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ENCAINIDE REDUCES HEART RATE VARIABILITY FRACTAL DIMENSION AMONG ARRHYTHMIC PATIENTS WHO SUFFERED ACUTE MYOCARDIAL INFARCT.

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ABSTRACT

The Autoregressive Dimensional Index (ARDI) was measured in a subset of R-R recordings corresponding to 257 patients from the Cardiac Arrhythmia Suppression Trial (CAST)-study, both before, and during treatment with the anti-arrhythmic drug Encainide (E). Encainide induced an average ARDI increase of 47% ($P < 0.001$, paired t-test). <>A similar analysis with 127 patients treated with Flecainide (F) did not reveal statistical differences related to treatment. Since ARDI is negatively correlated to the Fractal Dimension (FD) of HRV data (Hernandez et al, Electron J Biomed 2004;1:4-15) we conclude that E exerts a reduction in FD among these patients. Since changes suggesting FD reduction are predictive of health worsening and sudden death, our results may provide an explanation for the reported increase in mortality induced by E among CAST patients. The lack of effect from F may be in agreement with recent reports suggesting that this drug does not increase the risk of sudden death.

Keywords: Encainide, Heart Rate Variability, Complexity, Fractal dimension

RESUMEN

El Índice Dimensional Autorregresivo (Autoregressive Dimensional Index ARDI) fue evaluado sobre un subconjunto de registros de intervalos R-R correspondientes a 257 pacientes incluidos en el estudio "CAST", un conocido ensayo de supresión de arritmia en pacientes que sufrieron infarto agudo del miocardio. Los registros fueron obtenidos tanto antes como durante el tratamiento con el medicamento antiarrítmico Encainida (E). La Encainida inducía un incremento en el valor de ARDI de aproximadamente un 47% ($P < 0.001$, prueba de la "t" pareada).

Un análisis similar realizado con 127 pacientes tratados con Flecainida (F) no mostró ningún cambio significativa asociada al tratamiento. Por cuanto ARDI se correlaciona negativamente con la Dimensión Fractal (FD) de los datos de variabilidad de la frecuencia cardiaca (Hernández et al, Electrón J Biomed 2004;1:4-15), concluimos que E ejerce una acción reductora de la FD en ese grupo de pacientes. Por cuanto la reducción de la FD predice acerca del empeoramiento de la salud y de muerte súbita, nuestros resultados pudieran brindar una explicación al incremento de la mortalidad asociada a E entre los pacientes participantes del estudio CAST. La ausencia de efecto por parte de F puede concordar con reportes recientes que sugieren que este medicamento no aumenta el riesgo de muerte súbita.

Palabras clave: Encainida, Variabilidad de la Frecuencia Cardiaca, complejidad, dimensión fractal.

INTRODUCTION

Recently, the ARDI index was introduced as a complexity measure capable of discriminating between both clinically¹ and physiologically² different conditions assessed from Heart Rate Variability (HRV) data.

It was previously shown that ARDI is negatively correlated to the fractal dimension of both "pure fractal time series" and HRV data². On the other hand, we still lack an explanation for the paradoxical increase in mortality among acute myocardial infarction patients who were treated with the anti-arrhythmic drugs Encainide (E) and Flecainide (F)³⁻⁵.

There is mounting evidence suggesting that reduction in fractal dimension of HRV data is a strong predictor of severe health condition worsening⁶⁻¹².

Thus it seems plausible to explore how the ARDI index changes with anti-arrhythmic treatment of patients who suffered acute myocardial infarct.

MATERIALS AND METHODS**Data.**

Long term (24 hr.) R-R intervals were downloaded from the site <http://www.physionet.org>. It corresponds to a subset of survivors of myocardial infarction who participated in the Cardiac Arrhythmia Suppression Trial (CAST)¹². All recordings were scanned by an experienced research arrhythmia analyst, using standard Holter analysis procedures. Beat annotation files were edited in a second pass to identify improperly measured RR intervals to be excluded from further analysis. From the whole data base we selected only those recordings where traces were available for the same individual both before and during treatment E (n=257), as well as 127 pairs of recordings corresponding to patients treated with F.

For further details about the data the reader is referred to Ref. 12. The protocol followed with the doses of E and F for achieving an Arrhythmia Suppression is described in ¹⁶.

From the whole trace only the first 5000 data points were used for index estimation.

Autoregressive Dimension Index (ARDI).

For ARDI estimation a recording of duration $N = 5000$ was divided into 25 non overlapping segments 200 data points long each. To each segment the following non-linear autoregressive model was fit:

$$I_n = f(I_{n-1}, I_{n-2}, \dots, I_{n-m}) + \varepsilon_n \quad (1)$$

Where $I_{n-1}, I_{n-2}, \dots, I_{n-m}$ are the $Z_{n-1}, Z_{n-2}, \dots, Z_{n-m}$ intervals in the sequence.

We denote with f a multivariate non-linear function relating the n th interval to the m preceding intervals in the sequence. Under our assumptions,

$\{\varepsilon_n\}$ corresponds to a random, independent, identically distributed variable. The parameter m is defined as the order of the non-linear autoregressive model. The function f is estimated non-parametrically^{2, 14}. According to this method, the estimate at an arbitrary point $Z_{n-1}, Z_{n-2}, \dots, Z_{n-m}$ of the state space is obtained as a weighted average of the data^{2, 13}.

$$\hat{f}(z_{t-1}, z_{t-2}, \dots, z_{t-m}) = \frac{\sum_{i=m+1}^N x_i \prod_{j=1}^m K\left(\frac{|z_{t-j} - x_{i-j}|}{h}\right)}{\sum_{i=m+1}^N \prod_{j=1}^m K\left(\frac{|z_{t-j} - x_{i-j}|}{h}\right)} \quad (2)$$

Here, $K(\cdot)$ is the kernel function, and the parameter h is some positive real number ("bandwidth" of the kernel). Kernel function K is required to satisfy

$$\int K(u) du = 1, \quad (3)$$

$K(\cdot) \geq 0$ Specifically, we selected for our calculations the so called "Gaussian" kernel.

$$K(u) = \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}u^2} \quad (4)$$

The bandwidth parameter h determines the weight of each neighboring point in the phase space. If h is large, all data points have a similar weight, just as in a simple averaging. If h is very small only close neighbors will account. A minimal cross validation error criterion has been used for selecting the bandwidth parameter^{2, 13} After computing the optimal order m for each segment of the whole trace it is possible to compute ARDI as the proportion of m -values equal or higher than 18.

$$\text{ARDI} = \frac{\text{Number of segments with optimal order higher than 18}}{\text{Total number of segments.}}$$

Statistical analysis. For comparing groups a paired t-test was performed.

RESULTS AND DISCUSSION

Table I. changes in ARDI values due to treatment with E and F.

Drug	Before	After	n	% Increase	P (Paired t-test)
Encainide	16.88+- 15.88	24.88+-18.56	257	47%	<0.001
Flecainide	21.24+-16.56	24.0+-12.28	127	13%	n.s.

We obtained that ARDI is increased as patients were submitted to treatment with E. (see table I).

On the other hand, we could not demonstrate an increase of ARDI among patients treated with F.

All together these results indicate that anti-arrhythmic treatment reduces the complexity of HRV data among patients with acute myocardial infarction. This conclusion is supported by the previously demonstrated negative correlation between ARDI and the Fractal Dimension².

In our opinion, these results are encouraging for further research about the effect of anti-arrhythmic drugs on heart rate variability and the possible connection with health worsening risk. As a first priority we suggest to address whether the anti-arrhythmic effect is or not independent from the cardiac arrhythmia suppression effect. If the answer is positive, the initial hypothesis of the CAST study might be right.

It is interesting that the effects of F were less notable than those from E. Some recent reports indicate lack of evidence for a deleterious effect of F on certain groups of elderly patients. In particular, there is no evidence for an increased risk of sudden death with F¹⁵

Thus we conclude that treatment with the anti-arrhythmic E reduces the fractal dimension of HRV data among these patients. Since FD reduction is associated with increased risk of mortality, this could provide an explanation for the increased mortality of patients treated with antiarrhythmic drugs, as is was found from CAST.

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The authors study the possible relation between the changes in the complexity of HRV series and the administration of drugs like Encainide (E) and Flecainide (F) in patients with a specific illness (acute Myocardial Infarct). The statistics of the Autoregressive Dimensional Index (ARDI) that

they present is representative but they may be extended by using additional tools from non linear dynamics to obtain an accurate assessment of the complexity.

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Heart rate variability (HRV) has become one of the major indexes to assess cardiovascular health. While the research of HRV in different physiological states has advanced significantly in the past decades, the database for HRV under cardiovascular drug treatment is still lacking.

This study provides the reference for HRV under the influence of anti-arrhythmic drugs, Encainide and Flecainide. In particular, the authors attempted to relate the paradoxical increase of mortality in myocardial infarct patients under anti-arrhythmic drugs treatment to the well-known HRV phenomenology: reduction of fractal dimension of HRV in general heart diseased condition. They were successful in using Autoregressive Dimensional Index (ARDI) for this purpose. Since details of the population used in this study were unavailable, future study on larger and more designated groups should be considered. In addition, ARDI should also be compared with other approaches used in the HRV study in recent years, such as DFA and multifractal analysis.

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