Detrended Fluctuation Analysis of Atrial Signal during Adrenergic Activation in Atrial Fibrillation

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Abstract

Aim of the study was to assess the effect of the adrenergic stimulation on the dynamic of atrial signals (AS) during atrial fibrillation (AF). The AS, derived from surface ECG after having removed ventricular activity, were analyzed using the detrended fluctuation analysis. A sympathomimetic drug, the isoproterenol mimicking adrenergic activation, was administered in 13 patients with paroxysmal or persistent AF. Two situations were compared i) AF and ii) AF during isoproterenol administration (AFISO). The existence of two scaling regions in the AS has been documented in most of the recordings through the estimation of the scaling exponents (α_1 and α_2) and the crossover point (nCP). Adrenergic activation seems not to alter highly the correlation properties of the process. However, the crossover point is located at lower scales after isoproterenol infusion.

1. Introduction

Even if atrial fibrillation (AF) has been classically described as a random process, a few studies have recently documented, using various signal processing methods, the existence of some determinism underlying AF, suggesting that AF is temporally and spatially organized [1][2].

Analysis of atrial signals (AS) extracted from surface ECGs during AF have been documented to provide significant information on the properties of AF events and on the responsiveness to anti-arrhythmic drug or to cardioversion. Even if attention is mainly focused on the quantification of the main fibrillatory frequency (rate), we have recently shown [3] that analysis of the scaling behavior of AS using Detrended Fluctuation Analysis (DFA) may be useful to characterize AF episodes and to discriminate the self-terminating ones.

Among factors contributing to genesis and/or maintenance of circulating wavelets, the Autonomic Nervous System (ANS) seems to play a major pro-arrhythmic role [4]. The arrhythmogenic influence of sympathetic and vagal mechanisms has been observed in several clinical and experimental studies [5][6].

In this study we aimed to assess the effect of adrenergic stimulation on the dynamic of AS using DFA. Therefore, a sympathomimetic drug, the isoproterenol, was administered to patients suffering from AF and the DFA was performed in order to evaluate the scaling properties during AF and their changes after adrenergic stimulation.

2. Methods

2.1. Experimental protocol

Thirteen patients (9 males and 4 females; mean age 58±6 years) with an indication for left atrial radiofrequency ablation with encirclement of the pulmonary veins by transeptal approach were included in the study. All subjects were suffering from AF and were non responsive to anti-arrhythmic therapy. Paroxysmal and persistent AF episode were present in, respectively, 8 and 5 subjects. A history of AF was present for an interval ranging from 2 months to 10 years. All electrophysiological procedures were performed in the Electrophysiology Laboratory of the "Istituto Clinico Sant'Ambrogio" of Milan, Italy. Intracavitary electrocardiograms and standard surface ECG recordings were obtained during the electrophysiological procedure aimed at isolating arrhythmic foci by means of ablation. The Medical Ethical Committee approved this study and all subjects gave their written consent.

Two phases were compared: atrial fibrillation (AF) and atrial fibrillation during isoproterenol administration (AFISO). The isoproterenol is a sympathomimetic drug, thus it mimics the adrenergic activation. Isoproterenol was intravenously infused (0.01-0.02 mcg/kg/min) tiered to determine a 30% increase of heart rate. 90 seconds of AF and AFISO signals were registered and the standard

12 ECG leads were acquired (250 Hz sampling frequency) and processed.

2.2. Signal pre-processing

Extraction of the residual ECG was obtained through beat-to-beat subtractions of an averaged QRST complex [7][8]. Thus, the QRS detection was performed using interactive software. QRS onsets and widths were further refined by means of a second publicly available software, ECGPUWAVE [9]. Then, on a lead-by-lead basis, separate average templates were built for QRS and T waves. To take into account morphological changes and minor variations in the electrical axis induced by respiration, subtraction of the templates was performed after a warping procedure and consecutive templates were connected via linear interpolation. With the assumption that during fibrillation, atrial and ventricular activities are highly independent, the resulting rECG includes atrial activity only.

2.3. Detrended fluctuation analysis

The Detrended Fluctuation Analysis (DFA) permits the detection of long-range correlations embedded in a seemingly non-stationary time series, and also avoids the spurious detection of some apparent long-range correlations that are an artefact induced by non-stationarity [10].

In details, the AF signal series x of total length N is first integrated

$$y(k) = \sum_{i=1}^{k} \left[x(i) - x_{ave} \right] \qquad (1)$$

where x_{ave} is the signal average. Next, the integrated time series is divided into boxes of equal length n. In each box of length n, a least-squared line is fitted to the data, representing the trend in that box. Finally, the integrated time series is detrended by subtracting the local trend $y_n(k)$ in each box (Figure 1) and the root mean-square fluctuation of this integrated and detrended time series is calculated by

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} \left[y(k) - y_n(k) \right]^2} \qquad (2)$$

This computation is repeated over all time scales (box size) to provide a relationship between $F(n)$, the average fluctuation as a function of box size, and the box size n. The fluctuations can be characterized by a scaling exponent α, the slope of the line relating log($F(n)$) to log(n).

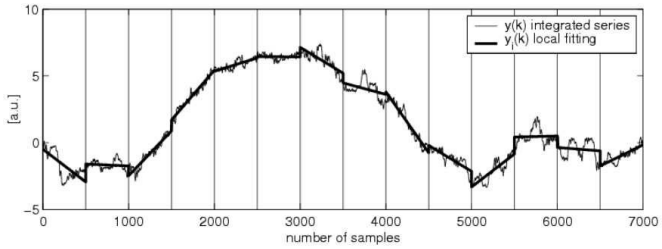

Figure 1: The signal is integrated and divided in boxes of equal size (n=500 in the plot). The local trend (bold line) is then removed in each block and $F(n)$ is computed (see text for details).

2.4. Scaling exponents and cross-over

For some biological signals [10], the DFA plot consisted of two distinct regions of different slopes separated at a break point. This observation suggests the existence of both a short-range scaling exponent, α_1, and a long-range exponent, α_2.

In this paper, the crossover point (nCP) and the two scaling exponents just mentioned were evaluated with two different methods.

First Methods (M1): In the simplest implementation (M1), fixed scaling windows were used and α_1 was defined as the slope in the range $6 \leq n \leq 32$, while α_2 in the range $110 \leq n \leq 600$ (samples). nCP was then obtained as the intersection between the two linear regressions computed over these windows (Figure 2a).

Second Method (M2): In the second method (M2), the DFA plot was fitted with a piece-wise model composed of two straight lines connected at the cross-over point. The piece-wise model which best fits the DFA was determined as follows. Let's consider a fixed window (centered in (2,1) in a log-log plot and with width equal to one fifth of the signal length n_{RANGE}) and let's split the DFA plot into two sub-windows at point n_i (see Figure 2b). For all possible choices of n_i ($n_i \hat{I} n_{\mathrm{RANGE}}$ and $n_{i+1} - n_i$ = 0.05 in logarithmic scale) two regression lines were computed in the regions $n < n_i$ and $n > n_i$. The cross-over point was obtained as the intersection between these two lines. Among all possible regression models (obtained at different n_i) the one who minimized the sum of the residuals of the two least-square regression lines was selected.

2.5. Statistical analysis

The statistical analysis was carried out using Student's t-test for paired data, comparing each rhythm before and after isoproterenol administration. The results of the two

methods were compared with the Student's *t*-test for unpaired data.

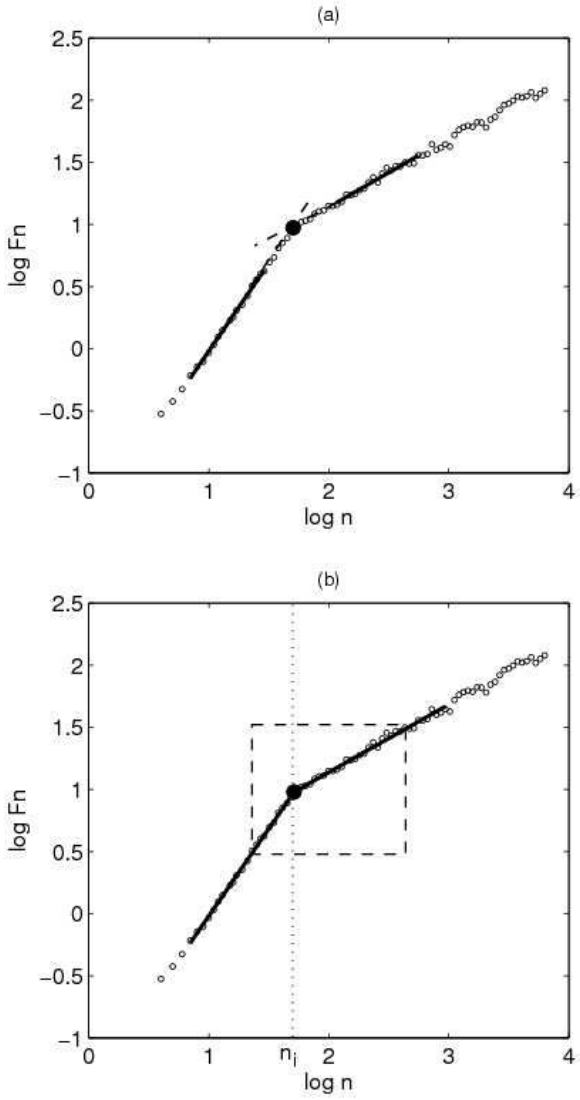

Figure 2: Example of a DFA plot, with the crossover point evaluated by means of M1 (a) and M2 (b).

3. Results

The existence of two scaling regions in the AS has been documented in most of the recordings through the estimation of the scaling exponents (α_1 and α_2) and the crossover point (nCP).

Figure 3 shows an example of the different behaviour after the administration of the isoproterenol in one patient in lead aVR.

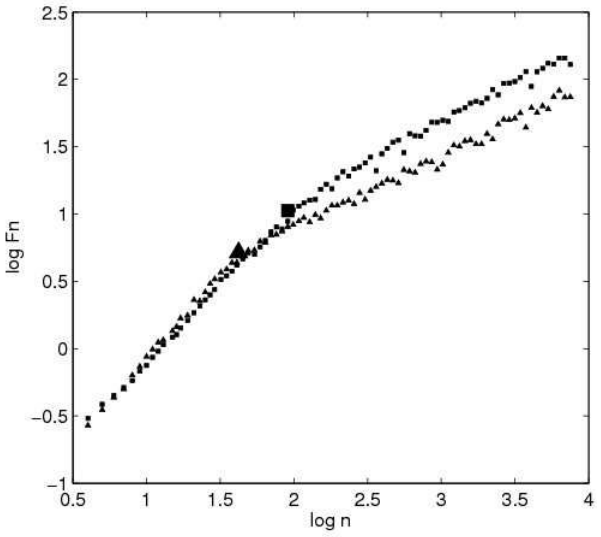

Figure 3: DFA plot in a patient during AF (squares) and AFISO (triangles). The bigger triangle and square represent the crossover point as estimated with method M1.

While the scaling exponents do not differ significantly before and during isoproterenol infusion, it is worth noting the shift of the position in the crossover point after the administration of the drug.

This behavior is confirmed by the analysis on the entire dataset whose results are shown in Table I. During AF and AFISO, the signal resembles a white noise process for long scale (n>200ms, α_2 = 0.55±0.10, M1; α_2 = 0.54±0.09, M2). On the contrary, for shorter scales slowly decaying correlations appear, similarly to an antipersistent fractional Brownian motion (n<150ms, α_1 = 1.29±0.13, M1; α_1 = 1.26±0.13, M2).

Comparing AF and AFISO, we observed no difference in short-term scaling exponent using both the methods (α_{1AF} = 1.29±0.13 vs. α_{1AFISO} = 1.29±0.11, M1; α_{1AF} = 1.26±0.13 vs. α_{1AFISO} = 1.25±0.11, M2), while for the long-term exponents a significant decrease after isoproterenol infusion was found using M1 (α_{2AF} = 0.55±0.10 vs. α_{2AFISO} = 0.52±0.11 p<0.05, M1; α_{2AF} = 0.54±0.09 vs. α_{2AFISO} = 0.52±0.09, M2).

Thus drug infusion seems not to alter the correlation properties of the process. However, the crossover point is located at lower scales after isoproterenol infusion (n_{AF} = 201±6 ms vs. n_{AFISO} = 184±5 p<0.05, M1; n_{AF} = 216±6 ms vs. n_{AFISO} = 200±5 p<0.05, M2).

No significant differences were found in the results obtained with Method 1 and Method 2.

	Method 1		Method 2	
	AF	**AFISO**	**AF**	**AFISO**
α1	1.29 ± 0.13	1.29 ± 0.11	1.26 ± 0.13	1.25 ± 0.11
α2	0.55 ± 0.10	0.52 ± 0.11 *	0.54 ± 0.09	0.52 ± 0.09
N (ms)	201 ± 6	184 ± 5 *	216 ± 6	200 ± 5 *

Table I: Mean values and SD for the analysed data
* $p < 0.05$

4. Discussion and conclusions

We investigated the scaling behaviours of rECG signals obtained from patients undergoing AF episodes aiming to highlight different properties during adrenergic stimulation, mimicked by isoproterenol. The analysis, performed with DFA, evidenced the existence of two scaling regions and a crossover phenomenon. Both the used methods revealed the same behaviour in AF signals. However, M2, with a window adapting to signal characteristics, may result more suitable for signals with different scaling regions.

While the scaling exponents did not differ significantly before and during isoproterenol infusion, a significant shift of the position in the crossover point after the administration of the drug was noted. The shift of the cross-over point may be interpreted as a reduction of temporal correlation in the atrial signals (slowly decaying correlations are noted for a reduced range of scales). This finding supports the hypothesis that the administration of isoproterenol, which mimics the effects of adrenergic activation, induces a decrease in the atrial organization. The sympathomimetic drug tends to disorganize the atrial activity thus contributing to arrhythmia maintenance [11].

References

[1] Sih HJ, Sahakian AV, Arentzen CE, Swiryn S. A frequency domain analysis of spatial organization of epicardial maps. IEEE Trans Biomed Eng. 1995;42:718-727.

[2] Liu ZW, Jia P, Biblo LA, Taccardi B, Rudy Y. Endocardial potential mapping from a noncontact nonexpandable catheter: a feasibility study. Ann Biomed Eng.1998; 26:994-1009.

[3] Mainardi LT, Sassi R. Analysis of scaling behaviour of ECG signal during atrial fibrillation. Computers in Cardiology 2005;32:627-630

[4] Coumel P, Autonomic arrhythmogenic factors in paroxysmal atrial fibrillation, in Atrial fibrillation: mechanism and therapeutic strategies, S.B. Olsson, M.A. Alessie, R.W. Campbell, ed., Armonk, NY: Futura Publishing Company, 1994, pp. 171–184.

[5] Liu L, Nattel S: Different sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol 1997, 273:H805-H816.

[6] Schauerte P, Scherlag BJ, Pitha J, Scherlag MA, Reynolds D, Lazzara R, Jackman WM: Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 2000, 102:2774-2780.

[7] Mainardi L, Porta A, Calcagnini G, Bartolini P, Michelacci A, Cerutti S. Linear and non-linear analysis of atrial signals and local activation period series during atrial-fibrillation episodes. Med Biol Eng Comput. 2001 Mar;39:249-54.

[8] Hoekstra BPT, Diks CGH, Allessie MA, De Goede J. Nonlinear analysis of epicardial atrial electrograms of electrically induced atrial fibrillation in man. J Cardiovasc Electrophysiol 1995; 6:419-440.

[9] Laguna P, Jané R, Bogatell E, Anglada DV. ECGPUWAVE, freely available from www.physionet.org.

[10] Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995; 5:82-87.

[11] Mainardi LT, Corino VDA, Lombardi L, Tondo C, Mantica M, Lombardi F, Cerutti S. Assessment of the dynamics of atrial signals and local atrial period series during atrial fibrillation: effects of isoproterenol administration. Biomed. Eng. Online. 2004; 3:37.

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