Non-Invasive Characterization of Atrial ActivityImmediately Prior to Termination of Paroxysmal Atrial Fibrillation

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Introduction and objectives. Detaited characterization of atrial activity can be achieved by analyzing invasive recordings. Nevertheless, electrocardiographic signal processing tools can nowadays obtain equivalent information in some cases. The aim of this work is to study the electrocardiographic alterations produced during the interval prior to spontaneous AF termination.

Methods. Fifty patients in paroxysmal AF with an episode lasting more than 2 hours were selected. The last minute prior to spontaneous AF termination (group S) and the central minute (group N) from each episode were analyzed. Ventricular response, *f* waves morphology, and atrial activity spectral and organization were studied through the use of signal processing tools.

Results. RR intervals variability was a discriminative parameter (group S 630 ± 200 ms vs group N 740 ± 100 ms; P=.034), although a low specificity was obtained (54.2%). Significant differences between both groups were not reported by the *f* waves morphological study. Group S presented a significant low dominant atrial frequency mean value than group N (group S 5.010 ± 0.671 Hz vs group N 6.514 ± 0.804 Hz, p=4.55×10^{-9}). Finally, group N showed a considerable low atrial activity organization degree than group S (group S 0.071 ± 0.012 vs group N 0.103 ± 0.013, p=6.73×10^{-12}).

Conclusions. The analysis of the electrocardiographic interval prior to spontaneous AF termination has revealed an atrial activity organization process, which cannot be observed by visual inspection of *f* waves morphology, but can be successfully quantified through signal processing.

Key words: *Atrial fibrillation. Electrocardiography. Cardioversion.*

Caracterización no invasiva de la actividad auricular durante los instantes previos a la terminación de la fibrilación auricular paroxística

Introducción y objetivos. Mediante procesado de señal se puede analizar la actividad auricular en fibrilación auricular (FA) desde los registros de superficie y obtener una información muy próxima a la de los registros intracavitarios. El objetivo del trabajo es estudiar las modificaciones electrocardiográficas en la FA durante el intervalo previo a su conversión espontánea a ritmo sinusal.

Métodos. De 50 pacientes, se seleccionó un episodio de FA paroxística de más de 2 h. De cada episodio se analizó el último minuto antes de la reversión a ritmo sinusal (grupo S) y el minuto central (grupo N). Se comparó a los dos grupos analizando la respuesta ventricular, la morfología de ondas *f* y el análisis frecuencial y de organización de la actividad auricular aplicando procesado de señal.

Resultados. La variabilidad RR fue un parámetro discriminativo, aunque con poca especificidad (grupo S, 630 ± 200 ms; grupo N, 740 ± 100 ms; p = 0,034). El análisis morfológico de ondas *f* no mostró diferencias significativas. El grupo S presentó una frecuencia auricular dominante media significativamente menor (grupo S, 5,01 ± 0,671 Hz; grupo N = 6,514 ± 0,804 Hz; p = 4,55 × 10^{-9}). La medida de organización de la actividad auricular fue significativamente mayor en el grupo S (grupo S, 0,071 ± 0,012; grupo N, 0,103 ± 0,013; p = 6,73 × 10^{-12}).

Conclusiones. El minuto electrocardiográfico previo a la conversión espontánea de la FA muestra un proceso de organización de la actividad auricular difícilmente apreciable mediante análisis morfológico de las ondas *f,* aunque predecible mediante procesado de señal.

Palabras clave: *Fibrilación auricular. Electrocardiografía. Cardioversión.*

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ABBREVIATIONS

AF: atrial fibrillation
DAF: dominant atrial frequency
PSD: power spectral density

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia found in clinical practice and can take various forms: paroxysmal, persistent, and permanent. It is common for the patient to undergo paroxysmal AF episodes with spontaneous conversion to sinus rhythm before becoming permanent.[1] Several studies have analyzed the electrophysiological alterations that occur during the first minutes of AF and have described a process of electroanatomic remodeling.[2,3] Other studies have specifically analyzed the final minutes of the arrhythmia after applying various therapeutic options, such as pharmacological treatment, electrical cardioversion, or ablation.[4,5] The effectiveness of these treatments seems to be related to factors such as how long the arrhythmia has been present, atrial size, patient age, etc, although electrocardiographic parameters with predictive value regarding therapeutic outcome have also been described, such as P wave amplitude,[6] RR interval variation,[7,8] or the dominant *f* wave frequency.[5,9] Nevertheless, to date, information is scarce on the interval prior to spontaneous cardioversion of AF to sinus rhythm unmediated by therapeutic intervention.[10-12]

Invasive recording techniques, such as intracavitary recording or epicardial mapping, have succeeded in characterizing local atrial activity[13,14] with a high degree of detail, and episodes of organized atrial activity have been detected during the final moments of AF.[15] In contrast, it is more difficult to analyze atrial activity using surface electrocardiographic recordings obtained with Holter monitoring (which continually stores the signal and thus can very easily detect spontaneous episodes of cardioversion to sinus rhythm), since this has a smaller amplitude, can be distorted by ventricular activity, and involves the drawbacks inherent to non-invasive recording. Nevertheless, computational techniques have been recently developed for electrocardiographic signal processing which are capable of analyzing atrial activity during AF from surface recordings offering results that in some cases are comparable to those obtained from intracavitary recording.[16,17]

Thus, the aim of this work was to study AF electrocardiographically during the interval prior to its conversion to sinus rhythm and in this way study the electrophysiological alterations produced. To this end, signal processing tools were used to analyze the parameters obtained from ventricular response, *f* wave morphology, spectral analysis of atrial activity, and organization.

METHODS

The study included 50 patients, whose demographic and clinical data are shown in Table 1. The patients had symptoms of palpitations, without structural pathology or other known cardiovascular risk factors, and were not under associated medical treatment during the study. All patients underwent Holter monitoring for 24 h. Every patient in paroxysmal AF with an episode lasting more than 2 h was selected, and 2 segments were analyzed: the last minute prior to spontaneous reversion to sinus rhythm, and the central minute of each episode, denominated group S and group N, respectively.

The atrial signal from lead V_1 was selected for this study. All the recordings were digitized at a sampling frequency of 128 Hz and at 16-bit resolution, although these were resampled at a frequency of 1 kHz to subtract the QRS-T complex with greater accuracy.[16]

To facilitate later electrocardiographic signal processing, baseline drift was eliminated by applying a bidirectional high-pass filter at a 0.5 Hz cutoff frequency,[18] high-frequency noise was eliminated by using a bidirectional 8-order low-pass Chebyshev IIR filter with a cutoff frequency of 70 Hz,[19] and powerline noise was eliminated with an adaptive digital notch filter, which achieves this without affecting the spectral content of the ECG.[20]

Given that AF is characterized by a random and irregular ventricular rate, we first analyzed RR interval variability, using Pan et al's[21] algorithm to locate each R wave. Subsequently, atrial activity was obtained from surface electrocardiographic recordings to characterize *f* wave morphology. To this end, an algorithm was used to cancel out ventricular activity based on extracting the QRS complex and the mean T wave[22] (Figure 1).

Once atrial activity was obtained, the *f* wave amplitude was obtained using Xi et al's[23] algorithm. In this algorithm, the *f* wave amplitude was obtained for each nonoverlapping 10-s segment as the mean value of the 4 waves with the greatest amplitude in that segment. To obtain another estimation of this amplitude, the total power of the atrial signal was also calculated. This power represents the energy contained in the *f* waves in the

TABLE 1. **Clinical Characteristics of the Patients**

Age, mean (SD), y	53 (9)
Men/women	31/19
Respiratory pathology, %	2 (4%)
Duration of symptoms, mo	8.6 (2-14)
Antiarrhythmic drugs used by the patient prior to the study, mo	6.1 (1-9)
Ejection fraction, %	51 ± 6%
Left atrial diameter, cm	33 ± 7
Mean duration of the episodes analyzed, h	2.7 ± 0.6

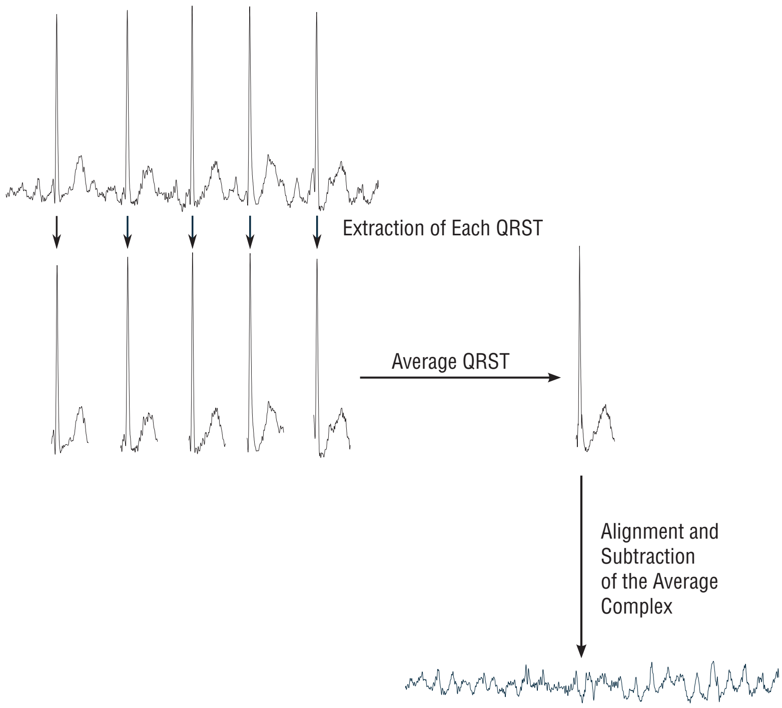

Figure 1. Algorithm to cancel out ventricular activity based on extracting the QRS complex and mean T wave T. Once all the R waves are detected an average complex is generated by aligning each one with their fiduciary point. Subsequently, the average complex is aligned with each ECG R wave, in such a way that by subtracting it from each individual complex a residual is obtained that basically represents the atrial activity in the analyzed lead.

time interval analyzed and, thus, it is a robust indicator of signal amplitude despite this being highly changeable. Total power was calculated by computing the quadratic sum of the standardized signal values at the time interval under analysis.[24]

Several studies have shown that the atrial signal can be considered as one or more frequency components within an amplitude of 3-9 Hz,[17,25] which is the reason for performing a spectral analysis of atrial activity. Thus, the power spectral density (PSD) was obtained for each nonoverlapping 10-s segment using the Welch periodogram with a 2048-sample Hamming window with a 50% overlap between consecutive windows as computational parameters.[26] The frequency with greatest amplitude within the amplitude 3-9 Hz was regarded as the dominant atrial frequency (DAF),[16] since it has been shown that in AF this is inversely related to atrial cycle length.[25] The standard deviation of this parameter was calculated at each 10-s interval to weight the stability and organization of the frequency. The frequency with the second largest amplitude (first harmonic) in the spectrum was obtained and the PSD value in each of these frequencies, since this is directly related to the amplitude of the wave produced by the reentries they represent.[10,27]

Finally, atrial activity organization was estimated by means of nonlinear regularity indices. Sample entropy was selected as the index, a tool that quantifies the predictability of fluctuations in the values of a time-series or, which is the same, their regularity, and assigns them a positive value that will be smaller the greater the quantity of repetitive patterns that it contains.[28,29]

Statistical Analysis

All the parameters analyzed were assessed in nonoverlapping 10-s segments with the aim of analyzing their temporal evolution with sufficient accuracy.

The results of the parameters are expressed as mean (standard deviation) for all the segments belonging to the same group, since all of them had a normal distribution as shown by the Shapiro-Wilks test. The Student t test for independent samples was used to compare group S and group N. A two-tailed p value less than .05 was considered statistically significant.

The value of each parameter that provided maximum discrimination between groups, that is, the optimum threshold, was obtained by means of receiver operating characteristic (ROC) curves. To obtain the curve of each parameter, several thresholds were automatically selected within a range of input values and the sensitivity-specificity pair calculated for each one. Sensitivity was defined as the number of correctly classified segments in group N, and specificity, as the proportion of correctly discriminated segments in group S. The optimal threshold chosen was the one whose sensitivity-specificity pair presented the minimum distance to the point with 100% sensitivity and specificity.

RESULTS

Table 2 shows the mean values and standard deviations obtained for each group for each parameter analyzed, statistical significance, and the sensitivity and specificity of the discrimination process.

Analysis of Variation in Ventricular Response

Mean RR interval variability was less in group S which presented greater regularity in ventricular frequency. This was 630 ± 200 ms in group S and 740 ± 100 ms (p=.034) in group N.

Morphological Analysis of the f Wave

Analysis of the electrocardiographic signal of the *f* wave indicated a greater mean *f* wave amplitude in the segments in group S throughout the entire minute analyzed, although this difference was not statistically significant. Thus, amplitude was 0.884 ± 1.012 mV in group S and 0.653 ± 0.356 mV (p=.278) in group N.

Regarding the total power of the atrial signal, a higher value was also observed in group S throughout the entire minute analyzed, although this difference was not statistically significant. The power of the segments in group S was 1495 ± 4481 mV^2 and 450 ± 456 mV^2 in group N (p=.239).

Spectral Analysis

Group S presented a significantly lower mean DAF (group S, 5.01 ± 0.671 Hz; group N, 6.514 ± 0.804 Hz; $p=4.55\times10^{-9}$), which would correspond to a longer cycle length (group S, 199.601 ± 23.623 ms; group N, 153.518 ± 16.812 ms). Figure 2 demonstrates the temporal stability of the mean DAF and its standard deviation throughout the minute analyzed, with significant differences in each 10-s segment. The frequency with the second largest amplitude (first harmonic) presented a mean value in group S of 9.965 ± 1.338 Hz vs 12.961 ± 1.557 Hz in group N ($p=2.86\times10^{-9}$).

Regarding the PSD of the peak of these frequencies, the segments in group S had greater values than those in group N. Thus, the peak power in the dominant frequency was 55.147 ± 92.991 mV^2 in group S and 31.336 ± 36.241 mV^2 in group N, whereas power in the first harmonic was 15.353 ± 41.830) mV^2 in group S and 3.076 ± 3.042 mV^2 in group N. However, in both cases the differences were not significant, and the sensitivity and specificity obtained in both cases were low (Table 2).

Organization Analysis

The sample entropy analysis showed that the degree of atrial activity organization was greater in group S with spontaneous reversion. Entropy was 0.071 ± 0.012 in group S and 0.103 ± 0.013 in group N ($p=6.73\times10^{-12}$). The temporal variability of sample entropy was minimal during the time analyzed, and showed a significant difference between groups S and N in every 10-s segment analyzed before spontaneous cardioversion.

DISCUSSION

This study analyzed the patterns of atrial activity during the minute prior to spontaneous conversion of AF to sinus rhythm by means of surface electrocardiographic recording from lead V_1. Thus, *f* wave morphology was analyzed, specifically focusing on their amplitude and total power, and other analyses were conducted based on signal processing tools: spectral analysis and organization analysis. The different degrees of discrimination obtained when predicting the likelihood of AF reversion to sinus rhythm yielded the following results: *a)* morphological analysis of the electrocardiographic f waves had little discriminatory power and the regularity of the RR interval was a more

TABLE 2. **Mean Values and Standard Deviation in Each Group, and Statistical Significance (*P*), Sensitivity, and Specificity of the Parameters Analyzed**

	Group S	Group N	P*	Specificity	Sensitivity
RR variability	630 ± 200 ms	740 ± 100 ms	.034	54.2%	88.5%
f wave amplitude	0.884 ± 1.012 mV	0.653 ± 0.356 mV	.278	61.5%	58.3%
Total power	1495 ± 4481 mV^2	450 ± 456 mV^2	.239	57.7%	58.3%
DAF	5.01 ± 0.671 Hz	6.514 ± 0.804 Hz	4.55×10^{-9}	87.5%	84.6%
First harmonic of the DAF	9.965 ± 1.338 Hz	12.961 ± 1.557 Hz	2.86×10^{-9}	83.2%	88.5%
PSD of the DAF	55.147 ± 92.991 mV^2	31.336 ± 36.241 mV^2	.232	63.6%	54.2%
PSD of the first harmonic of the DAF	15.353 ± 41.83 mV^2	3.076 ± 3.042 mV^2	0.142	59.2%	58.3%
Sample entropy	0.071 ± 0.012	0.103 ± 0.013	6.73×10^{-12}	87.5%	96.1%

PSD indicates power spectral density; DAF, dominant atrial frequency.
*Student *t* test.

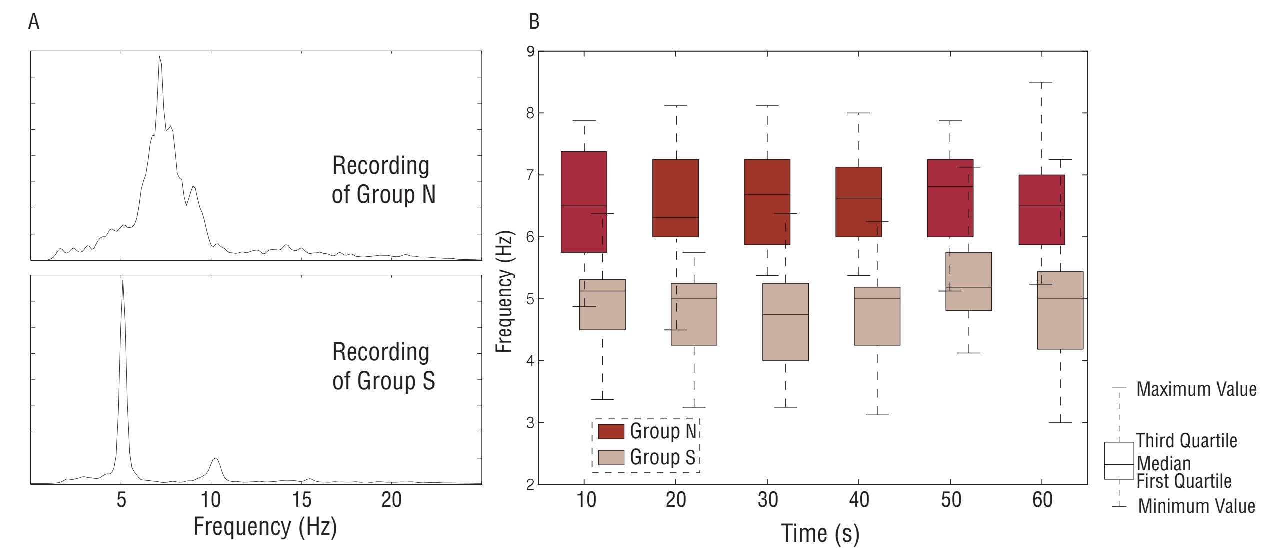

Figure 2. A: an example of the power spectral density (PSD) in a segment from group N and one from group S. B: temporal evolution of the mean dominant atrial frequency (DAF) in each group during the minute analyzed.

sensitive parameter than the *f* wave amplitude itself; *b)* specific analyses by means of electrocardiographic signal processing had greater discriminatory power to predict AF termination than *f* wave morphological analysis*; c)* spectral analysis and sample entropy analysis indicated an atrial activity organization process during the instants prior to spontaneous conversion to sinus rhythm; and *d)* the organization process was continuous and maintained during the entire recording process studied.

In the ECG morphological analysis, RR interval variability was the only discriminatory parameter, since there were no significant differences in *f* wave amplitude and the total power of the atrial signal between the two groups, thus making it impossible to discriminate conversion to sinus rhythm. This predictive capacity of the ventricular response, which is characterized by low specificity, is consistent with the results obtained in other studies. Thus, van den Berg et al[8] reported that electrical cardioversion would be more effective in patients presenting greater regularity in the RR intervals, and Gelzer et al[30] also found an increase in RR regularity before AF conversion in an animal study.

Other studies have demonstrated that, during AF, atrial electrograms show continuous changes in its morphology, which accurately depicts the irregular and chaotic process of atrial depolarization and thus the difficulties involved in analyzing AF from surface recordings. Nevertheless, various current electrocardiographic signal processing techniques make it possible to obtain valuable information on atrial activity during AF from surface recordings,[16,17] and, in addition, several studies have shown that such information is similar to that obtained by means of invasive recordings.[16,17,31-33] In this regard, intracavitary AF mapping has revealed intervals with more organized atrial activity and with a greater degree of electrocardiographic regularity[34] that, on certain occasions, have been the prelude to spontaneous conversion to flutter,[35] and this study detected more organized atrial activity during the minute prior to spontaneous AF reversion. Furthermore, this increase in organization at the end of paroxysmal episodes is similar to the atrial activity organization process that seems to be produced during catheter ablation of atrial tissue, which in turn appears to be directly related to suppression of the arrhythmia.[5] Other studies have shown the close correlation between successful ablation and electrical cardioversion to the degree of organization in postoperative atrial activity.[36,37] Thus, sample entropy, which is an index of nonlinear regularity, may enable reliable estimations of atrial activity organization obtained from surface recordings. This nonlinear index has also been applied in other fields of medicine, such as in the analysis of electroencephalographic background activity in Alzheimer's disease patients[38] or to assess changes in the complexity of the heart rate to predict AF onset.[39,40]

Spectral analysis of atrial activity shows that the only parameters that make it possible to discriminate conversion to sinus rhythm are the mean dominant frequency and its harmonic, since there are no significant differences between their PSD values. In this case, the decrease in the dominant atrial frequency — which is inversely related to atrial cycle length[25] and that, in turn, is directly related to atrial refractoriness,[41] — in the last instants prior to conversion to sinus rhythm is also consistent with the results obtained from invasive recordings during ablation of atrial tissue to terminate AF.[5] Furthermore, similar results have been obtained in other studies which have analyzed variations in this frequency using non-invasive techniques.[17]

Study Limitations

Lead V_1 only was used and the potential information provided by other leads was excluded. However, this lead seems to be the most appropriate for this type of study, since Husser et al[31] showed that, in patients with AF, there was a significant correlation between the atrial frequency obtained through time-frequency analyses from lead V_1 and that obtained by intraatrial recording. Another limitation of the study lies in the lack of a specific analysis to identify the mechanisms involved in electrocardiographic changes prior to AF termination, since only a descriptive study of these was made. In this regard it would be of interest to know if differences exist in relation to persistent AF, especially as Bollmann et al[42] have found that the dominant atrial frequency is around 6.9 Hz in patients with persistent AF who are not under associated antiarrhythmic therapy. On the other hand, the time interval analyzed was short, and thus the onset of the atrial activity organization process in each patient was not specified, which could be very variable, or if there are other periods with organized activity that do not terminate with spontaneous AF conversion, as other authors have pointed out.[43]

CONCLUSIONS

Analysis of the electrographic interval one min prior to spontaneous AF conversion to sinus rhythm shows an atrial activity organization process and increased regularity which cannot be observed by visual inspection of *f* wave morphology, although these are detectable through noninvasive electrocardiographic signal processing techniques, such as spectral analysis or sample entropy.

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