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A Study of Pharmacological vs. Pathological Autonomic Nervous System Blockade in Humans, using Heart Rate Chaotic Dynamics

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Abstract. Pathological blocking of the Autonomous Nervous System (ANS) is diagnosed for patients having Autonomic Neuropathy passing a well - defined set of criteria. In this work, It is shown that standard analysis can be complemented by a study of the chaotic dynamics of the Heart Rate (HR), over a period of 12min in the resting position. It was found that patients who suffering from ANS blockade, typically exhibit a smaller degree of fractality and complexity of the chaotic attractor reconstructed from the time series of the HR signal. These dynamical measures are more evident in normal human subjects that have been subjected to pharmacological ANS blockade.

1. Introduction

Standard analysis of diabetic patients that show symptoms of pathological ANS blockade proceeds by testing whether the patient passes a number of well - defined criteria [1,2]. These criteria include:

1) Valsava test
2) Short hyperventilation test
3) Isometric exercise
4) Postural hypotension reflex.

Even after this analysis has been completed, one would like to estimate, as reliably as possible, the degree to which the ANS of the patient has been affected by pathological blockade.

Chaotic dynamics has already been applied to a variety of time series obtained from ECG and heart rate [3,4,5,6,7] measurements by many other researchers. Concerning ANS blockade, Mansier et al. [4] have used chaotic dynamics to analyse the heart rate of mice, while Hagerman et al.[6] have used Lyapunov exponents in humans.

In this paper we use, for the first time, chaotic dynamic analysis of patients with pathological ANS blockade and we introduce the estimation of fractality as a novel method to be used in association with heart rate dynamics.

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A new set of criteria were applied to study ANS blockade by examining the dynamical properties of the time series obtained from HR measurements, over a period of 12min in the resting position. These criteria are borrowed from the field of chaotic dynamics and refer to the fractality and complexity of the HR attractor, embedded in a space of appropriate dimension.

We find that patients exhibiting symptoms of pathologically ANS blockade, present a chaotic attractor for heart rate with significantly lower dimension than normal subjects. The importance of this observation is strengthened by the fact that the dimension of the heart rate attractor for normal subjects is found to decrease , under the effect of pharmacological ANS blockade and this decrease is more pronounced than in the ANS blockade patients. Thus, one can suggest that the degree of pathological ANS blockade can be quantified according to the dimensionality of the heart rate attractor.

The paper is organised as follows: In section 2 we briefly outline the principles and techniques of chaotic dynamics used in this work (generalized dimensions and correlation dimension). In section 3 we describe the cases we studied and the main results, while our conclusions are discussed in section 4.

2. Attractor reconstruction, generalized and correlation dimensions

A number of measures of complex time series have been developed based on concepts of non-linear dynamics. These include correlation dimension [10] and generalized dimensions [8,9] of the time series from the analysed system. The correlation dimension gives a statistical measure of the geometry for reconstructed attractor. In deterministic chaotic systems the correlation dimension is frequently (but not always !) a fractional number and is independent of the embedding dimension m when m is large enough [8,9,10].

The procedure to calculate the correlation dimension requires constructing time-delayed copies of the matrix

$$a_k=[\, X(t_k),\, X(t_k+\tau),\, \times(t_k+2\tau),\ldots,\times(t_k+(m-1)\,\tau)]$$

from the input signal X(t) , where τ is the delay time and m is the embedding dimension. The correlation integral is given by the equation

$$C(r)=\frac{1}{N^2}\sum_{k,j=1}^{N} H(r-|a_k-a_j|)\ ,\ a_k\neq a_j$$

where r is the radius of the located hyperspheres, $|a_k-a_j|$ is the Euclidean distance between the vectors a_k and a_j , N is the total number of elements of the signal, and H is the Heaviside function. The Heaviside function is equal to 1 if $r > |a_k-a_j|$ and is equal to 0 if $r \leq |a_k-a_j|$. The correlation dimension D is the slope of the line log(C(r)) versus log(r) [12-15].

To calculate the generalized dimensions it is necessary to use the following generalized integral:

$$C_q(r)=\frac{1}{N}\sum_{k}\Big[\ \frac{1}{N}\sum_{j} H(r-|a_k-a_j|)\ \Big]^{q-1}\ ,\ a_k\neq a_j$$

It is obvious that $C_2(r)$ is equal to correlation integral C(r). The dimension D(q) is the slope of the line log(C(r)) versus log(r) divided by q-1

$$D(q) = \frac{1}{q-1} \frac{d \log(C_q(r))}{d \log(r)}$$

It is also obvious that D(2) is equal to correlation dimension D.
From function D(q) one can measure the fractality of the signal X(t). The slope of this function is a quantitative measure of the fractal nature of the signal [8,9].

3. Study cases and results

In this study, three groups of human subjects were tested. In the first group 17 healthy volunteers were studied and in the second group the same 17 healthy persons were studied after propranolol administration for 15 minutes (0.013 mgr/Kgr/min) followed by atropine administration for 5 minutes (0.008 mgr/Kgr/min). In the third group 17 diabetic patients were included suffering from pathological ANS blockade (Autonomic Neuropathy).

For each subject from all three groups, the ECG was recorded for 12min in the resting position. For ECG recording a CASE 15 MARQUETTE system was used. The ECG signal was sampled with 256 Hz. Consecutive QRS complexes (RR intervals) were extracted off-line from the ECG signal. Using the formula HR=60/RR(sec) the time series of successive RR intervals was transformed to time series of HR for each subject. The mean values and standard deviations of the HR were calculated for all subjects, and for them their mean values and standard deviations were calculated for each group.(Table 1).

Table 1. *Mean values and Standard Deviations for each group*

	Group 1 Normals		Group 2 Drugs		Group 3 Patients	
	Mean	Std	Mean	Std	Mean	Std
mean	78.3147	4.0327	92.9045	1.1637	74.0086	2.5577
std	12.6012	1.2965	12.1344	0.5577	11.4539	1.3884
p			0.00193	1.5E-07	0.13971	0.0129

Using the algorithm of Grassberger-Procaccia [10] the correlation dimension was calculated using embedding dimension 10 and delay time close to the value of the first minimum of mutual information for each subject, and for them their mean values and standard deviations were calculated for each group.

Table 2. *Mean value of Correlation dimension for each group*

	Group 1 Normals	Group 2 Drugs	Group 3 Patients
Mean	5.29±0.40	3.19±0.58	4.25±0.61
p		1.85E-10	1.69E-05

The correlation dimension is independent from the embedding dimension m for m>8 (Figure 1). From the D(q) function (q=2 to 10) of each subject the mean values of D(q) for each group were calculated and the slope was determined using the first three points of the diagrams of every group. (Figure 2, Table 3).

Table 3. Slopes for generalized dimensions using the first four points for each group.

	Normals Category 1	Drugs Category 2	Patients Category 3
Mean slopes	-0,2321	-0.1031	-0.1950

A paired t-test used to compare the normal subjects (group 1) before and after drug administration (group 2) and an unpaired t-test was used to compare the normal subject (group 1) with pathological ANS blockade patients (group 3).

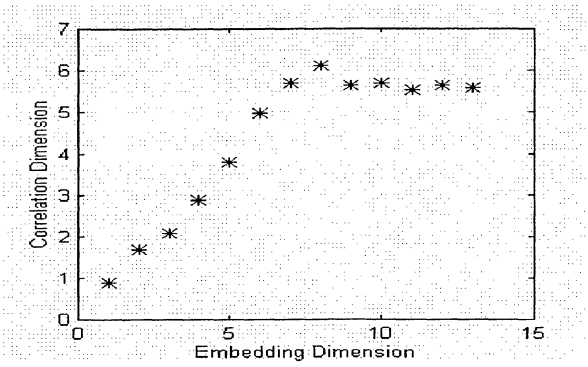

Figure 1. Correlation dimension for a normal subject vs. embedding dimension.

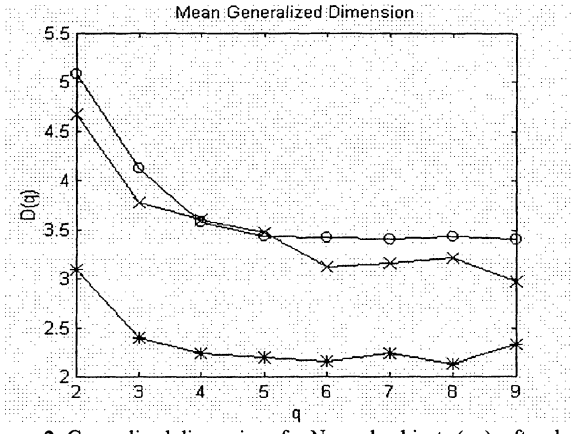

Figure 2. Generalized dimensions for Normal subjects (o), after drugs administration (*), ANS blockade patients (X).

4. Discussion

The mean value of HR increases significantly after drug administration. HR is not significantly different for normal subjects (group 1) and pathological ANS blockade. Standard deviation in normal subjects (group 1) is significant greater than after drug administration

more constant in pathological or pharmacological ANS blockade subjects than normal subjects.

The correlation dimension in normal subjects is significantly greater than ANS blockade and this difference is more evident before and after drug administration for normal subjects. This means that HR in normal subjects is more complex than in ANS blockade. The correlation dimension can be used as a new tool to complement standard methods to diagnose pathological ANS blockade. For normal subjects the correlation dimension is around 5 or greater and for the other two groups it is between 2 and 5.

Normal subjects (group 1) show higher slope for the mean value D(q) function from ANS blockade cases. This is a sign of higher "multifractality". The fractality of HR can be used in association with correlation dimension for improving diagnostic efficiency for ANS blockade.

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