# Predictive Value of Entropy Analysis for Atrial Fibrillation Recurrence after Ablation Procedures

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## Abstract

*The aim of this work is to improve AF dynamics understanding through predicting the reversion to sinus rhythm in the procedures of ablation. Signals from intracardiac recordings previous to ablation were characterized using entropy measurements. The database includes intracardiac recordings from 22 AF patients submitted to an ablation procedure. Four electrodes were located at the right atrium (RA) and 4 more at the left atrium (LA). All patients were monitored after ablation, and were divided in 2 groups according to AF recurrence outcome: 11 of them remained in sinus rhythm, whereas the other 11 turned back to AF. Sample entropy was applied to these signals, in order to characterize different non-linear AF dynamics at RA and LA independently. Results showed statistical significant differences along the atria between both groups (p=0.031). When analyzing regional results, these differences were emphasized at the RA. However, non-statistically significant results were obtained at the LA. Moreover, regional differences were analyzed in both groups separately. In the recurrent group, nonstatistically significant differences between both atria were found, although in the non-recurrent group they were found, p=0.038. These findings show the potential of entropy measurements as useful predictors of AF recurrence after successful ablation of AF.*

## 1. Introduction

Atrial Fibrillation (AF) is the most frequent arrhythmia in clinical practice, with a prevalence of 1,5% in the general population [1]. Its incidence increases with age, reaching 10% in octogenarians [1]. With AF the sinus node does not start the electrical activity; signals come from other spots in the right or left atrium. It causes the heart to beat irregularly and at times very fast. Some people experience AF is terminated without treatment and is classified as paroxysmal. Some people experience AF that needs to be terminated with some type of treatment to revert to normal sinus rhythm and that is classified as persistent. Some people are always in AF and even with treatment they stay in AF and that is classified as permanent.

Several randomized clinical trials [2–5], important studies have found that attempting to restore and maintain sinus rhythm with antiarrhythmic drugs imparts no significant benefit in terms of survival compared with a strategy of controlling the heart rate only [4]. However, recent studies suggest that if sinus rhythm (SN) could be achieved without the adverse effects of antiarrhythmic drugs , then rhythm control may have a survival benefit over rate control. The observation that ectopic beats originating from the pulmonary veins could act as triggers for the initiation of AF opened up the possibility of curative treatment by catheter ablation [6]. During this therapy energy is delivered through the tip of the catheter to tissue that is targeted for ablation. The energy is applied around the connections of the pulmonary veins to the left atrium. Frequently, other areas involved in triggering or maintaining AF are also targeted. The potential for curative treatment of the most common cardiac arrhythmia, with its association with significant morbidity and mortality, has generated much interest in catheter ablation for AF [7, 8]. In a meta-analysis of studies [9] published several years ago as it has been in recent prospective randomized trials and entailed a much lower risk of complications than what was seen in a similar meta-analysis of antiarrhythmic drug trials, according to researchers who ran the numbers on both treatment approaches. On the other hand, the complications from RF ablation tended to be far more serious than the antiarrhythmic complication.

In addition, the limited success rates, often with the need for repeat procedures, recurrence of AF following successful ablation remains an important problem. The outcome of patients with recurrence of AF after ablation procedure is still controversial [10, 11]. Understanding the predictors of late recurrence could improve the patient selection criteria for ablation, and improve ablation technique in the future. In this study we investigated

entropy measurement such as predictors for recurrence of AF after 3 months catheter ablation of arrhythmogenic foci of AF in patients with paroxysmal and persistent AF.

## 2. Materials

Intracardiac recordings during AF before ablation procedure and during the anesthetic effect, were taken from 22 AF patients (9 paroxysmal AF and 13 persistent AF) submitted to an ablation procedure. The main age was 53 ± 12 years, 73% male, and mean left atrial size was 44.5 ± 9.8mm. In the paroxysmal AF group. A 24-pole catheter (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing) was inserted through the femoral vein and positioned in the right atrium (RA) with the distal dipoles into the coronary sinus (CS) to record left atrial (LA) electrical activity as well. The medium and proximal group of electrodes were located spanning the RA free-wall peritricuspid area, from the coronary sinus ostium to the upper part of the inter-atrial region. Using this catheter, 12 bipolar intracardiac electrograms from the RA (dipoles from 14-15 to 23-24) and LA (dipoles 1-2, 3-4 and 5-6), were digitally recorded at 1 kHz sampling rate (16 bit A/D conversion; Polygraph Prucka Cardio-Lab, General Electric). Thirty to 60 seconds recordings from paroxymal and persistent AF patients were analyzed and compared. Four of these electrodes were located at the RA and 4 more at the LA were analyzed. All patients were monitored after ablation, and were divided in 2 groups according to AF recurrence outcome: 11 of them remained in SR, whereas the other 11 turned back to AF, 4 with paroxysmal AF and 7 with persistent AF.

## 3. Methods

Entropy measurements were extracted to the signals after a preprocessing step, in order to characterize different non-linear AF dynamics at RA and LA independently.

Signal preprocessing was applied by two sequence filters. Initially, atrial activity waveform from recordings was band-pass filtered using a 40-to 250-Hz second-order digital Butterworth filter. The absolute value of the filtered waveform was low-pass filtered using a 20-Hz second order digital Butterworth filter [12].

Sample entropy (SampEn) was applied to the filtered signals. This is a similar, but less biased measure than the Approximate Entropy (ApEn) family of parameters, introduced by Pincus [13] to quantify the regularity of finite length time series. The main difference is that SampEn simply excludes self-matches in the definition of ApEn and does not employ a template wise strategy for calculating probabilities [14].

From a time series $\{x_1, x_2,...,x_N\}$ of length N, consider the m-length vectors: $u_m(i)=[x_i ... x_{i+m-1}]$, with $1 \leq i \leq N -$ (m−1). Let $n_i^m(r)$ represent the number of vectors $u_m(j)$ within distance $r$ of $u_m(i)$, where $j \neq i$ to exclude self matches. The probability that any vector $u_m(j)$ is within distance $r$ of $u_m(i)$ is computed as:

$$c_i^m(r) = \frac{n_i^m(r)}{(N-(m-1))} \quad (1)$$

and

$$U^m(r) = \frac{1}{N-(m-1)} \sum_{i=1}^{N-(m-1)} \ln c_i^m(r) \quad (2)$$

represents the probability density of occurrence of the vector $u_m(i)$ within a chosen distance $m$. SampEn is defined as:

$$SampEn(m,r) = \lim_{N \to \infty} \left\{ -\ln \frac{U^{m+1}(r)}{U^m(r)} \right\} \quad (3)$$

For finite length N the SampEn is estimated by the statistics:

$$SampEn(m,r) = -\ln \frac{U^{m+1}(r)}{U^m(r)} \quad (4)$$

that is the natural logarithm of the ratio between the probability of occurrence of sequences close to each other (according to a threshold value r to measure the distance between sequences) for $m$ consecutive data points and the probability of occurrence of sequences close to each other when one more point is added to each sequence. Larger SampEn values indicate greater independence, less predictability, hence greater complexity in the data.

For the study discussed in this paper, SampEn is estimated using the widely established parameter values of $m=2$, and r =0.25σ, where σ represents the standard deviation of the original data sequence, as suggested by Pincus [13].

## 4. Results

Results were inspected in the whole atria, and between both chamber in both groups, and inside of each group.

### 4.1. Whole atria results

Results showed statistical significant differences along the atria between both groups. The ROC curve allows to fix the optimum threshold of SampEn to discriminate between recurrent and non-recurrent AF groups (figure 2), with a statistical significative area under curve (AUC) (Table 1).

Considering the global information of both atria, a value of SampEn higher than 1.1, was associated with the 100% of recurrences.

Indeed, both groups are statistically distinguishable, given that the statistic significance obtained by the t-student test of 0.031, with 0.868 ± 0.132 in the non-

recurrent AF group vs. 1.027 ± 0.097 in the recurrent AF group (figure 1).
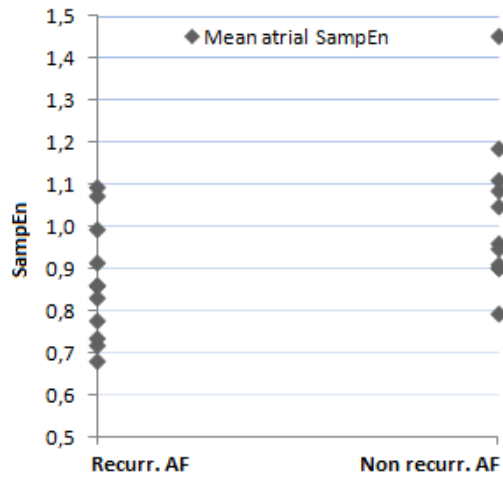


Figure 1. SampEn along the atria in recurrent and non recurrent group.

## 4.2. Regional atrial difference results for both groups

When analyzing regional results, these differences were emphasized at the RA. However, non-statistically significant results were obtained at the LA. In fact, at the RA, entropy values were 0.817 ± 0.104 in the non-recurrent AF group vs. 1.042 ± 0.098 in the recurrent AF group (p=0.025), whereas at the LA, entropy was 0.919 ± 0.151 in non-recurrent group vs. 1.013±0.108 in recurrent group (p=0.349). In addition, these results were represented by a ROC curve (figure 2), where AUC showed non-statistical significative differences between both groups in the LA (Table 1).

Table 1. Area under curve ROC.

|  | AUC | Std. Error | Asymptotic Sig. |
|---|---|---|---|
| Atria | 0.826 | 0.090 | 0.009 |
| RA | 0.752 | 0.109 | 0.045 |
| LA | 0.695 | 0.119 | 0.123 |

## 4.3. Separate group results for regional atrial differences

Moreover, regional differences were analyzed in both groups separately. In the recurrent group, non-statistically significant differences between both atria were found (LA 1.013 ± 0.199 vs. RA 1.041 ± 0.266, p=0.290), although in the non-recurrent group they were (LA 0.919 ± 0.258 vs. RA 0.816 ± 0.153, p=0.038). In addition, the entropy values were higher in the persistent AF group than in the patients with paroxysmal AF, with a average value along the atria of 1.006 ±0.212 in the persistent groups vs. 0.899 ± 0.134 in patients with paroxysmal AF (p=0.151).
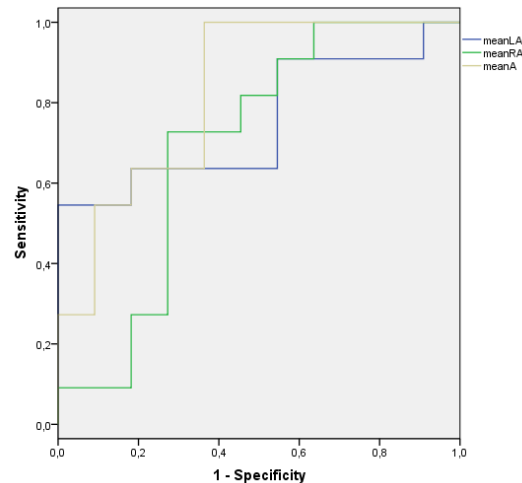


Figure 2. ROC in recurrent and non recurrent AF groups along the whole atria (A), in the RA and in the LA.

## 5. Conclusion

Curative ablative treatment for AF is a clinical reality, but has its limitations, including failure rates and recurrences. When AF recurs during the three to 12 months after ablation, it is characterized as late or long-term recurrence. Late recurrence is not uncommon following pulmonary vein isolation.

Analysis showed that hypertension and high cholesterol predicted the recurrence. The size of the left atrium has also been shown to predict recurrence for certain patients. Mayo Clinic followed 428 patients with paroxysmal AF and 356 patients with persistent or longstanding persistent AF after catheter ablation. At two years, 29% of patients with paroxysmal AF had a recurrence, and only a large left atrium (> 45mm) was associated with this recurrence. For all patients, diabetes and persistent AF were predictors of very late recurrence.

In addition, AF dominant frequency has been reported to play a role as a predictor of AF ablation outcome [15]. Multivariate analysis also showed that larger LA diameter and the presence of RA non-pulmonary veins ectopy during the procedure can predict late recurrence during long-term follow-up [16]. In fact, studies showed that patients with left atrial disease, with electrophysiological and anatomic heterogeneity, which enables the formation of stable rotors in areas outside the pulmonary veins, such

as the posterior, inferior, and septal parts of the left atrium, which could drive AF have lower success rate [17]. From this point of view it could be expected that atrial activity should be less organized and less regular in the LA than in the RA, and different in both group of patients.

The purpose of the present study was to analyze this hypothesis, considering the differences of regularity in each chamber regions, in two very similar size and quality groups of patients with paroxysmal and persistent AF and patients that remain or not in sinus rhythm.

The application of SampEn in the intracardic electrograms can predict AF recurrences after successful ablation of pulmonary veins. Values of entropy higher than 1.1, without a gradient between both atria predict bad results. It suggests that when the atrial electrical activity is more irregular and similar in both atria, the reversion to sinus rhythm is more difficult. These findings show the potential of entropy measurements as useful predictors of AF recurrence after successful ablation of AF.

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