# Ventricular response regularity in atrial fibrillation and its relationship to successful catheter ablation


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***Abstract*—Atrial rate is known to modulate ventricular response during atrial fibrillation (AF). The resulting pulse irregularity translates into widely varying inter-beat intervals (IBIs) extracted from recorded surface electrocardiogram (ECG) activity. In AF, the random nature of the IBIs makes them difficult to analyze using traditional methods, and little work has investigated the relationship between ventricular response and persistent AF (persAF) disease progression. In this paper, we propose nonlinear approaches for characterizing IBI dynamics in patients undergoing catheter ablation for the treatment of persAF.**



***Keywords—Atrial fibrillation, electrocardiogram, heart-rate variability, recurrence plot, nonlinear signal processing***


## I. Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide and is associated with increased morbidity and mortality. Catheter ablation (CA) has emerged as a non-pharmacological technique to restore sinus rhythm in patients with AF [1]. The pulmonary vein isolation (PVI) technique targets AF triggers, while the more complex fractionated atrial electrogram (CFAE) and linear ablation techniques aim to target sites of AF maintenance in patients with persistent AF (persAF) [2], [3]. Despite its prevalence, CA long-term effectiveness for restoring sinus rhythm (SR) in such patients varies widely [4]. Of clinical interest are automatic, non-invasive diagnostic tools to help understand underlying disease dynamics and severity in patients prior to CA.

In healthy individuals, heart rate changes constantly in response to modulation by the autonomic nervous system. The resulting heart-rate variability (HRV) can be quantified using inter-beat intervals (IBIs), i.e. the times between successive heart beats extracted from the recorded surface electrocardiogram (ECG) [5]. In individuals with AF, the heart rate is further influenced by rapid and irregular atrial fibrillatory waves [6]. It has been shown that the elevated atrial fibrillatory rate may be related to HRV in patients with AF [7], though this phenomenon remains largely uninvestigated. Therefore, this study aims to investigate whether HRV may be used to reveal differences in AF disease dynamics in patients, with special attention paid to their procedural outcomes following CA.

## II. Methods

### A. Patient population and ablation procedure

The study includes 40 patients with persAF (38 M/2 F, 61 ± 8 years) referred for a first ablation after displaying resistance to pharmacological and electrical cardioversion interventions. The patients were suffering from AF for 6 ± 4 years, sustained for 19 ± 11 months before ablation. All patients discontinued antiarrhythmic drugs at least five half-lives prior to the CA, except for amiodarone and beta-blockers. Oral anticoagulation was taken by all patients for at least one month prior to the procedure.

Stepwise CA was performed as described in [8], with patients under general anesthesia. The protocol prescribes a stepwise approach beginning with PVI, followed by CFAE ablation, and ending with linear ablation (left atrium roof and mitral isthmus). Termination of AF into either SR or atrial tachycardia at any step of the ablation constituted the procedural endpoint. When AF did not terminate, electrical cardioversion restored SR. Surface ECGs were continuously recorded for off-line analysis at a sampling frequency of 2 kHz (Axiom Sensis XP, Siemens) at baseline (i.e. before ablation), as well as throughout the CA procedure. The study protocol was approved by the Lausanne University Hospital Human Research Ethics Committee, and all patients provided written informed consent.

Based on the ablation procedural outcome, the study population was divided into the following two groups: (1) left-terminated (LT, n = 28), patients in whom AF terminated within the left atrium into SR or atrial tachycardia during the ablation; (2) not terminated (NT, n = 12), patients in whom stepwise CA failed to terminate AF. Note that the mean sustained AF duration of the NT group (26 ± 15 months) was significantly longer than that of the LT group (16 ± 7 months, $p < 0.05$). Otherwise, the two groups did not present significant clinical differences.

For each patient, one approximately five-minute segment of ECG data recorded prior to ablation and one segment of about the same duration recorded just prior to AF termination (for LT patients) or cardioversion (for NT patients) formed the two study databases: baseline (BL) and end-ablation (endABL), respectively.

## B. *Signal processing*

**Inter-beat interval data extraction.** Sequences of successive IBIs were constructed for the five-minute ECG BL and endABL data segments from each patient. The 40 patients in this study provided therefore 80 IBI sequences for analysis. The difference between the times at which two successive R-peaks are detected defines an IBI. Reference [9] describes the detection algorithm. Thus, from each five-minute segment of ECG samples was created a new data series, consisting of times between successive heartbeats. This type of data presents several advantages, as the ECG is non-invasively recorded, and the IBIs are easily extracted. Note, IBIs were detected using the signal recorded on ECG lead II, as in general this lead provides sufficient quality for accurate R-peak detection. Ventricular ectopic beats were not removed from ECG data prior to IBI extraction. All measures described below were calculated separately for each IBI sequence.

**Recurrence quantification analysis (RQA).** Recurrence plots (RPs) are visual tools that were created to analyze and reveal recurring behavior in a dynamical system and can be extended for use with experimental time series [10]. Interpretation of an RP relies on RQA to quantify point density and structures present in line segments. This type of analysis, when performed on an experimental time series, may reveal otherwise hidden dynamical system patterns and periodicity.

Recurrence plot construction and nonlinear data analysis in general require that the system phase space be available. However, in an experimental setting, one usually has only a discrete time sequence of a single observed system variable. These nonlinear techniques therefore necessitate phase space reconstruction, often performed using time delay embedding [11]. For a sequence of IBIs, one creates embedded vectors, the $i^{th}$ of which has the following form, $x_i=\{IBI_i\ IBI_{i+\tau}...IBI_{i+(m-1)\tau}\}$ , for embedding dimension $m$, and sample delay, $\tau$. From these embedded vectors, each point $R_{i,j}$ in the recurrence plot is either filled in with a black dot, or not, for the Euclidean distance between the two embedded vectors $x_i$ and $x_j$ either less than or greater than a chosen threshold $\varepsilon$. The resulting properties of the RP then clearly depend on the parameters $m$, $\tau$, and $\varepsilon$. Different methods have been proposed for choosing suitable embedding and threshold parameters, with a delay of $\tau = 1$ IBI sample appropriate for an irregularly sampled discrete time sequence [12], [13]. Here, the embedding dimension $m$ was also taken to be two, and the threshold distance was calculated separately for each RP as 15% of the standard deviation of the IBI sequence from which the embedded vectors are formed, in line with suggestions that the threshold distance be a percentage of the system phase space diameter.

Once the RPs are created for each IBI sequence, RQA can be performed. Many RQA measures exist; here the percent recurrence and percent determinism measures proposed in [14] were used. The percent recurrence, *REC,* describes the percentage of points in the recurrence plot for which $R_{i,j}$ equals one. Percent recurrence simply measures the percentage of embedded vectors close to each other in the $m$ dimensional space; the more periodic are the system dynamics, the higher the percent recurrence.

Percent determinism, *DET*, describes the percentage of recurrence points forming line segments greater than some length, here $l_{min} = 2$, and parallel to the main, upward diagonal. It is calculated using a histogram of diagonal line lengths. Diagonally adjacent points for which $R_{i,j} = 1$ form line segments; therefore, a diagonal line segment is distinct from individual recurrent points, indicating that (at least) two states, or embedded vectors, appearing at times $i,i+1$ repeat themselves at time $j,j+1$. This indicates possible periodicity in the IBI sequences.

**Sample Entropy (sampEn).** Sample entropy was introduced as a more consistent alternative to approximate entropy for estimating system regularity and complexity based on a noisy or short time series [15]. It is less dependent on time sequence length than approximate entropy. Lower sampEn values indicate less complexity and more regularity in the time series. One could expect the sample entropy calculated on IBI sequences containing repeating patterns to be lower; thus, sampEn should be negatively correlated with REC and DET.

**Skewness (skew).** One salient feature of IBIs during AF is their asymmetrical distribution, as seen in the IBI sequences plotted in the first row of Fig. 1, and also noted in [16]. This asymmetry is mainly caused by large positive peaks, that is long IBIs, present in the IBI sequences and can be quantified using skewness (normalized third-order moment) estimation. A positive estimate indicates right-side extension of the IBI distribution.

**Peak difference (peakDiff).** We extended the skewness-based analysis to investigate the behavior of peaks in IBI sequences. These peaks indicate a lengthening in the time interval between successive heart beats, thus a change in ventricular response. The ventricular response in AF depends primarily on atrial tissue activity and atrioventricular node refractory period. Lengthening in IBIs may indicate reduced AF dynamics and thus a ventricular response less influenced by atrial activity. Since there is a possible link with atrial rate, its analysis bears interest as a potential indicator of changing AF dynamics.

Peaks within the IBI sequences were found using the findpeaks function provided by Matlab ®. As an indicator of the regularity of lengthened IBI peaks, the mean of the absolute differences between the amplitudes of consecutive detected peak IBIs was computed. Small differences indicate that peak IBIs are more regular, while large differences indicate that these peaks are more disorganized. This regularity may be related to a reduced number of AF activation wave fronts reaching the atrioventricular node [6].

## C. *Statistical Analysis*

All values are expressed as mean ± standard deviation. Statistical comparisons between group means were performed using one-sided rank order tests. Differences in group means are considered statistically significant for $p$-values less than 0.05.

# III. Results

## A. *Recurrence quantification analysis*

**Illustrative Example.** Fig. 1 shows changes in the IBI recurrence plot dynamics of an LT patient at BL and endABL. Note the increased percent recurrence and determinism, as well as increased structure, observed in the endABL RP compared to that at BL. This indicates more regularity in the IBI sequence at endABL compared to that at BL and thus a more regular ventricular response just prior to AF termination in this patient.

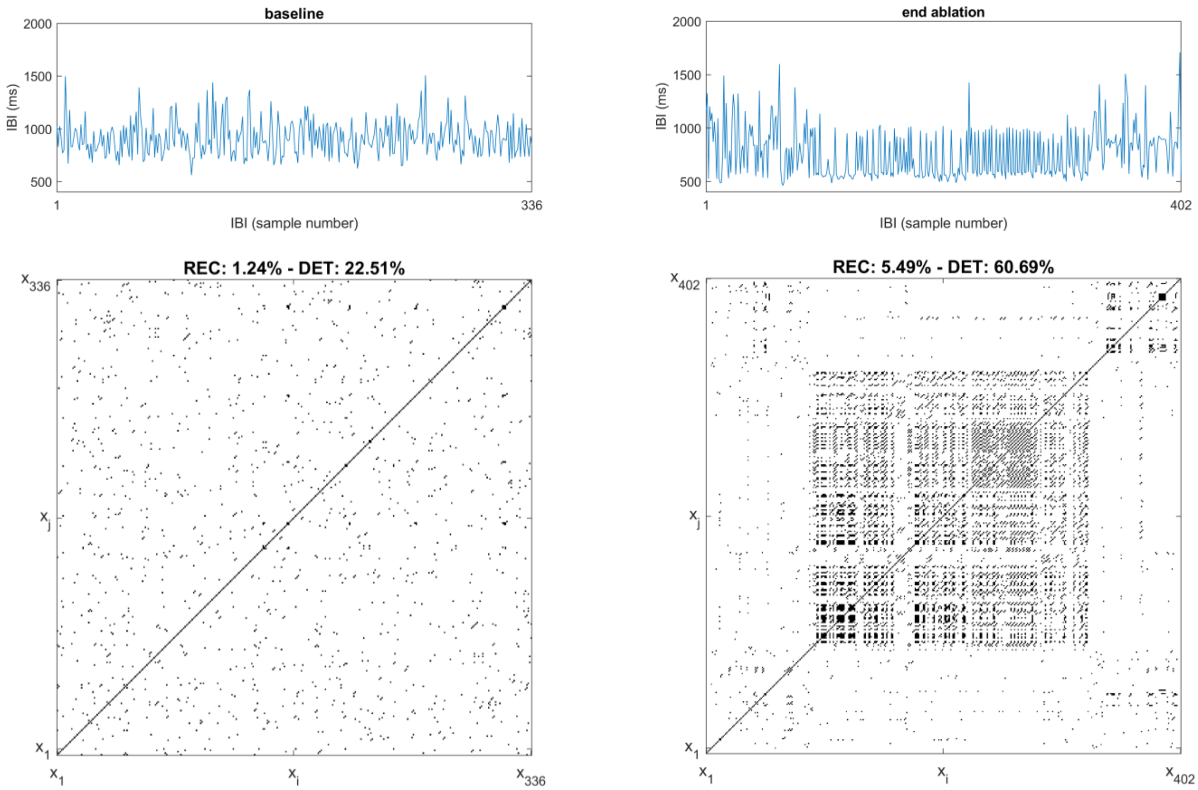


Fig. 1. Changes in IBI recurrence plot dynamics for an LT patient. Top left: IBIs extracted from 5-minute baseline (pre-ablation) ECG segment. Bottom left: Recurrence plot found using embedded vectors from IBI sequence. Right columns: same plots found using 5-minute ECG segment recorded at end of ablation just before spontaneous AF termination.

**Patient group dynamics.** Fig. 2 shows the distribution of these two parameters for all patients. At BL, nearly all patients were in the region defined by REC less than 3% and DET less than 35%. However, at endABL, the REC and DET values of 10/28 LT patients, but no NT patients, increased beyond this region. This indicates a tendency for the ventricular response to become more regular in patients in whom AF terminated, immediately prior to that termination. As shown in the top row of Fig. 3, LT patients displayed greater mean REC values than NT patients at both BL and endABL. For REC, this difference was significant only at endABL. In addition, LT patients displayed significantly greater mean REC at endABL than at BL. While NT patients also showed increasing recurrence measures, this difference was not statistically significant.

Table 1 shows the means and standard deviations of all nonlinear measures calculated from IBI sequences from the LT and NT patients at BL and endABL. The resulting observations parallel those of the REC measures. The sampEn value is significantly higher at BL than endABL in the LT group. In addition, at both BL and endABL, sampEn is significantly smaller in the LT group than NT, again indicating increased regularity in the ventricular response.

The skewness observed in every IBI sequence was positive at both BL and endABL. In general, this was caused by a small number of larger (greater than 1000 ms) IBIs appearing among many smaller IBIs. The mean skewness was more positive at endABL than BL in both the LT and NT groups (though not significantly so), and the degree of positive skewness is higher in the LT group than NT at BL and endABL (significant only at BL). The increasing skewness from BL to endABL could suggest the presence of more relatively higher IBIs. Furthermore, the mean of the differences in peak IBI amplitudes (peakDiff) is significantly smaller at endABL than BL in both groups.

| | **LT** | | | **NT** | | | **LT vs NT** | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | BL | endABL | pLT | BL | endABL | pNT | pBL | pEndABL |
| **REC** | 0.02±0.01 | 0.03±0.02 | 0.011 | 0.02±0.01 | 0.02±0 | 0.503 | 0.079 | 0.003 |
| **DET** | 0.26±0.05 | 0.34±0.14 | 0.002 | 0.22±0.06 | 0.24±0.04 | 0.214 | 0.018 | 0.002 |
| **sampEn** | 2.13±0.2 | 1.94±0.35 | 0.011 | 2.25±0.22 | 2.23±0.16 | 0.411 | 0.042 | 0.002 |
| **skew** | 1.03±0.47 | 1.09±0.59 | 0.341 | 0.72±0.3 | 0.99±1.22 | 0.32 | 0.015 | 0.406 |
| **peakDiff (ms)** | 137±52 | 84±31 | 0.001 | 152±43 | 106±76 | 0.033 | 0.191 | 0.151 |

Table 1. Changes in all nonlinear measures calculated between BL and endABL, for LT and NT groups. One-sided *p*-values are shown for differences in group means at BL and endABL (pLT and pNT), as well as differences across groups, at BL and endABL (pBL and pEndABL).

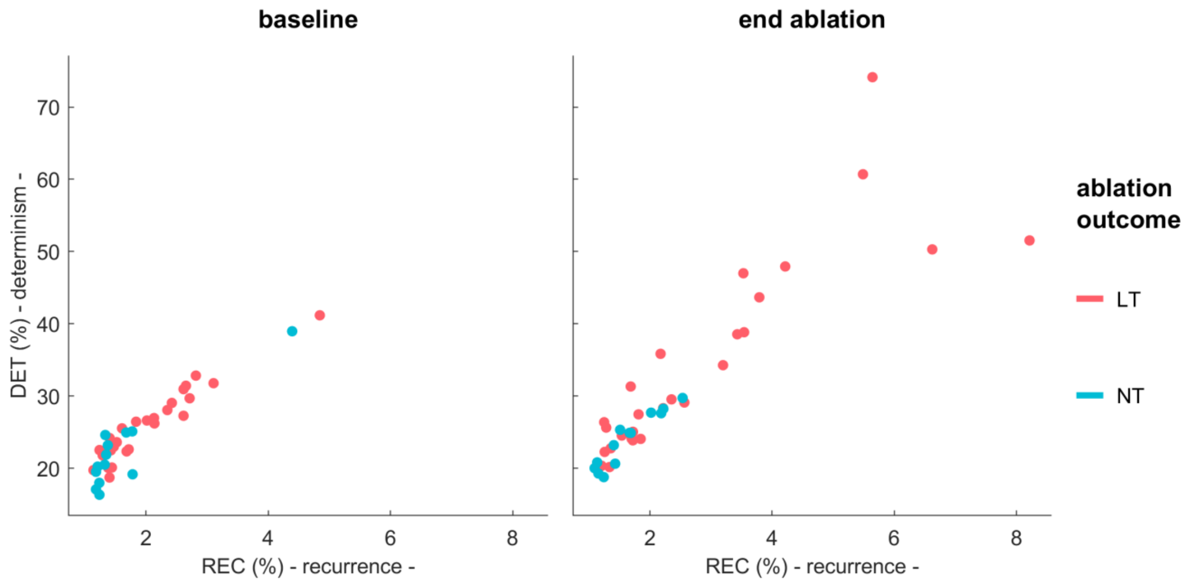


Fig.2. Each dot represents the distribution of percent recurrence and determinism parameters calculated for each patient prior to (at left) and at the end of (right) his or her ablation procedure. The dots are color-coded according to patient ablation outcome.

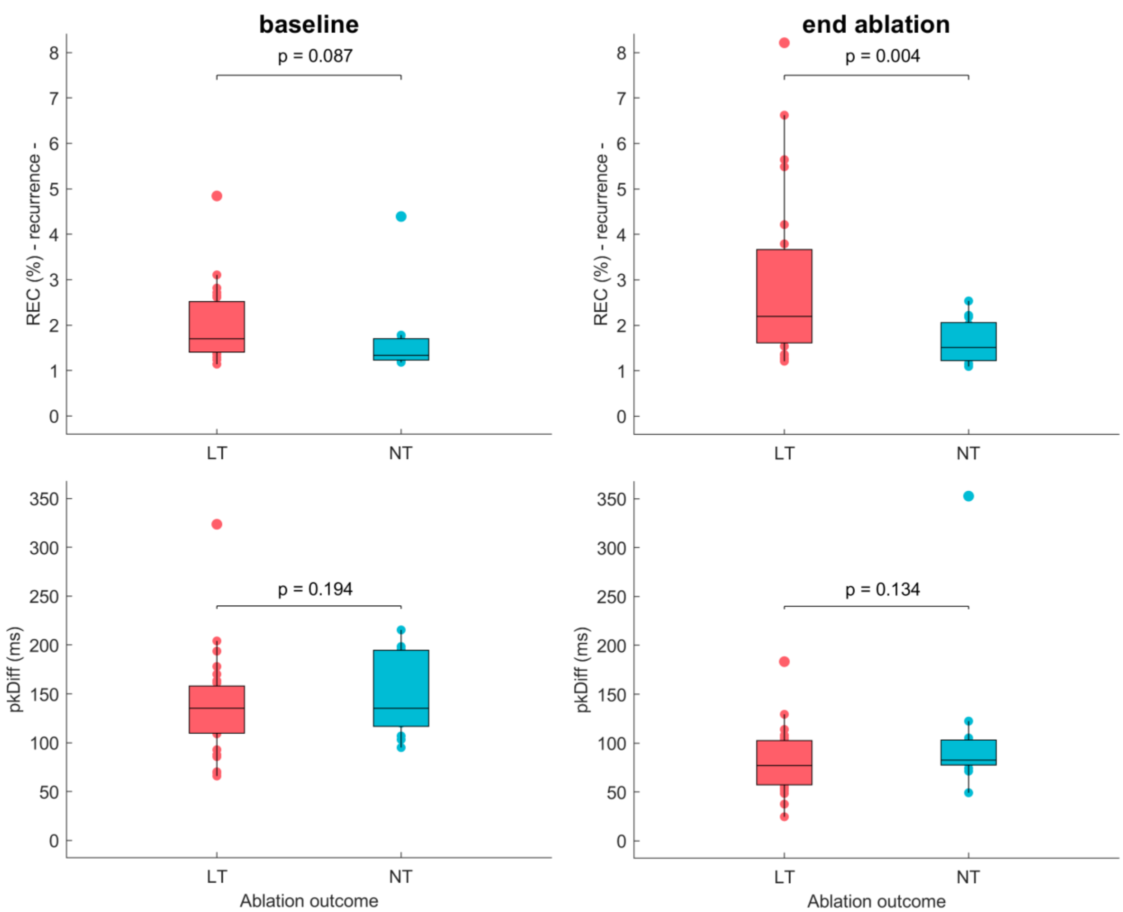


Fig. 3. Significance levels between LT and NT group means observed at BL (left) and endABL (right), for percent recurrence (top) and peakDiff (bottom).

## IV. Discussion

Atrial fibrillatory activity is known to influence the irregular ventricular response seen in AF [6], [7]. While this irregular response had been considered random, several studies have indicated otherwise. In [17], IBI clustering in patients with AF and its relation to the success of electro-cardioversion in restoring SR were investigated using 24-hour Holter recordings. Of the 47% of patients in whom clustering was found, SR restoration was achieved in 94% of cases. This efficacy reduced to 71% in patients in whom no clustering was found. Ref. [18] used IBI sequences of similar lengths to those in the present study, and reported the presence of autocorrelation (indicating non-random behavior) between consecutive IBIs in 30% of AF patients, with the remaining 70% not displaying significant correlation. Our results suggesting that SR restoration by CA is more successful in patients who, as a group, showed increasing organization of IBIs, complement these studies. In particular, the distributions given by REC and DET at BL and endABL demonstrate that while all NT patients remain in a region of space defined by low REC and DET values, some LT patients (10/28) move into a new region of space defined by higher values, indicative of increasing organization and regularity in the ventricular response. Decreasing sampEn in the LT group from BL to endABL indicates a reduction in AF disease dynamics not experienced in the NT group over the course of CA. The skewness and peakDiff parameters indicate that larger IBIs, corresponding to a lengthening of the time between successive heartbeats, are more present both at endABL than BL, and in the LT group than NT group. This is suggestive of an atrial response which exercises less influence over the ventricular response. The electrophysiological mechanisms responsible for the presence or lack of increasing organization, and why it arises only in some patients, cannot however be explained without access to atrial fibrillatory wave data.

Finding definitive measures to select patients with high likelihoods of successful catheter ablation outcomes remains elusive. However, the nonlinear measures presented in this study extend the analysis performed in [19], which concluded that patients with successful CA outcomes show greater AF organization at baseline than those with unsuccessful outcomes.

## Conclusion

In patients with persAF resistant to existing noninvasive pharmacological treatments, catheter ablation is often used for sinus rhythm restoration. However, selection of patients for whom this goal can be achieved on both the short and long-term is imperfect. In this study, nonlinear tools are applied to IBI sequences to investigate changes in the ventricular response between baseline (prior to ablation) and endABL (immediately prior to the procedural endpoint). We show that nonlinear dynamics indicative of increasing organization in the ventricular response are associated with better ablation procedural outcomes. We also demonstrate the feasibility and interest of using IBI sequences, robust from a signal processing perspective, for this type of investigation. The extension of this analysis to long-term clinical freedom from arrhythmia, as well as its relation to atrial response, constitute areas of interest for which the results of this study could be extended.

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