Association between Abnormal Electrocardiogram and Less Complex Heart Rate Variability Estimated by the Correlation Dimension

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ABSTRACT

Objective: To compare the correlation dimension (CD) of heart rate variability (HRV) in adults with and without abnormal electrocardiogram (ECG).

Methods: A 24-hr Holter and a standard ECG were recorded from 100 university workers. After exclusion of 10 recordings with more than 5% of false RR intervals, a total of 90 subjects (age 46.2 ± 8.7 years old, 45 were women) were included in the study. Two cardiologists classified 29 standard ECG as abnormal. CD was calculated from HRV time-series of 10,000 beats in the morning (from 11am), afternoon (from 5pm) and night (from 2am). Demographical characteristics were compared by ANOVA (considering ECG diagnosis and sex as independent factors) or by Fisher's exact test. Mean CD values were compared by analysis of variance considering as independent factors the ECG diagnosis, sex and time of day.

Results: All demographical characteristics were similar except for a higher proportion of males with abnormal ECG (69%) than with normal ECG (41%). CD was not different with respect to the time of day, but it was higher in subjects with normal ECG (10.86 ± 2.41) than those with abnormal ECG (10.20 ± 2.48), and it was also higher in females than males: 11.04 ± 2.14 versus 10.63 ± 2.71 (normal ECG group), 10.84 ± 2.41 versus 9.92 ± 2.44 (abnormal ECG group).

Conclusion: The finding of abnormal ECG is associated with HRV decreased complexity in adults.

Keywords: **adult humans, circadian, correlation dimension, gender-based differences, nonlinear analysis.**

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RESUMEN

Objetivo: Comparar la dimensión de correlación (DC) de la variabilidad de la frecuencia cardiaca (VFC) entre adultos con electrocardiograma (ECG) normal y anormal.

Métodos: Se registró un Holter de 24 horas y un electrocardiograma (ECG) estándar de 100 trabajadores universitarios. Después de la exclusión de 10 registros con más de 5% de intervalos RR falsos, se incluyeron en el estudio a 90 sujetos (edad 46.2±8.7 años, 45 mujeres). Dos cardiólogos clasificaron 29 ECG estándar como anormales. La DC se calculó en series de tiempo de VFC de 10,000 latidos en la mañana (desde las 11:00), tarde (desde las 17:00) y noche (desde las 2:00). Las características demográficas fueron comparadas mediante análisis de varianza (considerando diagnóstico de ECG y sexo como factores independientes) o con prueba exacta de Fisher. Los valores promedio de DC fueron comparados con análisis de varianza considerando como factores independientes el diagnóstico de ECG, sexo y hora del día.

Resultados: Las características demográficas fueron similares excepto por mayor proporción de hombres con ECG anormal (69%) que normal (41%). La DC no fue diferente con respecto a la hora del día, pero fue mayor en sujetos con ECG normal (10.86 ± 2.41) que con ECG anormal (10.20 ± 2.48), y también fue mayor en mujeres que en hombres: 11.04 ± 2.14 vs 10.63 ± 2.71 (grupo de ECG normal), 10.84 ± 2.41 vs 9.92 ± 2.44 (grupo de ECG anormal).

Conclusión: El hallazgo de ECG anormal en adultos está asociado con menor complejidad de la VFC.

Palabras clave: **humanos adultos, circadiano, dimensión de correlación, diferencias de género, análisis no lineal.**

INTRODUCTION

Heart rate variability (HRV), usually measured from RR intervals of normal sinus to normal sinus beats of the electrocardiogram (ECG), it is the oscillation in the interval between consecutive heart beats [1, 2]. HRV fluctuations are the result of interactions between the autonomous nervous system and the cardiovascular system [3], along with many other factors [4]. HRV fluctuations occur even during rest, and therefore there is a normal variability which has been very useful for research of heart rate regulation physiology and it has diagnostic and prognostic applications [2].

There are several methods for HRV analysis [2]. Traditional ones include time domain and frequency domain techniques. Time domain methods are based on estimation of statistical parameters such as mean and standard deviation. Frequency domain methods are based on estimation of the power spectral density in order to obtain indexes derived from the area under the curve at different frequencies; some of these indexes are used as indicators of sympathetic and parasympathetic modulation of the heart rate [1, 5]. These methods are useful for the diagnosis and characterization of several pathologies, including the prediction of morbidity and mortality in patients with myocardial infarction [6], diabetes mellitus [7], heart failure [8], and multiple organs dysfunction [9]. In most of instances, morbidity and mortality is associated with reduction in HRV. However, decreased HRV is also associated with aging [10].

HRV has been recognized as a signal with complex behavior, and it has been studied with different methods to evaluate nonlinear characteristics and complexity [11, 12]. Complexity of a system or dynamic process might be viewed as "some increasing function of the degree to which its components engage in structured, organized interactions" [13]. Complex systems cannot be explained as a sum of its parts, since there

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are interactions between its components that are nonlinear. Several studies have shown the nonlinear nature of cardiac processes suggesting that the fluctuations in the inter-beat intervals of a healthy heart could be the result, at least in part, of an intrinsic variability of the autonomous nervous system which has nonlinear behavior [14]. Several investigations have supported the hypothesis of the healthy heart having a complex behavior, while aging and disease are usually accompanied with increasingly regular behavior. Irregularity and unpredictability are characteristic features associated with a healthy condition, while decreased in complexity and increase in periodicity are factors associated to disease [15-21].

The aforementioned changes are usually not detectable by time domain and frequency domain methods but can be measured with methods derived from complexity analysis [18, 19]. According to this approach, many diseases that alter the autonomic function lead to a loss of physiological complexity and therefore, to larger regularity or periodicity. Comparisons of HRV time-series from patients with diverse pathologies (including those with risk of sudden death or heart failure) have supported these ideas [18]. The sinus rhythm dynamics is typically less complex in these types of patients than in healthy individuals [15-22].

There are many methods to estimate complexity including correlation dimension (CD), Lyapunov exponent, approximate entropy, multiscale entropy, Shannon entropy and Lempel-Ziv complexity [15, 18-22]. The approach of this work is based on dimensional analysis, which allows estimation of the degrees of freedom of a system, i.e. the number of variables that are necessary to describe the system. From this point of view, a system is more complex as more variables are required for its description, and therefore, a higher dimension indicates higher complexity [23]. Several forms to measure dimensionality of a

system have been proposed, such as capacity dimension, information dimension and CD. The latter is frequently used to characterize HRV complexity, although its estimation requires definition of certain parameters for a correct algorithm functioning. Previous research with CD of HRV in healthy persons and pathologies such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis had revealed significant differences of CD when compared by several factors such as day versus night, patients versus healthy controls, and women versus men, in subjects from Poland and Germany [24-26].

The aim of this work was to compare the CD of HRV in adults with and without abnormal ECG. Since decreased complexity in HRV has been observed in many pathologies [18-21], we hypothesize that subjects with an abnormal ECG (regardless of etiology) have decreased HRV complexity, which would be reflected in lower CD values (compared to those with normal ECG).

METHODOLOGY

Participants

The study includes a randomly selected sample of 100 adult academic and administrative workers from a Mexican public University (UABC-Mexicali) in the northwest of the country. All participants filled out a questionnaire and signed an informed consent. The questionnaire collected basic anthropometric information such as age, height and weight. Body mass index (BMI) was estimated as weight/height^2 (Kg/m^2). A 24-hr ambulatory ECG (Holter) and a standard ECG were recorded from each participant.

Equipment characteristics and data processing

A portable Omron Digital Wrist Blood Pressure Monitor (Model HEM-609, Omron Health Care Inc) was used to obtain the

mean of three repeated measures of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mmHg. After 8 hours fasting, blood glucose (mg/dL) was measured with portable One-Touch Ultra equipment (Lifescan, Johnson and Johnson Co.).

The ECG Holters were recorded with a Trillium 3000 system (Forest Medical) using two simultaneous channels with a sample rate of 256 samples per second per channel. Detection of the R-wave of each heartbeat was performed with software provided by the same Holter system. RR intervals, measured in milliseconds (ms) were calculated from consecutive normal (sinus) heartbeats. False RR intervals due to artifacts and RR intervals of ectopic heart beats were eliminated with an adaptive filtering technique [27]. After elimination of 10 records with less than 95% of sinus RR intervals, 90 records were included in the HRV analysis of this study.

The standard ECG of each participant was obtained at rest with an electrocardiograph Cardiax PC EKG (IMED Co. Ltd.) with a sample rate of 500 samples per second. Each ECG was assessed by two cardiologists. 29 ECGs were classified as abnormal based on several findings: old myocardial infarction ($n = 4$), low voltage in the frontal plane ($n = 3$), nonspecific ST-segment changes ($n = 2$), incomplete bundle branch block ($n = 5$), right bundle branch block ($n = 1$), early repolarization pattern ($n = 3$), sinus bradycardia ($n = 3$), left atrium hypertrophy ($n = 2$), left ventricular hypertrophy ($n = 1$), myocardial ischemia ($n = 2$), short PR interval ($n = 1$), and sinus tachycardia ($n = 2$). The 10 subjects excluded from the study due to insufficient (less than 95%) number of sinus RR intervals corresponded to 3 with abnormal ECG and 7 with normal ECG.

Correlation dimension analysis

CD is associated with the number of independent variables that would be necessary to describe the dynamical system (degrees of freedom). Estimation of correlation dimension from a time-series requires adequate algorithm selection and the definition of several parameters: time delay value (τ), embedding dimension (m) and number of time-series points (heartbeats). Details about parameters selection and other methodological aspects are described elsewhere [26]. The Grassberger-Procaccia algorithm was used in this work [28]. From a vector defined as y_i, $i = 1$, N, N points are embedded in an m-dimensional phase space, in order to obtain,

$$\vec{x}_i \equiv \left(y_i, y_{i+\tau}, y_{i+2\tau}, ..., y_{i+(m-1)\tau} \right) \quad (1)$$

where τ is the time delay, wherein express as number of heartbeats. For each embedding dimension m, a preliminary correlation dimension (CD) can be estimated from the following equation,

$$CD = \lim_{r \to 0} \left[\frac{\log_2(C_m(r))}{\log_2(r)} \right] \quad (2)$$

where $C_m(r)$ is the integral correlation. The integral correlation measures the number of x_j points, which are correlated in a hyper-sphere of radius r around the point x_i.

The integral correlation is defined by,

$$C_m(r) = \lim_{N \to \infty} \frac{1}{N^2} \sum_{i=1}^{N} \sum_{j=1}^{N} \Theta \left(r - ||\vec{x}_i - \vec{x}_j|| \right) \quad (3)$$

where N is the number of points and $\Theta(z)$ is the Heaviside function, that is,

$$\Theta(z) = 0, \quad \text{if } z \leq 0$$
$$\Theta(z) = 1, \quad \text{if } z > 0$$

and $||\vec{x}_i - \vec{x}_j||$ stands for the distance between the attractor pairs of points, which is formed in the phase space. This distance was calculated as the Euclidian norm,

$$||\vec{x}_i - \vec{x}_j|| = \sqrt{\sum_{k=1}^{m} \left(x_{i,k} - x_{j,k} \right)^2} \quad (4)$$

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where m represents the embedding dimension.

When $\log_2(C_m(r))$ is plotted versus $\log_2(r)$, a curve is obtained for each embedding dimension k, for $k = 1, 2, \cdots m$, which in small values of r (equation 2), is a straight line. This region where there is a linear behavior is called the scaling region. The slope of this straight line, determined by the linear regression is the CD for this embedding dimension. The slope is plotted versus the embedding dimension in order to obtain a curve, which tends to constant values for higher values of m (saturation value). This saturation value is the estimated CD of the studied system.

CD estimations were carried out with programs developed in C^{++} and Matlab. The parameter values chosen for the algorithm were: $\tau = 5$ heartbeats, $m = 20$ and $N = 10,000$ heartbeats. In order to test differences between morning, afternoon, and night time, segments of 10,000 consecutive RR intervals were selected starting at 11:00, 17:00 and 2:00 hours for each subject.

Statistical analysis

The statistical analysis was performed with the software NCSS 2007 version 07.1.5 and the software SPSS version 15.0. Normal distribution of CD values was tested with the Kolmogorov-Smirnov test, with Lilliefors correction. Then, homoscedasticity was tested with the Levene test. In all cases normal distribution and homoscedasticity were confirmed. Mean CD values were compared by analysis of variance (ANOVA) with the following independent factors: (i) time period (morning, afternoon or night), (ii) sex (male or female) and (iii) ECG diagnosis (normal or abnormal). Multiple comparisons a posteriori were performed with the Tukey-Kramer test. Demographical characteristics were compared by ANOVA (considering ECG diagnosis and sex as independent factors) or by Fisher's exact test.

RESULTS AND DISCUSSION

Compared by ECG diagnosis (normal or abnormal) and sex (female or male), all demographical characteristics were similar except for a higher proportion of males with abnormal ECG (20 out of 29) than with normal ECG (25 out of 61) (Table 1).

The results of CD analysis are shown in Table 2. Females had larger CD values than males, and participants with abnormal ECG had smaller values than those with normal ECG. There were no significant differences of CD values with respect to the time periods.

Table 1. Demographical characteristics of the study participants*. Results are shown as mean ± standard deviation, or absolute values.

	Normal ECG ($n = 61$)		Abnormal ECG ($n = 29$)	
	Female ($n = 36$)	Male ($n = 25$)	Female ($n = 9$)	Male ($n = 20$)
Age (years)	46.0 ± 7.0	47.0 ± 9.5	41.3 ± 5.1	48.1 ± 11.1
Body mass index (kg/m^2)	22.5 ± 4.5	24.6 ± 3.6	22.7 ± 4.4	23.5 ± 2.9
Glucose (mg/dL)	99.8 ± 17.6	108.5 ± 22.9	103.6 ± 14.9	103.9 ± 21.8
SBP (mmHg)	116.7 ± 16.0	124.0 ± 17.9	115.8 ± 15.3	124.8 ± 26.9
DBP (mmHg)	70.6 ± 12.7	73.3 ± 13.0	69.7 ± 18.5	75.8 ± 19.5

* There was larger proportion of female subjects with normal ECG and male subjects with abnormal ECG ($p < 0.001$, Fisher's exact test), and there were no differences among all other variables ($p > 0.05$, ANOVA with sex and ECG diagnosis defined as independent factors).

Table 2. Correlation dimension estimated from heart rate variability time-series. Results are shown as mean ± standard deviation. Mean CD values were compared by ANOVA (with time period, sex and ECG diagnosis defined as factors) and multiple comparisons a posteriori by Tukey-Kramer tests.

	Normal ECG ($n = 61$)			Abnormal ECG ($n = 29$)		
	Female ($n = 36$)	Male ($n = 25$)	All	Female ($n = 9$)	Male ($n = 20$)	All
Morning	11.20 ± 2.32	10.14 ± 2.82	$10.77 \pm 2.52^{\&}$	11.43 ± 2.67	10.29 ± 2.84	10.64 ± 2.79
Afternoon	10.88 ± 2.36	10.31 ± 2.88	$10.65 \pm 2.57^{\&}$	10.02 ± 2.08	9.18 ± 2.46	9.44 ± 2.34
Night	11.03 ± 1.74	11.40 ± 2.42	$11.18 \pm 2.02^{\&}$	11.06 ± 2.48	10.28 ± 2.03	10.52 ± 2.17
All	$11.04 \pm 2.14^{*}$	10.63 ± 2.71	$10.86 \pm 2.41^{\&}$	$10.84 \pm 2.41^{*}$	9.92 ± 2.44	10.20 ± 2.48

* $p < 0.05$, female *versus* male. $^{\&}$ $p < 0.05$ normal ECG *versus* abnormal ECG.

HRV is an output signal from a complex nonlinear control system (*i.e.*, the cardiovascular system), which has many redundant mechanisms [4]. In healthy humans, HRV displays a highly irregular self-correlated behavior and it can be considered as a complex signal, as it has been documented with several indexes of complexity (*e.g.* Shannon Entropy, Lempel-Ziv complexity, correlation dimension) [26, 29]. In many circumstances, when the cardiovascular system is submitted to stressful stimulus, HRV CD has shown evidence of less complex behavior (*e.g.*, high altitude [30], mental stress [22], and daily life tasks that require voluntarily manage attention [31]. Furthermore, in the presence of chronic pathologies, CD also evidences a decrease in HRV complexity (*e.g.*, diabetes mellitus, hypertension, congestive heart failure and hyperthyroidism) [26, 32, 33].

Herein, adults with abnormal ECG had smaller CD compared to those with normal ECG. The difference was significant, even with the highly heterogeneities of ECG abnormalities between subjects. This is consistent with other studies that show decreased CD associated with specific cardiac conditions, such as aortic stenosis [25] and congestive heart failure [26]. The complex dynamics of the heart rhythm and other systems, which are modulated by the autonomous nervous system, could be interpreted as functional advantages

[4]. Complex systems operate under a wide range of conditions and, therefore, they are adaptable and flexible. These characteristics allow them to deal with demands from a changing environment that can be highly unpredictable. Several analyses with nonlinear HRV indexes had been proposed as clinical indicators of diverse physiological status, from subjects during fetal development [21, 34], normal adults [15, 22, 31], as well as within a large variety of cardiovascular pathologies, such as ventricular fibrillation [19], and sudden cardiac death [18, 35].

Most of the studies report a decrease in HRV complexity associated to specific pathologies or as physiological response to stress [18-21]. Moreover, new evidences of the autonomous nervous system control upon HRV have been documented with these indexes [36, 37].

Our finding of decreased HRV complexity in persons with abnormal ECG suggests that the presence of an ECG abnormality is associated with a decreased adaptability of the mechanisms that regulate heart rate, including the autonomous nervous system (i.e. an abnormal unbalance between sympathetic and parasympathetic nervous system is reflected in abnormal behavior of HRV, usually oriented towards decreased complexity). Elucidation of the clinical impact of decreased complexity in the presence of abnormal ECG requires further

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studies. However, decreased complexity in HRV is associated with lower survival in various pathologies (heart failure, coronary artery disease, cardiac arrhythmia, renal dysfunction, diabetes mellitus and low serum potassium) [32].

The current study found a significantly higher CD in women than men, which is consistent with other study performed in Poland [24]. Regarding the time of day, no difference in CD between morning, afternoon and night was found, which contrast with other two studies which showed circadian CD behavior with lower CD values during morning, increased CD during the afternoon and the highest CD values during night [24, 26]. Nevertheless, the CD values of our study from subjects with normal ECG are within the range of CD values during the night reported on both of these studies [24, 26]. Among the potential explanation of these discrepancies are two factors: (1) the subjects were selected from different geographical zones (it is not known if this factor influence CD) and (2) the comparison criteria are different (previous studies focused on patients with specific cardiac pathologies and clinically healthy individuals while the current study compared subjects non-specific abnormal ECG).

Limitations

There are many known risk factors for cardiac mortality which were not considered in the current study (e.g., smoking, sedentary life style, family history of cardiovascular disease, current cardiovascular disease, pharmacological treatment, previous diagnosis of abnormal ECG and phase of menstrual cycle or menopause). A study with a larger number of participants is needed in order to assess the contribution of these factors to the association between decreased HRV complexity and an abnormal ECG finding. The influence of the unbalanced number of samples per group was not controlled in the design of the study, because

the ECG diagnosis was an outcome and not a selection criterion. However, from the statistical point of view, we consider that is enough the estimation of the statistical significance (*p*-values) with consideration of the degrees of freedom (as part of the ANOVA test). Further research is needed to expand the current assessment of CD and abnormal ECG finding in order to include other methods that estimate complexity (e.g. Shannon entropy and Lempel Ziv complexity).

CONCLUSIONS

Several studies show that when there is an imbalance in the autonomic nervous system (i.e. imbalance between the sympathetic nervous system and the parasympathetic nervous system), an abnormal behavior in HRV is observed. For lower HRV, greater imbalance of the autonomic nervous system is expected. Several specific pathologies have shown to alter HRV behavior. However, our study analyzed HRV (through CD) not aimed towards a specific disease group, but a group of individuals with and without electrocardiographic abnormalities identified in the standard ECG. It was observed that subjects with abnormal ECG had a less complex HRV. The observation of the standard ECG abnormalities associated with a decreased complexity of HRV in adults could help to identify early onset of cardiovascular disease and even early detection of risk of sudden cardiac death.

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