Ventricular Response during Atrial Fibrillation: Evaluation of Exercise and Flecainide Effects

VDA Corino[1], LT Mainardi[1], D Husser[2], HU Klein[2], A Bollmann[2]

[1]Dipartimento di Bioingegneria, Politecnico di Milano, Milano, Italy
[2]Department of Cardiology, University Hospital Magdeburg, Magdeburg, Germany

Abstract

Ventricular response (VR) during atrial fibrillation (AF) is a complex process, which is modulated by the autonomic nervous system (ANS). The purpose of this study was to characterize VR to both exercise as ANS stimulus and flecainide which is also supposed to have effects on the ANS. RR series were analyzed by means of time domain parameters and non-linear methods. In 15 patients (10 male, aged 55 ± 13 years) with persistent AF (mean AF duration 13 ± 24 months), time domain parameters and indexes assessing the predictability of the time series, (regularity index, approximate entropy and an index for linear predictability) were evaluated. VR during exercise resulted modulated by adrenergic stimulation. Flecainide exhibited vagolytic activity especially during exercise. Thus, monitoring of exercise-induced and antiarrhythmic drug effects on ANS is possible with parameters derived from time domain and non-linear analysis.

1. Introduction

Atrial fibrillation (AF) is not a fully random process, as illustrated by previous studies [1][2], in which transient instances of atrial regularity have been observed. Also the irregular ventricular response (VR) intervals in AF, often described as chaotic, have been proved to be not completely random [3][4]. It has also been reported that reduced variability of the ventricular response interval during AF may predict an adverse prognosis [5].

The autonomic nervous system (ANS) [6] plays an important role among the factors influencing VR in AF by modulating refractoriness of the atrioventricular node, that is mainly dependent on vagal tone [7]. Thus, a first purpose of the study is to characterize VR during AF to changes of the autonomic balance induced by exercise.

Antiarrhythmic drugs are frequently prescribed in AF to terminate AF and to prevent its recurrence [8]. Besides electrophysiological effects, they may alter autonomic tone. The latter effects are not routinely evaluated in the clinical setting. Consequently, the second purpose of this study is to elucidate the influence of flecainide on the autonomic nervous system and, especially, whether its administration varies the dynamics of VR during exercise.

2. Methods

2.1. Experimental protocol

Fifteen patients (10 men/5 women, mean age 55 ± 13 years), referred for cardioversion of AF, were included in this study. A history of AF was present for an interval ranging from some hours to 96 months (mean AF duration 13 ± 24 months). Echocardiographic characteristics were: left atrial diameter 46 ± 4 mm, and left ventricular ejection fraction 60 ± 6 %. The pharmacological therapy included digitalis in 7 patients, calcium channel blockers in 6 and beta blockers in 7 (more than one drug is possible for each patient).

Patients underwent symptom-limited bicycle exercise stress testing using a 3-minute step-up protocol. Workload increase was chosen according to age- and gender-predicted values, aiming for a test duration of 8 to 12 minutes. Exercise testing was repeated after 3 – 5 days of flecainide loading (200 mg bid po). Thus, four clinical experimental conditions were defined: i) baseline (B); ii) exercise (E); iii) baseline with flecainide (BF); iv) exercise with flecainide (EF). Six patients underwent only phases B and E, while nine completed all the four protocol phases.

ECG was continuously recorded during the experiment (sampling rate 2 KHz). For each phase, two-minute ECG segments were analyzed. QRS detection and RR interval measurement were automatically performed. RR interval series were visually checked and missed/misdetected beats were corrected using an interactive software. PVC or beats with aberrant conduction were excluded.

2.2. Time domain parameters

Time domain indexes of ventricular response were computed following the recommendations for heart rate variability [9]. Time domain analysis includes the mean (M) and the standard deviation (SDNN) of all RR intervals, the minimum (MIN) and the maximum (MAX)

RR interval, the root of the mean squared differences of successive RR intervals (rMSSD) and the percentage of interval differences of successive RR intervals greater than 50 ms (pNN50).

2.3. Regularity

The regularity (R) index is related to the degree of recurrence of a pattern in a time series and it 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. For a given signal, M different patterns of length L can be obtained (the J-th of them is indicated as x_L^J). *CE* is defined as [10]

$$CE(L) = -\sum_{J=1}^{M} p(x_{L-1}^J) \sum_{i=1}^{N} p(x(i)/x_{L-1}^J) \log(p(x(i)/x_{L-1}^J)) \qquad (1)$$

where $p(x_{L-1}^J)$ 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 [10] 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:

$$R_x = 1 - \min(NCCE(L)) \qquad (2)$$

R_x tends to 0 if x is a fully unpredictable process, it tends to 1 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

2.4. Approximate entropy

Approximate Entropy (ApEn), reflecting the likelihood that "similar" patterns of observations will not be followed by additional "similar" observations, is a measure quantifying the 'opposite' of the regularity of time series. A regular and predictable series, has a relatively small ApEn; a less predictable, i.e. more complex, process has a higher ApEn [11].

Given a time series x of length N and a criterion of similarity r, an estimate of ApEn can be obtained by computing the following function

$$C_{im}(r) = \frac{n_{im}(r)}{N - m + 1} \qquad (3)$$

The quantity $C_{im}(r)$ is the fraction of patterns of length m that resemble the pattern of the same length that begins at interval i, that is $p_m(i)$, $n_{im}(r)$ is the number of patterns that are similar to $p_m(i)$ [11]. $C_{im}(r)$ can be calculated for each pattern i, and $C_m(r)$ is defined as the mean of these $C_{im}(r)$ values. The quantity $C_m(r)$ expresses the prevalence of repetitive patterns of length m in the series. Finally, the approximate entropy, for patterns of length m and similarity criterion r, is define as

$$ApEn(x, m, r) = \ln\left[\frac{C_m(r)}{C_{m+1}(r)}\right] \qquad (4)$$

i.e., as the natural logarithm of the relative prevalence of repetitive patterns of length m compared with those of length $m+1$.

2.5. Level of predictability

A discrete time series $x(n)$ can be modeled as the output of an autoregressive model of p order

$$x(n) = \sum_{k=1,p} a_k x(n-k) + w(n) \qquad (5)$$

where n is the discrete-time index, the a_k are the model coefficients and $w(n)$ is a Gaussian white noise process of variance σ^2 feeding the model. The actual sample differs from its model prediction, thus generating the prediction error

$$e(n) = x(n) - \sum_{k=1,p} a_k x(n-k) \qquad (6)$$

An index of the level of predictability (*LP*) may be defined as follows

$$LP = (1 - \sigma_e / \sigma_x) \cdot 100 \qquad (7)$$

where σ_e is the standard deviation of $e(n)$ and σ_x is the standard deviation of the process x. *LP* measures the percentage of power which may be predicted by the autoregressive model. In the case of a purely random signal (σ_e is quite close to σ_x) *LP* tends to zero, while in the case of a linearly predictable signal (σ_e tends to zero) the index tends to one and it assumes intermediate values for those processes that may be partially predicted from the model.

2.6. Statistical analysis

Data are reported as mean ± one standard deviation. The statistical analysis was carried out using Student's t-test for paired data. A p value of at least 0.05 was considered statistically significant.

			FLECAINIDE	
	BASELINE	**EXERCISE**	**BASELINE**	**EXERCISE**
RR Mean	725 ± 163	571 ± 153 **	702 ± 121	525 ± 94 **
SDNN	168 ± 50	131 ± 47 **	161 ± 55	112 ± 44 **
MAX	1301 ± 275	1075 ± 337 **	1250 ± 345	986 ± 243 **
MIN	441 ± 102	344 ± 78 **	424 ± 82	333 ± 59 *
pNN50	77 ± 11	71 ± 11 *	80 ± 6	55 ± 22 * †
RMSSD	243 ± 81	178 ± 69 **	227 ± 84	140 ± 58 ** †
LP	1.29 ± 0.92	2.54 ± 3.27	1.31 ± 0.80	5.27 ± 4.21 *
R	0.05 ± 0.05	0.06 ± 0.06 *	0.06 ± 0.05	0.15 ± 0.17 *
ApEn	1.08 ± 0.08	1.12 ± 0.09 *	1.12 ± 0.11	0.97 ± 0.29

Table 1: Mean values ± one SD during the four phases of the protocol.
* $p<0.05$; ** $p<0.001$ (exercise effect); † $p<0.05$ (flecainide effect)

3. Results

Table 1 summarizes the mean values and the standard deviations of the parameters during the four experimental conditions.

Exercise effect. The effect of exercise in VR modulation was evident both with (BF vs. EF) and without (B vs. E) flecainide administration. A significant decrease ($p<0.001$) was observed in all time domain parameters, all evidencing a reduction in the RR beat-to-beat variability.

On the other hand, the LP and R indexes, reflecting linear and non-linear series predictability, tended to increase during exercise. Both the LP and R values are very low compared to sinus rhythm [12], thus the predictability degree of VR is very small. Nevertheless, in particular the R index, taking linear and non-linear dynamics into account, succeeds in underlining the increased predictability of VR during exercise.

Flecainide effect. Flecainide had no effects under baseline conditions. However, response to exercise was more pronounced after flecainide initiation which is illustrated in Figure 1. To assess drug effect on the response to exercise, the delta (i.e. the difference between exercise and basal values) is computed for each parameter. In particular, almost all time domain indexes show less scattered values, resulting in a more compacted boxplot. On the contrary, the predictability indexes have a less compact box plot.

4. Discussion and conclusions

VR during AF is a complex process, which is modulated by the ANS. However, there is paucity of data and methods to describe this process. The purpose of this study was to characterize VR to both exercise as ANS stimulus and flecainide which is also supposed to have effects on the ANS. The results concerning VR during exercise underline the relevant activity played by the autonomic nervous system in patients with AF, as time domain parameters decreased and predictability indexes increased. On the other hand, an interesting finding regarding flecainide effect is its possible vagolytic effect, as evidenced by the more pronounced decrease of rMSSD and pNN50 indexes, both highly related to vagal activity. Monitoring of exercise-induced and antiarrhythmic drug effects on ANS is possible with parameters derived from time domain and non-linear analysis. This may prove useful for better characterization of AF modulating factors in the individual patient.

References

[1] Sih HJ, Zipes DP, Berbari EJ, Olgin JE. A high-temporal resolution algorithm for quantifying organization during atrial fibrillation. IEEE Trans Biomed Eng 1999;46:440-450.

[2] Censi F, Barbaro V, Bartolini P, Calcagnini G, Michelucci A, Gensini GF, Cerutti S. Recurrent patterns of atrial depolarization during atrial fibrillation assessed by recurrence plot quantification. Ann Biomed Eng 2000;28:61-70.

[3] Stein KM, Walden J, Lippman N, Lerman BB. Ventricular response in atrial fibrillation: random or deterministic? Am J Physiol. 1999;277:H452-8.

[4] Hayano J, Yamasaki F, Sakata S, Okada A, Mukai S, Fujinami T. Spectral characteristics of ventricular response to atrial fibrillation. Am J Physiol. 1997;273:H2811-6.

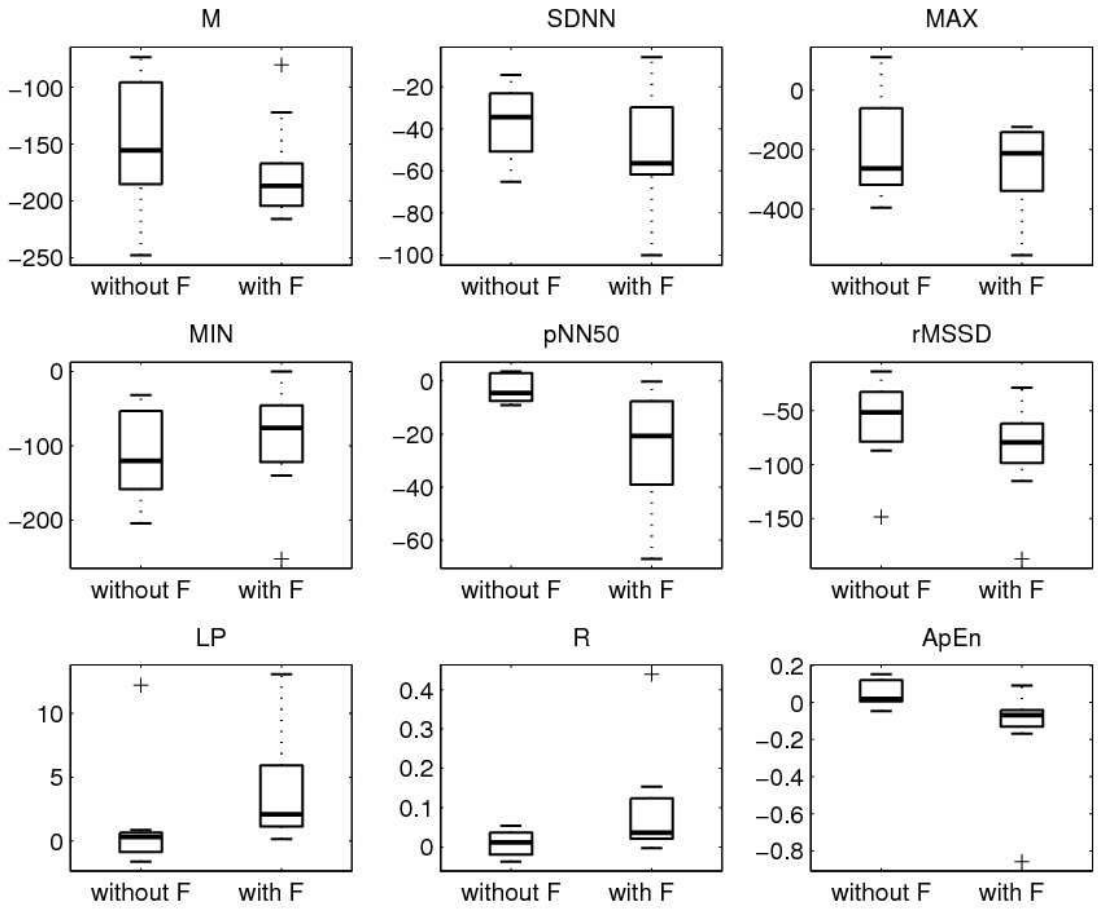

Figure 1: Box plots of the differences (E-B) and (BF-EF) for all parameters derived from time domain and non-linear analysis. Each box plot has the following structure. The box itself contains the middle 50% of the data and the line in the box represents the median value of the data. The lower and upper edges of the box indicate respectively the 25th and the 75th percentile of the data set. Points at a greater distance from the median than 1.5 times the inter-quartile range are plotted individually as crosses. Please note the more pronounced changes in pNN50 and ApEn after flecainide initiation ($p<0.05$).

[5] Frey B, Heinz G, Binder T, Wutte M, Schneider B, Schmidinger H et al. Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. Am Heart J. 1995;129:58-65.

[6] Coumel P, Attuel P, Lavallée JP, Flammang D, Leclercq JF, Slama R. Syndrome d'arythmie auriculaire d'origine vagale. Arch Mal Coeur 1978;71:645-656.

[7] Toivonen L, Kadish A, Kou W, Morady F. Determinants of the ventricular rate during atrial fibrillation. J Am Coll Cardiol 1990;16:1194-1200.

[8] Husser D, Stridh M, Sornmo L, Geller C, Klein HU, Olsson SB, Bollmann A. Time-frequency analysis of the surface electrocardiogram for monitoring antiarrhythmic drug effects in atrial fibrillation. Am J Cardiol. 2005;95:526-528.

[9] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability: standars of measurament, physiological interpretation, and clinical use. Circulation. 1996;93:1043-1065.

[10] Porta A, Baselli G, Liberati D, Montano N, Cogliati C, Gnecchi-Ruscone T, Malliani A, Cerutti S: Measuring regularity by means of a corrected conditional entropy in sympathetic outflow. Biol Cybern 1998, 78:71-78

[11] Pincus SM. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA. 1991 Mar 15;88(6):2297-2301.

[12] Mainardi LT, Corino VD, 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.

Address for correspondence
Ing. Valentina DA Corino
Dipartmento di Bioingegneria, Politecnico di Milano
Via Golgi 39 20133 Milano, Italy
E-mail: valentina.corino@polimi.it