebo (group C). Three patients who were given ibutilide received procainamide too. Of 10 patients in Ibutilide group, one patient received 0.005 mg/kg of ibutilide, 4 received 1mg+0.5mg, 2 received only 1 mg of ibutilide, and the remaining 3 patients were given 1mg+1mg of ibutilide. There was a 10 min of interval between first and second dose of ibutilide.

Procainamide dosage was 15 mg/kg. Blood level of ibutilide, procainamide and NAPA was measured 5 minutes after completion of each drug infusion. All patients were in type I atrial fibrillation per criteria of Wells et al.[13]

Electrophysiologic and drug studies, data analysis: A steerable catheter (MAP Pacing™ Catheter, EP Technologies, Boston Scientific Corporation, USA) with a distal pair of Ag/AgCl electrodes and a proximal pair of platinum ring electrode was used for recording MAP and bipolar electrograms, respectively. Catheters were positioned where a stable MAP recording was obtained, usually in low right atrium or right atrial appendix where a relatively organized atrial electrical activity was observed. Signals were recorded digitally at a sampling rate of 1024/sec using Prucka EP system (Prucka Engineering Inc., Houston, Texas).

These signals were played back and analog output was recorded digitally at a rate of 3000 Hz to a computer system for further analysis. A maximum of 5-min recording of atrial fibrillation at baseline and following each drug administration was divided into the segments of 214/3000 sec (approximately 5.5 sec). Row data first were filtered by moving average algorhythm to minimize the high frequency artifacts. Hamming window was then applied to prevent the onset and offset of the MAP recording from introducing artifact. Fast Fourier transformation analysis was performed and the region of the interest was focused. The discrete harmonic peaks were ignored for analysis. The software used for the recording and the spectral analysis was LabView and DADISP, respectively. The region of the interest in the spectral distribution was analyzed for the minimal and maximal peak frequencies, the width of frequency distribution, the first 5 peaks of frequencies, and the average of these frequency peaks. The frequency peak of which the base is less than 0.5 Hz was ignored for analysis. Figure A-D depicts the step-by-step analysis of the row recordings. In 8 patients both MAP and bipolar simultaneous recordings were analyzed separately and the results were compared to evaluate the correlation between them in detecting the frequency of atrial fibrillation.

Statistics: Independent-Samples T test (Mann-Whitney U test when Levene test is significant) was used to compare continuous variables between groups and paired-samples T test (Wilcoxon signed-rank test when appropriate) within groups. Chi square analysis was used to compare categorical variables. One-way ANOVA test was used to disclose difference between groups. In the presence of the significant difference, Post Hoc pairwise multiple comparisons (ANOVA-Benferroni) were used to compare continuous variables within groups.

RESULTS

Study population: Mean age of the patient population was 66±20 years. All of the patients were men. Mean atrial fibrillation duration was 29±43 days. The incidence of coronary artery disease (CAD), hypertension (HTN) and congestive heart failure (CHF) was 60%, 44% and 20%, respectively. Left ventricular ejection fraction (EF) was 42±10% and left atrial size (LA) measured 43±8 mm. The clinical characteristics of the each group were summarized in table-1. Comparison of the clinical characteristics did not reveal any statistical difference between groups except for the duration of AF. Procainamide group has significantly longer duration of atrial fibrillation than the control group (44±20 vs. 12±12 days, p=0.001).

Comparison of bipolar and MAP recordings: Both MAP and bipolar electrograms in 9 patients (4 patients in group-I, 2 in group-P, 3 in group-C) were recorded at baseline and after the first drug infusion. Quality of bipolar recording was not satisfactory in 3 patients. Fast Fourier transformation analysis was performed in the same way described in methods and the results were compared. Parameters analyzed from baseline recordings were presented in table-2. Although statistically not significant, there was a tendency to have a higher frequency in data derived from MAP recordings in comparison to bipolar recordings. Similar results were found between MAP and bipolar electrograms following drug infusion. The data from MAP recording revealed an averaged

Table 1. Characteristics of the study population

CHARACTERISTICS	IBUTILIDE	PROCAINAMIDE	PLACEBO	P value
Number of patients	10	10	7	-
Age (year)	66±9	68±6	64±7	.547
Hypertension	5 (%50)	6 (%60)	3 (%43)	-
Congestive heart failure	3 (%30)	4 (%40)	1 (%14)	-
Coronary artery disease	6 (%60)	7 (%70)	5 (%71)	-
Duration of AF (day)	28±13	44±20	12±12	0.001*
LA size (mm)	40±8	44±5	46±4	0.245
EF (%)	44±12	43±7	40±11	0.736

Table 2. Comparison of MAP and bipolar recording before any drug infusion

PARAMETERS	MAP recording (n=6)	BIPOLAR recording (n=6)	P value
Recording time (sec)	234±71	253±22	*
Max. frequency (Hz)	7.6±1.2	7.2±1.7	*
min. frequency (Hz)	4.7±.4	4.6±1.2	*
1st max. peak f (Hz)	6.0±1.0	6.0±1.3	*
2nd max peak f (Hz)	6.1±1.1	5.8±1.0	*
3rd max. peak f (Hz)	6.4±.8	6.1±1.1	*
4th max. peak f (Hz)	6.3±.9	6.2±1.2	*
5th max. peak f (Hz)	6.7±.8	6.0±1.1	*
Average frequencies (Hz)	6.4±.9	6.0±1.1	*
The width of the distribution (Hz)	2.9±1.0	2.5±.9	*

** P>0.03*

CL approximately 8 msec shorter than the CL derived from bipolar recordings.

Analysis of baseline recordings between groups: A total of 27 baseline recordings were analyzed. The recording time analyzed was 159±99, 198±70 and 202±74 sec and peak frequency of atrial fibrillation was 6.2±.6, 6.5±1.1 and 6.6±.5 Hz in groups I, P and C, respectively. Although none of the parameters of FFT analysis was significantly different between groups, atrial fibrillation in control group has a tendency to be faster than the others.

The effect of first dose of ibutilide on atrial fibrillation: Ibutilide 1mg given intravenously in 10 minutes decreased the atrial fibrillation rate significantly ($p<0.05$). Average frequency of atrial fibrillation decreased from 6.1 to 4.4 Hz. A subanalyis revealed that the effect of ibutilide on frequency of atrial fibrillation started to reach statistically significant level in 30 sec. following drug infusion. All of the FFT parameters were found to be decreased significantly (table-4). Of 3 patients converted to sinus rhythm, two received 1 mg single dose of ibutilide, one patient received 1+1 mg ibutilide.

Comparison of the parameters after first and second ibutilide: Seven patients were given the second dose of ibutilide after 10 minutes from completion of the first dose of ibutilide. The total dose of ibutilide given per patient was 1.4±0.6 mg. Maximal frequency decreased further (from 5.5±.7 to 4.9±.5 Hz, p=.112), but minimal frequency reached a statistically significant level from 3.5±.4 to 3.2±.3 (p=0.008). The difference between the max and min frequency (width of frequency) was not significant when compared before and after the second dose of ibutilide. There was significant decrement in 2nd and 3rd peak frequencies. Average of peak frequencies also showed a significant slowing of atrial fibrillation between first and second ibutilide infusion (from

Table 3. Comparison of the baseline data between groups

PARAMETERS	GROUP-I	GROUP-P	GROUP-C	P value
Recording time (sec)	159±99	198±70	202±74	*
max. frequency (Hz)	7.6±1.0	7.9±1.5	8.2±.3	*
min. frequency (Hz)	4.6±.5	5.0±.9	4.8±.5	*
1st max. peak f (Hz)	6.2±.6	6.5±1.1	6.6±.5	*
2nd max peak f (Hz)	6.0±.6	6.4±1.3	6.8±.5	*
3rd max. peak f (Hz)	6.0±.6	6.5±1.1	6.7±.5	*
4th max. peak f (Hz)	6.0±.7	6.5±1.0	6.6±.8	*
5th max. peak f (Hz)	6.2±1.6	6.3±0.8	7.0±.6	*
Average frequencies (Hz)	6.1±.6	6.5±1.1	6.7±.5	*
The width of the distribution (Hz)	3.0±.7	2.9±1.1	3.4±.5	*

* *P>0.2*

Table 4. Comparison of the parameters before and after ibutilide and procainamide drug infusion

PARAMETERS	Before ibutilide	After ibutilide	P value	Before procainamide	After procainamide	P value
Recording time(sec)	159±99	230±49	0.045	198±70	227±60	0.43
max. frequency (Hz)	7.6±1.0	5.5±.7	*	7.9±1.5	5.3±.8	*
min. frequency (Hz)	4.6±.5	3.5±.4	*	5.0±.9	3.7±1.0	*
1st max. peak f (Hz)	6.2±.6	4.3±.3	*	6.5±1.1	4.5±.8	*
2nd max peak f (Hz)	6.0±.6	4.3±.4	*	6.4±1.3	4.5±.8	*
3rd max. peak f (Hz)	6.0±.6	4.4±.4	*	6.5±1.1	4.5±.8	*
4th max. peak f (Hz)	6.0±.7	4.4±.2	*	6.5±1.0	4.5±.8	*
5th max. peak f (Hz)	6.2±1.6	4.2±.5	*	6.3±0.8	4.5±.8	*
Average f (Hz)	6.1±.6	4.4±.3	*	6.5±1.1	4.5±.8	*
The width of f distribution (Hz)	3.0±.7	2.0±.5	*	2.9±1.1	1.7±.6	0.021

p<0.05

4.3±.3 to 4.0±.36 Hz, p=.049). The mean serum concentration of ibutilide in 8 patients was 5.43±4.46 ng/mL (range 11.91-0.94).

The effect of procainamide on atrial fibrillation: Ten patients received 1240±221 mg procainamide intravenously. Procainamide decreased the mean frequency of atrial fibrillation significantly from 6.5±1.1 to 4.5±.8 Hz. The other parameters also decreased significantly similar to the effects of ibutilide on AF (table-4).

Procainamide dosage given was 1241±210 mg (15 mg/kg) and serum procainamide concentration in 8 patients was 10±2 mg/L. None of the patients in group-P was converted to sinus rhythm.

Table-4 compares the effects of ibutilide and procainamide on atrial fibrillation. None of the FFT parameters was significantly different between groups.

Comparison of converted and nonconverted patients; predictors of successful cardioversion: Ibutilide was successful in restoring sinus rhythm in 30% of patients, while procainamide was not effective at all. The mean time to cardioversion after initiation of ibutilide was 16±10 minutes. Comparison of the FFT parameters at baseline before any drug infusion between converter and nonconverters are summarized in table-5. Serum ibutilide concentration was significantly higher in converted patients (7.88±3.81 vs. 1.99±0.99 ng/mL). Cardioverted patients had significantly slower AF rate than nonconverted patients. The first maximal peak frequency before drug infusion was 5.7±0.3 and 6.4±.06 Hz in converted

Table 5. Comparison of parameters at baseline between converted and nonconverted patients in group-I.

PARAMETERS	Converted group (n=3)	Nonconverted group (n=7)	P value
LA size (mm)	36±15	43±4	*
EF (%)	50±10	41±12	*
Ibutilide serum concentration (ng/mL)	7.88±3.81	1.99±0.99	0.028
Duration of AF (days)	21±16	30±12	*
Recording time (sec)	198±104	142±100	*
max. frequency (Hz)	7.4±1.8	7.6±.6	*
min. frequency (Hz)	4.8±.8	4.5±.5	*
1st max. peak f (Hz)	5.7±.3	6.4±.6	0.048
2nd max peak f (Hz)	5.8±.5	6.1±.6	*
3rd max. peak f (Hz)	5.6±.3	6.2±.7	*
4th max. peak f (Hz)	6.2±1	5.9±.7	*
5th max. peak f (Hz)	5.5±2.8	6.4±.6	*
Average f (Hz)	5.8±1.0	6.2±.5	*
The width of f distribution (Hz)	2.5±1.0	3.1±.3	*

** P>0.05*

and nonconverted patients, respectively. Comparison of the FFT parameters derived from recordings 5 minutes before cardioversion between converter and nonconverters are summarized in table-6. In converted patients, the first, second and third peak and the averaged frequency were found to be decreased significantly more than it was in nonconverted patients.

DISCUSSION

Fast Fourier Transformation (FFT) is a spectral analyzing method that decomposes a waveform into its components according to its frequency and contribution. It has been applied in a variety of studies eliminating the need of manual measurement of cycle length of atrial fibrillation waves [8,14,15]. This study tested whether the analysis of FFT of atrial fibrillation waveform could predict the success of drugs in converting atrial fibrillation.

The waveform of MAP recordings resembles action potential and presents an ideal shape for FFT analysis since it looks like a sinusoidal waveform. In contrast to MAP recording, bipolar recordings have sharp and narrow deflections which decrease the power spectrum due to decreased integral of the recordings and give a biphasic potential which may cause difficulty in determining the baseline. Additionally, insufficient quality of bipolar recording was detected more frequently. This may drive from the design of the study since the quality of MAP recording has the priority over bipolar recordings. Despite of these disadvantages of bipolar recording in FFT analysis, comparison with MAP recording in a subgroup of patients disclosed a high correlation in detecting frequency of AF. Atrial fibrillatory CL derived from MAP recordings had a tendency to be slightly shorter than those obtained from bipolar electrogram. MAP potentials were noted to be more stable and revealed clear FFT analysis. However, bipolar electrograms can also be used with success for this purpose.

In a previous study by Bollmann et al.[16], spectral analysis of AF was performed from surface ECG and the baseline frequency of AF in patients with successful cardioversion with ibutilide was found to be significantly lower than that in those without success (5.63±0.92 vs. 7.27±1.12 Hz). In our study, these values were 5.7±0.3 vs. 6.4±0.6, respectively (p=0.048). Exclusion of the patients with AF more than 3 months in our study may attribute to a lower frequency (6.4±0.6 Hz) when compared to nonconverters in the previous study (7.27±1.12 Hz).

Effects of ibutilide and procainamide on atrial fibrillation: Both ibutilide and procainamide decreased

Table 6. Comparison of parameters between converted and nonconverted patients in group-I following ibutilide infusion

PARAMETERS	Converted group (n=3)	Nonconverted group (n=7)	P value
Recording time(sec)	215±79	237±37	*
max. frequency (Hz)	5.1±1	5.7±.6	*
min. frequency (Hz)	3.2±.2	3.6±.5	*
1st max. peak f (Hz)	4.0±.2	4.4±.3	0.066
2nd max peak f (Hz)	4.0±.1	4.5±.4	0.009
3rd max. peak f (Hz)	3.9±.3	4.6±.73	0.006
4th max. peak f (Hz)	4.3±.3	4.4±.2	*
5th max. peak f (Hz)	4.0±.6	4.4±.4	*
Average f (Hz)	4.1±.2	4.5±.3	0.036
The width of f distribution (Hz)	1.8±1	2.1±.6	*

** P>0.05*

AF frequency and dispersion of local atrial depolarization (changes in frequency) in a similar manner. This may be best explained by decreased numbers of, and/or increased wavelength of fibrillatory wavefronts. Although this study does not test this hypothesis, a number of studies support this phenomenon [4,5]. Ibutilide effected FFT parameters in a dose dependent manner. Serum concentration of ibutilide is a strong predictive of successful cardioversion. Ibutilide decreases the frequency of AF to a critical level (3.5±0.1 Hz) before cardioversion. Decrement in the frequency of peaks gained statistically significance within 30 sec from the initiation.

Procainamide was ineffective in converting AF into sinus rhythm. Relatively long duration of AF (44±20 days) may explain unsuccessful cardioversion in this group. Ibutilide was more effective than procainamide in converting AF.[17] The enhanced conversion efficacy of ibutilide compared with procainamide in atrial flutter was correlated with a relatively greater prolongation of atrial monophasic action potential duration than AFL cycle length [12]. In this study, this difference did not reach a statistically significant level. Prolonged duration of AF in group-P may partly explain this mismatch.

Limitations of the study: This study has the common limitations of a retrograde study. A comparison with high resolution mapping technique would be helpful for complete analysis of AF wavelets. Intra- or interobserver deviation was not studied. Group-P had a longer duration of AF. The MAP catheter is specifically designed catheter and may not be appropriate for standard usage. Determination of the width of frequency distribution was somewhat arbitrary, although 0.5 Hz width of the frequency peak was a prerequisite for evaluation. The amplitude of AF recording was disregarded due to calibration difficulties. Action potential duration was not measured in the study.

In conclusion, FFT analysis is valuable in predicting successful cardioversion of AF by ibutilide and serves as a means of new insights in detection of mechanisms of antiarrhythmic medications.

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