

# Combination of Clinical and Electrocardiographic Indices to Predict Cox-Maze Surgery Outcome at Discharge

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## Abstract

*The most effective procedure to terminate atrial fibrillation (AF) is the Cox-Maze surgery. After the intervention, independently of patient's rhythm, all are treated with oral anticoagulants and antiarrhythmic drugs prior to discharge. Moreover, patients still in AF before discharge are treated with electrical cardioversion (ECV). Therefore, an early prognosis of patient's rhythm at discharge would help to plan in advance drug therapy and ECV decisions. This work studies clinical and ECG indices to predict patient's rhythm at discharge. For this purpose, 29 preoperative standard ECGs from patients in AF have been analyzed. The dominant atrial frequency, the sample entropy and the fibrillatory waves amplitude were obtained as ECG indices. Additionally, patient's age, preoperative AF duration and atrial size were added as clinical indices. Then, a classification tree combining clinical and ECG parameters has been generated to predict patient's rhythm at discharge, yielding a sensitivity, specificity and accuracy of 87.5%, 100% and 93.1% respectively. These results suggest that an accurate prediction of AF termination at discharge is possible.*

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting up to 2% of the general population and more than 6% of people older than 65 years of age [1]. AF has several detrimental sequelae such as hemodynamic compromise, thromboembolic complications or symptoms from tachyarrhythmias. Thus, many treatment strategies have been developed to alleviate this disease [2]. To this respect, an effective surgical therapy for AF is the Cox-Maze procedure which was introduced by Cox in 1987 [3]. After two iterations, due to different postoperative drawbacks, the Cox-Maze III procedure was defined, remaining as the gold standard for AF treatment during decades [4].

After the Cox-Maze procedure, patients are treated with oral anticoagulants and antiarrhythmic drugs prior to discharge, independently of the patient's rhythm [5]. Moreover, some hospitals treat AF episodes before discharge with chemical and electrical cardioversion (ECV) [6]. Therefore, it would be clinically interesting to predict the patient's rhythm at discharge because of two reasons: to plan in advance cardioversion related decisions and to modulate antiarrhythmic and anticoagulant drugs treatment. However, most of the studies predicting the Cox-Maze outcome are addressed to long term prediction [3]. By contrast, the present work focuses on defining a method able to predict preoperatively patient's rhythm at discharge. To achieve this goal, clinical and ECG indices will be used and combined.

Previous studies related with long term prediction, have demonstrated that age, left atrial size (LA size) and preoperative time in AF are the parameters performing the most accurate predictions [3], however, these parameters have not been used to perform a prediction at discharge. Regarding ECG parameters, dominant atrial frequency (DAF), sample entropy (SampEn) and fibrillatory ( $f$ ) waves mean power (fWP) have provided auspicious results predicting immediate AF termination after the Cox-Maze procedure [7]. Hence, this six indices have been studied preoperatively and combined through a classification tree to predict Cox-Maze surgery outcome at discharge.

## 2. Materials

Twenty-nine patients (mean age  $68.5 \pm 8.99$  years) with permanent or persistent AF for at least 3 months composed the database. All patients underwent Cox-Maze III procedure concomitantly to another heart surgery. At discharge, 16 patients remained in AF (55%) whereas 13 patients reverted to NSR (45%).

To study the ECG indices, 20 seconds segments from preoperative standard 12-lead ECGs were recorded from each patient with a sampling frequency of 1kHz and an amplitude resolution of  $0.4 \mu\text{V}$ . Lead V1 was selected to

perform the study because atrial activity (AA) is dominant in this lead [8]. The ECGs were preprocessed by forward/backward highpass filtering (0.5 Hz cut-off frequency) to remove baseline wander. Next, lowpass filtering (70 Hz cut-off frequency) was used to reduce high frequency noise followed by adaptive notch filtering at 50 Hz to remove powerline interference. Moreover, a wavelet denoising was also applied to reduce muscle noise [9]. Finally, the AA was extracted by applying an adaptive QRST cancelation method [10].

### 3. Methods

#### 3.1. Clinical parameters

There are many studies using clinical parameters as risk predictors of AF recurrence after Cox-Maze surgery [3]. As a result, some of these indices have been established as predictors of failure. The most common are the preoperative time in AF, LA size and patient's age. Preoperative AF duration has been related with higher atrial remodeling, resulting in extensive fibrosis, electrical remodeling and loss of atrial muscle mass [4]. LA size affects to AF recurrence because the capability of the atria to fibrillate is determined by the ratio between the atrial effective refractory period and the available atrial area supporting the macroreentrant circuit [11]. Finally, patient's age would be related with the general state of the patient.

#### 3.2. ECG parameters

Previous works using ECG parameters to predict Cox-Maze outcome obtained accurate results by studying  $f$  waves organization and amplitude [7]. The  $f$  waves organization is studied by means of the DAF and SampEn while the  $f$  waves amplitude is studied using the fWP.

The DAF is a frequency domain parameter, its inverse being directly related to the atrial cycle length [12]. Previous studies have demonstrated that the atrial component during AF contains most part of its energy in the 3-9 Hz range [12]. Therefore, the DAF has been defined as the highest amplitude frequency within this range in the AA spectrum. In order to obtain the AA signal Power Spectral Density (PSD), the Welch method was used with a Hamming window of 4096 points in length, 50% overlapping between adjacent windowed sections and a 8192-points fast Fourier transform (FFT) [13].

On the other hand, SampEn is a non-linear index used as a measure of time series regularity, with larger values corresponding to more irregularity in the data [14]. It is defined as the negative natural logarithm of the conditional probability that two sequences, similar for  $m$  points, remain similar at the next point, where self-matches are not included in calculating the probability [14]. This index has

been widely used to measure AA organization [15]. Since SampEn is sensitive to noise and ventricular residua, it was computed over the main atrial wave (MAW) to reduce the influence of these nuisance signals [15].

Finally, the fWP represents the energy carried by the  $f$  waves within the interval under analysis. Thus, it can be considered as a robust indicator of the AA signal amplitude [16]. In order to avoid all the effects that can modify the ECG amplitude as a function of the different gain factors during recording, electrodes impedance, skin conductivity, etc., an intra-patient normalization was applied. Thus, each ECG segment was normalized to its maximum R peak amplitude before the AA signal extraction [17].

#### 3.3. Statistical analysis

The Shapiro-Wilk and Levene tests were used to study normality and homoscedasticity, respectively, in the parameters distributions. Next, the  $t$ -Student test was applied to parameters with normal and homoscedastic distribution and the U Mann-Whitney test was applied to those parameters with not normal and homoscedastic distributions. In both cases, a statistical significance  $p < 0.05$  was considered as significant.

The receiver operating characteristic (ROC) curve was used to obtain the optimum threshold, which is the value of each parameter that provide maximum discrimination between AF and NSR. The ROC curve is a graphical representation of the tradeoffs between sensitivity and specificity. Sensitivity represented the proportion of patients that were in AF at discharge correctly identified, whereas specificity was defined as the proportion of patients in NSR at discharge correctly classified. Thresholds that maximized diagnostic accuracy, defined as the total number of patients correctly classified, were selected from the ROC curve, and values of sensitivity and specificity were the ones corresponding to the threshold selected.

Finally, a binary classification tree (AF and NSR) was created using clinical and ECG indices. Each classification tree node analyzed the predictors values and is splitted selecting the lower impurity, which was measured with the Gini's diversity index [18]. The rule to stop splitting a branch was satisfied when a node contained only observations of one class or when there were fewer than 5 observations in a node.

#### 3.4. Nonlinear analysis applicability

Given that SampEn is a non-linear metric, data non-linearity was analyzed by means of the surrogate data test. This method consists of obtaining a surrogate dataset from the original data. Then, a number that quantifies some aspect of the series, called discriminating statistic, is computed over the dataset. When the original series discrim-

inating statistic is significantly different than the surrogate data values, non-linearity can be assumed [19]. In the present work 40 surrogate data were generated for each AA signal, being the analyzed statistic SampEn. The Wilcoxon T test was performed to compare the SampEn distributions from the original data and surrogate data.

#### 4. Results

The Wilcoxon T test showed statistical significant differences between original and surrogate data. Therefore, non-linearity could be assumed thus demonstrating the suitability of applying SampEn to the AA recordings.

With respect to the indices results, Table 1 shows their mean values, standard deviation and statistical significance for the groups in AF and NSR, respectively. As can be observed, they all are within their typical range of variation that will be next discussed.

Table 1. Mean, standard deviation and statistical significance of NSR and AF groups.

	NSR	AF	<i>p</i>
DAF (Hz)	6.15 ± 0.94	6.55 ± 0.94	0.231
SampEn	0.0848 ± 0.0194	0.0952 ± 0.0147	0.126
fWP	0.0451 ± 0.0189	0.0349 ± 0.0268	0.006
AF duration (years)	2 ± 1.8	5.28 ± 4.88	0.025
LA size (mm)	47.54 ± 7.56	46.69 ± 6.81	0.752
Age (years)	67.08 ± 10.66	69.75 ± 7.52	0.436

Regarding the classification results through the ROC curve study, Table 2 shows sensitivity, specificity and accuracy. Only fWP and AF duration are statistically significant, however SampEn presents higher accuracy than AF duration. On the other hand, the parameter with highest sensitivity, specificity and accuracy is fWP. Finally, it can be seen that in general, ECG parameters have a better performance than clinical parameters.

Finally, Figure 1 shows the classification tree generated after combining clinical and ECG parameters in order to enhance prediction capability. This tree improved performance yielding a sensitivity, specificity and accuracy of 87.5%, 100% and 93.1% respectively.

Table 2. Classification results provided by each individual preoperative index.

	Sensitivity	Specificity	Accuracy
DAF	75%	61.54%	68.97%
SampEn	81.25%	61.54%	72.41%
fWP	87.5%	84.62%	86.21%
AF duration	81.25%	53.85%	68.97%
LA size	56.25%	69.23%	62.07%
Age	56.25%	69.23%	62.07%

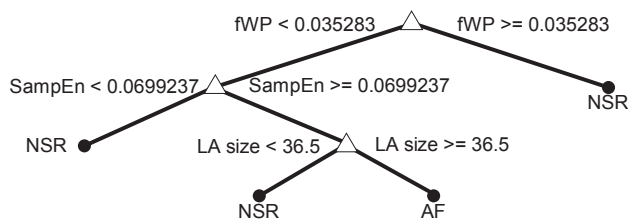


Figure 1. Classification tree generated by combining ECG and clinical parameters by thresholding the indices.

#### 5. Discussion

This work presents for the first time a combination of ECG and clinical indices to predict Cox-Maze surgery outcome at discharge. All clinical parameters presented accuracies below 70%. In fact, results obtained with LA size show greater values in the NSR group than in the AF group. In contrast, previous studies relate larger atrial sizes with higher likelihood of AF relapse [3]. Few months after the surgery, when the heart is fully recovered, some patients change their rhythm and clinical parameters would eventually improve their performance. Therefore, the clinical parameters need a blanking period before proper outcome prediction [20]. Anyway, although AF duration accuracy is below 70%, its results are statistically significant. This results agree with previous studies relating AF duration with both electrical and structural remodeling [4].

ECG parameters studied the heart’s electrical activity, being their accuracy better than the clinical ones. The fWP identified properly the rhythm at discharge in more than 85% of the cases. Moreover, *f* waves amplitude has been used previously with reliable results in long term studies and has been related with the amount of activated tissue [21]. SampEn obtained robust results predicting patient’s rhythm, with an accuracy over 70%. SampEn is related with the number of wavelets propagating along the atria [15] and, therefore, with the AA organization. Thus, patient’s rhythm at discharge would be related with electrical indices such as *f* waves amplitude and organization.

Finally, regarding the indices combination through the classification tree, results are very auspicious improving individual performances. The classification tree suggests that a patient with large *f* wave amplitude present a high reversion likelihood to NSR. Moreover, for patients with small *f* waves amplitude, AA organization is important, thus, a low SampEn would eventually revert also to NSR. Finally, patients with low *f* wave amplitude and organization depend on LA size. Therefore, a small LA size would improve the likelihood of recovering NSR whereas patients with a large LA size would maintain the AF.

## 6. Conclusions

There are no studies using clinical parameters to predict short term Cox-Maze surgery outcome. The state of the heart and the considerable transformation in the atrial substrate after the surgery lead the clinicians to define a blanking period where the rhythm is unstable and clinical predictions are inaccurate. However, this work has demonstrated that prediction at discharge is possible using ECG indices. Moreover, the combination of clinical and ECG indices improved individual performances. More studies are needed to validate the robustness of this new method and the repeatability of the obtained results on wider databases.

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