The Frequency Analysis of Signal-Averaged ECG of P Wave as Predictor of Efficacy of Class III Antiarrhythmic Drugs to Maintain Sinus Rhythm in Recurrent Idiopathic Atrial Fibrillation

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Background: The use of class III antiarrhythmic drugs (ADIII) has been considered a good predictor of sinus rhythm in patients post-cardioversion from atrial fibrillation (AF). Several studies using frequency domain analysis of signal-averaged ECG (FDSAECG) of the P wave were able to identify patients at risk for AF. The aim of this study was to assess the FDSAECG in predicting recurrence of idiopathic persistent AF (IPAF) in patients under ADIII therapy.

Methods: In 33 patients with two or more previous symptomatic episodes of IPAF, despite classes I and II therapy, the FDSAECG of the P wave was performed during sinus rhythm and free-drug state. The parameters were the mean and standard deviation of the frequency intersegmentar spectral correlation and the standard deviation of the signal frequency edge track. During the follow-up of 30 ± 18 months, all patients received either amiodarone or sotalol.

Results: During the follow-up, the patients were divided into two groups: Group I—frequent recurrence (≥ three events/year; 16 patients), and Group II—infrequent recurrence (< three events/year; 17 patients). With appropriate cutoff points for each parameter analyzed, intense fragmented electrical activity defined by the presence of at least two abnormal criteria were observed in 13 of 16 patients group I and in 3 of 17 patients group II ($P = 0.0003$). Sensitivity, specificity, positive and negative predictive values for frequent recurrence were 81.3, 82.4, 81.3, and 82.4, respectively.

Conclusions: The results suggested that FDSAECG analysis of the P wave accurately predicted patients whose ADIII therapy will be effective in maintaining the sinus rhythm without frequent recurrence of IPAF.

A.N.E. 2001;6(1):43–49

signal-averaged ECG; P wave, idiopathic atrial fibrillation; spectral-temporal mapping; antiarrhythmic therapy

Chronic or paroxysmal atrial fibrillation (AF) is the most frequent arrhythmia in human subjects. The prevalence of AF increases with age and may be as high as 10% in a population older than 75 years old.[1-3] The idiopathic form of AF occurs with a frequency ranging from 2.7 to 11.4% in the population suffering from this type of arrhythmia, with the most important complication being thromboembolism.[4-7] After the first episode, the rate of recurrence of lone AF ranges from 5 to 65% in a

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period of 1 year.[5,8-9] The number of episodes and the refractoriness to one or more antiarrhythmic agents seem to predict the rate of recurrence. The utilization of class III antiarrhythmic drugs (ADIII) in patients with AF has been considered a good predictor for maintenance of sinus rhythm.[10] However, there is no definite method in the literature to predict frequent recurrence or transition from paroxysmal to chronic AF in patients under ADIII therapy.

In the present study, we assessed the signal-averaged electrocardiogram of the P wave in the frequency domain (FDSAECG) as a predictor of frequent recurrence of idiopathic and persistent AF (IPAF) in patients under ADIII therapy and refractory to classes I and II antiarrhythmic drugs to maintain sinus rhythm.

METHODS

Study Population

Between 1992 and 1999, among 842 patients with AF scheduled for treatment at our arrhythmia control unit, 33 patients presenting two or more previous episodes of IPAF (mean ± SD; 57.1 ± 10.6 years old, 27 males), despite antiarrhythmic class I and II therapy, were eligible for the study. Idiopathic AF was defined on the basis of history, conventional electrocardiography, chest X-ray, echocardiography, stress testing if necessary, and thyroid function tests. The mean number episodes of AF per patient before enrollment in the study was (mean ± SD) 2.8 ± 0.7. All patients provided informed consent before the start of the investigation.

Each patient had the SAECG of the P wave recorded with a modified orthogonal system comprising of three bipolar leads (Predictor IIc, ART Corazonix, TX, USA). The X lead was standardized for P wave coherent-averaging on the second intercostal space at the right sternal border and on the left lower rib border at the hemiclavicular line. The Y lead was placed on the fifth interscostal space at the left and the right mid axillary lines. The Z lead was placed anteriorly at the level of the fourth intercostal space to left sternal border and its projection in the back. Positive reference electrodes were placed inferior, left and anterior, respectively to the leads X, Y, and Z. The position of X and Y electrodes were switched, when compared with conventional orthogonal leads, to allow the system to average a larger and taller P wave.

The sampling frequency was set at 2.0 KHz. The fiducial point was shifted to the right, and the P wave and PR segment were exposed. The noise window was placed on the T-P segment with a duration on 50 ms. The averaging was conducted using a R-triggered technique with a correlation window of 40 ms placed on the ascending limb of P wave and a correlation coefficient of 0.99. The final noise estimate was equal or lesser than 0.3 μv in all measurements.

Each patient discontinued all classes I and II antiarrhythmic medications for at least five half-lives before signal-averaging.

Frequency Domain Analysis

After signal averaging, the analytic region in the X-modified lead was preprocessed to extract the first derivative and the mean value. The region for frequency analysis was constructed using a 16 ms Blackmann-Harris window segment and the boundaries of the region were placed 16 ms prior to the onset of the P wave and on a point moved forward 200 ms onto the PR segment. The power spectral amplitude distribution of each segment was generated with a 512-point FFT at intervals of 2 ms. Noise ratio was fixed in 30. Spectral analysis was carried out by calculating the mean (MEC) and the standard deviation (SEC) of intersegmental spectral correlation and the standard deviation (SET) of signal frequency edge track. The spectral correlation analysis employed the linear correlation coefficient between successive spectral segments along the atrial activation, generating a time series from which MEC and SEC were extracted. A perfect correlation would have MEC equal to 1 (r = 1) with SEC equal to zero and would represent, hypothetically, an absolutely uniform conduction of the electrical signal. To make its reading and management easier, the correlation indexes were multiplied by 100. The signal frequency edge track identifies, for each spectral segment, the frequency that limits its energy concentration at 80% of the area, within atrial activation. The standard deviation of consecutive frequency limits are extracted and expressed in Hz. We assume that a greater conduction disturbance will present higher indexes of SEC and SET and lower the values of MEC, defining the presence intense fragmented electrical activity in atria (FEA).

Follow-up

During a follow-up of 30 ± 18 months, all patients had contact by scheduled clinic visits. Information relative to AF recurrences during follow-up was obtained from patient interviews and from review of the medical records. Persistent AF recurrence was defined as the recurrence of this arrhythmia with ECG documentation and necessity of medical intervention for restoration of the sinus rhythm as the result of either increment of drug therapy or electrical cardioversion. The endpoint of the study was chronic AF, and the results of study were analyzed by December 1999.

At the end of the follow-up period, the patients were divided into two groups, according to the average number of recurrences/year/patient. Group I (GI) comprised patients with frequent recurrence of AF defined as three or more events/year, and Group II (GII) included those with infrequent recurrence of AF defined as two or less events/year.

Antiarrhythmic Treatment

After conversion to sinus rhythm and signal-averaged ECG recorded, ADIII therapy was prescribed at the discretion of the primary evaluation. Amiodarone was prescribed with a loading dose of 800 mg/day during 7 days and initial maintenance dose 200 mg/day; DL-sotalol was prescribed with initial dose 80 mg bid. According to the rate of recurrence, maintenance doses ranged from 200 to 600 mg/day for amiodarone and from 80 to 160 mg bid for DL-sotalol. Change of medication between DL-sotalol and amiodarone was allowed.

Statistical Analysis

The continuous variables were expressed as mean ± SD and compared between the groups using Student *t*-test. The discrete variables were reported as ratio or percentage and analyzed by either chi-square or Fisher's exact test, when appropriate. The frequency domain variables were dichotomized to provide an optimal discrimination. Diagnostic performance of the P wave SAECG for IPAF was assessed by sensitivity, specificity, positive and negative predictive values. Considering the presence of FEA as an exposure factor for recurrence of AF, the odd ratio for frequent recurrence and its exact 95% confidence interval were calculated. Alpha error level was set at 0.05.

RESULTS

Clinical Characteristics

At the end of the follow-up, 16 patients were included in GI and 17 patients in GII. The clinical characteristics of the groups are summarized in Table 1. Age and gender distribution did not show significant differences between GI and GII. The rate of recurrence of AF was significantly higher in the GI than in the GII (P = 0.006). The follow-up period of GI was shorter then GII due to the greater number of patients who developed chronic AF in the former. The mean age of the patients that evolved chronic AF was significantly higher than in patients who remained in sinus rhythm (64.1 ± 6.2 vs 55.2 ± 10.8 years old; P = 0.04).

Frequency Domain Analysis

The values of MEC, SEC, and SET are presented in Table 1. The values of MEC and SEC in GI were

Table 1. Distribution of the Clinical Characteristics and FDSAECG Results of the Groups

	Group I (N = 16)	Group II (N = 17)	P
Age (y.o.)*	58.6 ± 8.7	58.6 ± 8.5	NS
Gender (M/F)	14/2	13/4	NS
Follow-up (months)*	13.7 ± 2.4	47.2 ± 8.2	<0.001
Events/year**	4.6 ± 1.2	1.5 ± 0.6	0.006
Evolution to chronic AF	7/16	0/17	0.006
MEC*†	73.4 ± 8.9	84.3 ± 3.8	0.04
SEC*†	38.4 ± 11.8	26.8 ± 8.3	0.002
SET*†	72.6 ± 14.6	68.7 ± 20.3	NS

* Mean ± SD; † Parameters of the FDSAECG (see text for details).

significantly different from GII (MEC: 73.4 ± 8.9 vs 84.3 ± 3.8; P = 0.04 and SEC: 38.4 ± 11.8 vs 26.8 ± 8.3; P = 0.002). The values of SET were found to be slightly larger in GI than GII but did not achieve statistical significance (SET: 72.6 ± 14.6 vs 68.7 ± 20.3 Hz; P = 0.53).

With the cut-off points of abnormality at MEC < 79, SEC > 32 and SEt > 75, FEA defined by the presence of at least two abnormal criteria was observed in 13 of 16 patients in GI and 3 of 17 patients in GII (P = 0.0003) (Fig. 1). The FEA identified both groups with a sensitivity of 81.3% (P ≪ 0.001) and a specificity of 82.4% (P ≪ 0.001). The positive and negative predictive values of FEA for frequent recurrence of IPAF were 81.3% (P ≪ 0.001) and 82.4% (P ≪ 0.001), respectively. The odds ratio of FEA for frequent recurrence of IPAF in patients with ADIII was 20.2, with P = 0.003 (Table 2). The mean age of the patients with and without FEA did not show significant difference (56.8 ± 8.6 vs 56.4 ± 12.1 years old, respectively; P = 0.93). Examples of FDSAECG are displayed in Figure 2.

Antiarrhythmic Treatment

At the end of the follow-up, 22 patients (59.4 ± 9.1 years old; 17 males) were using of amiodarone and 11 patients (52.5 ± 12.2 years old, P = NS; 10 males, P = NS) were using DL-sotalol. The relative distribution of ADIII in both groups showed an increased usage of amiodarone compared with Dl-sotalol in GI but did not achieve a statistically significant difference. Also, the distribution of ADIII regarding the prevalence of FEA was found to be statistically not significant. Table 3 summarizes the results of the antiarrhythmic treatment.

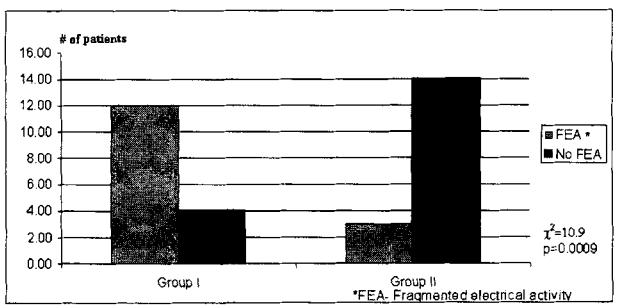

Figure 1. Distribution of fragmented electrical activity regarding the frequency of recurrence of AF, under class III antiarrhythmic therapy. (See text for details).

Table 2. Diagnostic Performance of the Frequency Domain Analysis of the SAECG According to Rate of Recurrence of Idiopathic Persistent Atrial Fibrillation

	Value	95% Confidence Interval
Sensitivity	81.3%	53.7%–95.0%
Specificity	82.4%	55.8%–95.3%
Positive predictive value	81.3%	53.7%–95.0%
Negative predictive value	82.4%	55.8%–95.3%
Odds ratio for FRAF*	20.2	2.8–171.6

* FRAF = frequent recurrence of atrial fibrillation.

DISCUSSION

P-Wave SAECG

The SAECG of the P wave has become a promising tool for understanding the mechanism of AF and the identification of a potentially vulnerable heart.[11]

In the time domain, the characterization of abnormal P waves has been extensively studied. The criteria for analysis has undergone substantial variations as a consequence of the averaging protocol or the filter settings employed for analysis, yielding controversial results.[12]

However, the positive identification of P-wave late potentials can be difficult due to the activation pattern of the atria. In contrast to the ventricles, the end of the activation of the right overlaps the beginning of the activation of the left chamber, limiting the detection of late potentials arising in the right atrium. This condition is especially relevant in the diagnosis of idiopathic AF or flutter, because the reentry circuits are frequently located in the right atrium and are unlikely to produce low energy potentials at the terminal portion of the P wave.

Frequency Domain Analysis

Several authors have found significant results using FDSAECG, particularly those concerned with the identification of the electrical substrate of ventricular tachycardia inside the QRS complex.[13-16] Fragmented electrical activity arising from regions of slowed conduction in damaged myocardium produces high frequency components, which can be detected by Fourier decomposition of the surface ECG signal. In this context, Kellen et al. developed a method that was able to detect variations of the energy content of the ven-

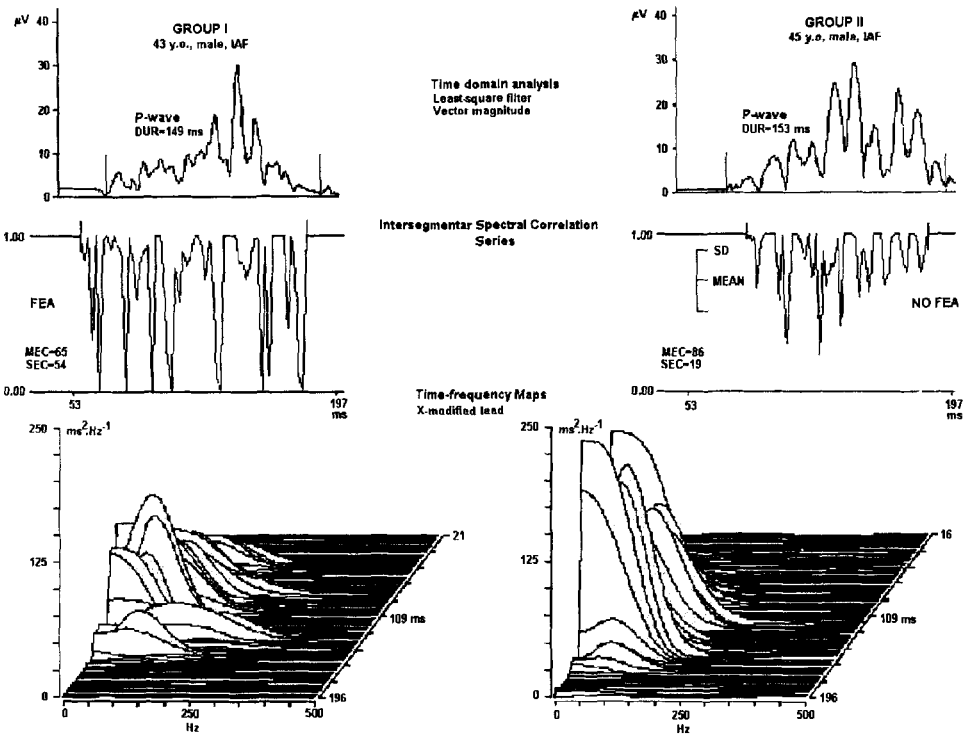

Figure 2. In the upper left and right corners, the time domain analysis of two patients with frequent recurrence (Group I) and infrequent recurrence of persistent IAF (Group II), respectively. In lower left and right corners the frequency domain analysis of the same patients. In the middle left and right, the intersegmentar spectral correlation series generated from each time-frequency map. Note that in spite of the same P wave duration in both patients, the one in GI with FEA, the value of MEC was 65 and SEC was 54, indication turbulence. (DUR: Duration of the P wave; FEA: Intense fragmented electrical activity; IAF: Idiopathic atrial fibrillation)

tricular activation wavefront by the application of Pearson's correlation coefficient between adjacent short-time FFT-calculated spectral segments of the QRS complex, naming adverse results as spectral turbulence.[17] During sinus rhythm, these conduction disturbances produced continuous and abrupt changes in the frequency content of the electrical signal, which were considered to cause low intersegmental spectral correlation of the signal energy.

The inter- and intra-atrial conduction may be disturbed in patients with IPAF.[18-20] Histological studies reveal the presence of fibrosis and amyloid infiltration in the atrial myocardium in patients with rheumatic and nonrheumatic AF, indicating a formal substrate for slow and nonuniform anisotropic conduction.[21-23]

Several investigators have centered attention on the frequency distribution or the energy content

Table 3. Distribution of the Results of the Antiarrhythmic Treatment

	Amiodarone (N = 22)	DI-Sotalol (N = 11)	P
Age (y.o.)*	59.4 ± 9.1	52.5 ± 12.2	NS
Gender (M/F)	17/5	10/1	NS
Prevalence of recurrence (GI/GII)**	13/8	3/9	NS
Prevalence of FEA (+/−)***	12/10	4/7	NS

* Mean ± SD; ** GI = frequent recurrence of AF; GII = infrequent recurrence; *** + = Positive FEA; − = negative FEA

during atrial activation using SAECG of P wave. Yamada et al. used frequency analysis of the atrial SAECG and demonstrated that the terminal portion of the P wave contains more components in the 20 to 50-Hz range in patients with than without AF.[24] Hiraki et al. investigated the usefulness of both time and frequency domain analysis of the P wave for detecting patients with paroxysmal AF and found a predictable accuracy in the frequency domain of 83%.[25] Stafford attempted to evaluate the frequency spectrum of both the entire P wave and its terminal portion in patients with idiophatic AF.[26] Analysis of the entire P wave was less influenced by variations of its endpoint than analysis of the terminal portion alone, and was more efficient in predicting paroxysmal AF. All of those studies have demonstrated an increase in the voltage at higher frequencies in patients with paroxysmal AF when compared with control subjects. Most studies evaluated markers of abnormal atrial conduction from the third quarter of the P wave.

In a previous study, we used an adaptation of the spectral correlation method, here described, for the analysis of atrial activation and tested the efficacy of the method in identifying individuals with idiopathic AF after the first episode.[27] The sensitivity and specificity for patients with and without AF were found to be 71 and 92%, respectively. However, spectral turbulence was not able to identify frequent recurrence of idiopathic AF. In a previous report, using a similar technique of time-frequency analysis, Stafford observed a slight trend towards higher spectral turbulence in patients with lone AF than in control subjects.[28] However, the differences were small and not statistically significant. One possible reason for these different findings between both studies is the variation in the method used. In Stafford's study, the correlation coefficients were calculated in frequencies of 80 - 400 Hz for each lead, and a mean value for all three leads was derived. We analyzed the frequency range from 0 to 300 Hz and the correlation coefficients were calculated in the X-modified lead that was able to show a taller and larger P wave. Michellucci et al. reported that the Y lead better dichotomized patients with lone AF from controls and established that more than 95% of the energy content of the P wave in both groups was concentrated below 50 Hz, indicating an optimal range for frequency domain analysis.[29]

In the present study, we have found that in a selected group of patients with recurrent lone and persistent AF refractory to class I and II antiarrhythmic drugs, spectral turbulence is a marker of frequent recurrence ($\geq$ 3 events per year) despite of the use of ADIII therapy. This observation provides not only a detailed and noninvasive characterization of the disturbed atrial activation, but also indicates that these abnormalities are closely associated with idiophatic AF. Spectral turbulence is believed to reflect the fractionation of the underlying activation wavefront and is able to detect timed abnormality. Idiopathic AF is associated with the fractionation of conduction occurring into the both left and right atria.[30] Thus, these conduction disturbances may be most apparent in the center of the P wave (simultaneously, right and left atrial activation) and not only in the terminal portion (predominant left atrium activation), validating the spectral segmentation for analysis of the P-wave.

Follow-up and Antiarrhythmic Treatment

In our study, the rate of recurrence and the evolution to chronic AF was found to be higher than previous reports.[5,31-32] This finding can be explained by the fact that all patients were refractory to class I and II antiarrhythmic drugs and presented several episodes of idiopathic and persistent AF (mean $\pm$ SD; events 2.8 $\pm$ 0.7) before enrollment.

DL-sotalol usually shows similar efficacy in maintaining sinus rhythm as group I antiarrhythmic drugs, after successful cardioversion of patients with AF.[33-35] It has been frequently employed as the first choice due to its beta-blocking activity for controlling the ventricular rate.[36] However, amiodarone is considered to be more efficient than DL-sotalol in maintaining sinus rhythm after cardioversion.[37] However, its use is limited due to possible side effects. In our study, there were no side effects that needed interruption of the treatment.

At the end of the study, the distribution of drugs showed a trend toward an increased usage of amiodarone rather than DL-sotalol in GI. The primary choice of ADIII treatment, increment of doses, and change between DL-sotalol and amiodarone were at the discretion of the assistant physician and may account for the slight prevalence of amiodarone in GI.

CONCLUSION

The FDSAECG is able to predict accurately the effectiveness of ADIII therapy in reducing the rate of recurrence when administered to a selected group of patients with persistent and idiopathic AF refractory to class I or II antiarrhythmic therapy.

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