Non-Linear Analysis of Atrial Signals for Assessing the Effects of Adrenergic Activation in Sinus Rhythm and Atrial Fibrillation

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Abstract

Aim of this study is to understand the effects of sympathetic nervous system stimulation during atrial fibrillation. A non-linear analysis is presented and used to characterize the dynamics in both intra-atrial signals (atrial electrograms) and Local Atrial Period (LAP) series. In particular, the level of organization between two electrograms or two LAP series was assessed by the synchronization index (S), based on the corrected cross-conditional entropy. Besides, the degree of recurrence of a pattern in a signal was defined by the regularity index (R), based on the estimation of corrected conditional entropy. Adrenergic activation was induced by infusing small doses of isoproterenol. The parameters obtained from both analysis underline a trend of reduction of spatial organization after isoproterenol administration both in sinus rhythm and in atrial fibrillation.

1. Introduction

Among the factors contributing to the genesis and/or to the maintenance of the typical circulating wavelets of atrial fibrillation (AF), the Autonomic Nervous System (ANS) seems to play an important role [1] including both sympathetic and vagal actions. The arrhythmogenic influence of the ANS has been illustrated in several experimental studies showing that both vagal and adrenergic stimulation might increase or favor the perpetuation of AF [2][3].

AF is not a fully random process, as illustrated by previous studies [4][5]. Transient instances of regularity have been observed during AF using various signal processing methods. In particular non-linear patterns have recently been observed in atrial signals during AF [6], revealing the possible existence of a non-linear mechanism behind the waveform propagation of AF.

Therefore in this paper we use non-linear parameters, providing a general description of both the level of organization and the atrial signal's links during AF, to assess the effects of adrenergic activation in sinus rhythm and atrial fibrillation. In particular, we use the regularity (R) and synchronization (S) indexes [6], based on the estimation of the corrected conditional entropy and the corrected cross-conditional entropy respectively, to try to describe the fine changing characteristic of atrial signals and local atrial period (LAP) series during adrenergic activation mimicked by isoproterenol infusion.

2. Methods

2.1. Regularity

The evaluation of the regularity (R) index, defined as the degree of recurrence of a pattern in a signal, is based on the Conditional Entropy (*CE*) i.e. the amount of information carried by the most recent sample $x(i)$ of a normalized realization of x when its past L-1 samples are known. *CE* is defined as [8]:

$$CE(L) = -\sum_{L-1} p(x_{L-1}) \sum_{i/(L-1)} p(x(i)/x_{L-1}) \log p(x(i)/x_{L-1})$$

where $p(x_{L-1})$ represents the probability of the pattern $x_{L-1}(i)$ and $p(x(i)/x_{L-1})$ the conditional probability of the sample $x(i)$ given the pattern x_{L-1}. The estimation of *CE(L)* is no longer statistically consistent when L increases, therefore the Corrected Conditional Entropy (*CCE*), sum of *CE(L)* and a corrective term, must be introduced to perform a reliable measure over short data series. The *CCE* is then normalized by the Shannon entropy of the process to derive an index independent of the different probability distribution of the processes, obtaining the Normalized Corrected Conditional Entropy (*NCCE*). The R index may be defined as:

$$R_x = 1 - \min(NCCE(L))$$

R_x tends to zero if x is a fully unpredictable process, it tends to one if x is a periodic signal and it assumes

intermediate values for those processes that can be partially predicted by the knowledge of the past samples.

2.2. Synchronization

The evaluation of the synchronization (S) index, related to the repetition of a complex pattern involving two signals, is based on the cross-conditional entropy, defined as [6]:

$$CE_{x/y}(L) = -\sum_{L-1} p(y_{L-1}) \sum_{i/(L-1)} p(x(i)/y_{L-1}) \log p(x(i)/y_{L-1})$$

where $p(y_{L-1})$ represents the probability of the pattern $y_{L-1}(i)$ and $p(x(i)/y_{L-1})$ the conditional probability of the sample $x(i)$ given the pattern y_{L-1}. $CE_{x/y}$ suffers from the same limitations as CE, therefore a normalized and corrected $CE_{x/y}$ is introduced ($NCCE_{x/y}$). Besides, as no a priori knowledge about the causal relationship between x and y is given, the uncoupling function (UF) is defined:

$$UF_{x,y}(L) = \min(NCCE_{y/x}(L), NCCE_{x/y}(L))$$

in order to measure the amount of information carried by one signal that can't be derived from the knowledge of past samples of the other signal. The S index can be defined as:

$$S_{x,y} = 1 - \min(UF_{x,y}(L))$$

and it quantifies the maximum amount of information exchanged between the two signals.

$S_{x,y}$ tends to zero if the two processes are uncoupled, it tends to one if they are perfectly synchronized and it assumes intermediate values when the two signals are able to exchange a certain amount of information.

2.3. Statistical analysis

The statistical analysis was carried out using Student's *t*-test for paired data, comparing each rhythm before and after isoproterenol administration, as well as organized (SR) vs not organized rhythm (AF).

2.4. Experimental protocol

The study population consisted of six patients (6 males; mean age 62±6 years) who were referred for a left atrial ablation with encirclement of the pulmonary veins by transeptal approach. All subjects were suffering from atrial fibrillation (AF), 3 from paroxysmal and 3 from persistent AF. After informed consent was obtained, the electrophysiological study was carried out using a 20 pole St Jude catheter, the Lasso-Cordis Webster catheter (for mapping) and the Medtronic Sprinklr with irrigated tip electrode catheter (for ablation). For this study, one surface ECG tracing and nine intracavitary atrial electrograms were off line analyzed. In particular, the St Jude catheter was placed in contact with the right atrial wall and inserted in the coronary sinus below the left atrium, recording, in this way, four electrograms corresponding to the superior, middle, middle inferior and inferior wall of the right atrium; one corresponding to coronary sinus ostium; three to the inferior and the left wall of the left atrium and the last corresponding to the left superior pulmonary vein.

We considered the effect of adrenergic activation induced by infusion of isoproterenol on atrial electrical activity. Electrograms were recorded during sinus rhythm and after induction of AF. In both the rhythms the recording was repeated during intravenous infusion of isoproterenol (0.01-0.02 mcg/kg/min) until heart rate had increased by about 30%. We analyzed four clinical experimental conditions: sinus rhythm (SR), sinus rhythm during isoproterenol administration (SRISO), atrial fibrillation (AF) and atrial fibrillation during isoproterenol administration (AFISO). The recording sessions lasted for at least for 5 minutes during sinus rhythm and for at least 90 seconds during atrial fibrillation.

All signals were digitized to a 1000-Hz sampling rate at 16-bit resolution and then pre-filtered. In order to reduce the effects of ventricular interference (affecting especially recordings during sinus rhythm), a mean ventricular interference complex was measured and subtracted from each atrial signal according to Sih [9]. Then analogously with previous studies [10][11], all bipolar electrograms were band-pass filtered (40-250 Hz) to remove baseline shift and high frequency noise. The absolute value of the output of the band-pass filter was low-pass filtered (50 Hz) and then sub-sampled (100 Hz) principally to reduce signal length and computation time. From atrial signals, local atrial depolarization instants were detected by means of a derivative / threshold algorithm and then the local atrial period (LAP) series were derived as the sequence of temporal distances between two consecutive local atrial activations and then analyzed.

3. Results

3.1. LAP series

Figure 1 represents the mean values and the standard deviations of the parameters computed over the LAP series during SR, SRISO, AF, AFISO. Both the R and S indexes show a significant reduction after isoproterenol infusion during sinus rhythm and, as expected, passing

from organized to not-organized rhythms. During atrial fibrillation the R index exhibits a significant reduction too, while a subtle increase of the S index is observed. Therefore, while the degree of recurrence of a complex pattern in a series (R index) decreases during isoproterenol infusion in both the rhythms, the repetition of a complex pattern involving two series (S index) during drug administration underlines a reduction in SR and an increase during AF.

3.2. Atrial signals

Table 1 summarizes the average values and the standard deviations of the parameters computed over atrial signals, obtained as the mean of all patients recording sites during the four experimental conditions. Comparing the R index values with and without isoproterenol during the same rhythm, a reduction tendency is observed after drug infusion during both sinus rhythm and atrial fibrillation. In particular during sinus rhythm this decrease results statistically significant. Besides marked reductions ($p<0.0001$) are detectable passing from organized (SR) to not-organized (AF) rhythms. Also the level of synchronization between different sites decreases significantly ($p<0.0001$) passing from sinus rhythm to atrial fibrillation. The S index, contrary to R index, succeeds in finding a significant reduction after isoproterenol administration during atrial fibrillation.

	SR	SRISO	AF	AFISO
R	0.53 ± 0.07	$0.50 \pm 0.08^{\dagger}$	0.31 ± 0.08	0.30 ± 0.08
S	0.26 ± 0.03	0.26 ± 0.04	0.16 ± 0.06	$0.15 \pm 0.06^{\dagger}$

Table 1. Mean values ± SD computed over atrial signals in the four analysed phases: sinus rhythm (SR), sinus rhythm during isoproterenol infusion (SRISO), atrial fibrillation (AF), atrial fibrillation during isoproterenol infusion (AFISO). † $p<0.05$

Figure 2 illustrates an example of two atrial signals during AF and AFISO recorded at an interelectrode distance equal to one and the corresponding UF function. Passing from atrial fibrillation to atrial fibrillation during isoproterenol infusion, the minimum of UF (i.e. the opposite of synchronization because $S_{x,y} = 1 - \min(UF_{x,y}(L))$) increases noticeably, reflecting the global tendency of entire dataset.

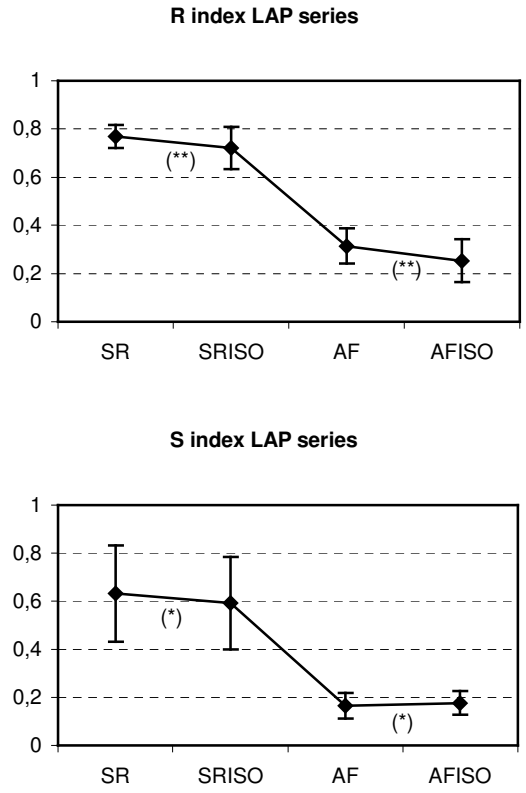

Figure 1. Performance of the R and S index computed over LAP series as a function of the four analysed phases: sinus rhythm (SR), sinus rhythm during isoproterenol infusion (SRISO), atrial fibrillation (AF), atrial fibrillation during isoproterenol infusion (AFISO). (**) $p<0.001$ (*) $p<0.05$

4. Discussion and conclusions

In this paper we exploit the capability of non-linear parameters (R and S indexes) to capture the modifications in the dynamics of atrial signals and LAP series during adrenergic activation induced by the injection of a sympathomimetic drug during both sinus rhythm and atrial fibrillation. Even if a small population is considered, the reported preliminary results evidence the capability of the proposed parameters to quantify the different dynamics of the analyzed signals during adrenergic stimulation. Both the parameters underline a tendency toward spatial organization reduction after isoproterenol administration in both the rhythms. In particular, in the atrial signals analysis, the R index succeeds in finding out significant differences comparing SR to SRISO, the S index comparing AF to AFISO. In the LAP series analysis both the indexes were able to discriminate the subtle differences due to isoproterenol infusion in both the rhythms.

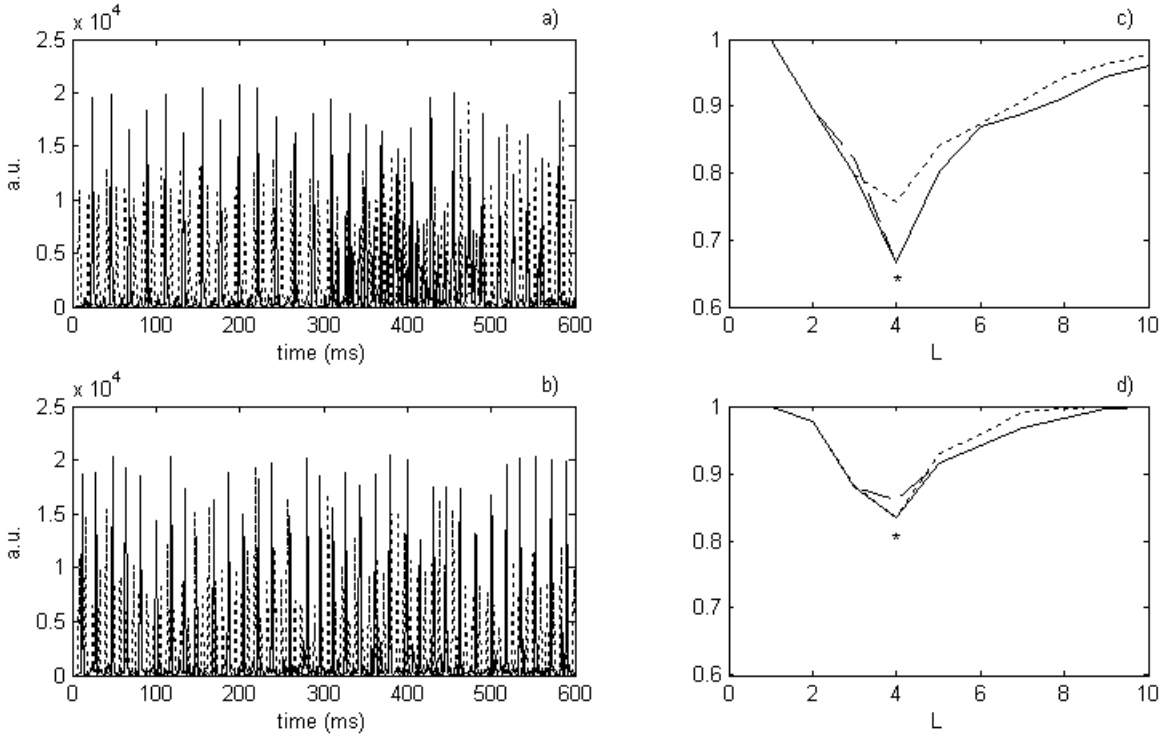

Figure 2. Example of atrial signals during (a) atrial fibrillation (AF) and (b) atrial fibrillation during isoproterenol infusion (AFISO); (c) (d) the corresponding *UF* functions (solid line) depicted as the minimum between $NCCE_{x/y}$ (dotted line) and $NCCE_{y/x}$ (dashed line). A clear increase in the minimum value (*) can be observed passing from AF to AFISO.

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