Journal of Medicine and Medical Sciences Vol. 4(2) pp. 79-84, February 2013
Available online http://www.interesjournals.org/JMMS

Full Length Research Paper

Chaotic cardiac law: Developing predictions of clinical application

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Abstract

Cardiac chaotic dynamics have been evaluated from dynamic system theory, fractal geometry, and a power law that deduces all possible discrete chaotic attractors allowing the development of a diagnostic method with clinical application. To confirm the clinical applicability of the diagnostic method based on the exponential law in normal and with different cardiac pathologies cardiac dynamics, heart rates and number of beats per hour from 115 Holters were measured: 15 diagnosed as normal and 100 with different pathologies, in order to build a blind study. Attractors were constructed to calculate fractal dimension through the box-counting method, and their respective occupation spaces were quantified. These values were used to determine the mathematical physical diagnosis based on the power law. Subsequently, the diagnostic concordance respect to the Gold Standard was evaluated by calculating specificity, sensitivity and Kappa coefficient. Normal cases were differentiated from those with various pathologies, obtaining sensitivity and specificity of 100% and Kappa coefficient of 1. The applicability of the methodology for the clinical diagnosis of cardiac dynamics was confirmed. The cardiac chaotic attractors evaluated with an exponential law show a causeless self-organization of cardiac dynamics that allow predicting the clinical diagnosis.

Keywords: Dynamical systems, fractals, chaos, heart rate, diagnosis.

INTRODUCTION

The delay maps are abstract spaces where the path defined by the evolution of a dynamic system is geometrically represented. They allow defining the behavior of the system in geometrical terms, finding two types of attractors: predictable and unpredictable. The last one, known as chaotic attractor, is quantified by fractal geometry (Devaney, 1992; Peitgen *et al.*, 1992). Usually the chaos theory is divided in two types: the first one, known as deterministic chaos, is characterized by the nonlinearity of the system. Since it has no accuracy and it's not able to determine long term predictions, knowledge of the behavior and statistical properties of the paths become relevant (Girón, 2008). The second one, called stochastic chaos, is where the probability of occurrence of an event is tied to a chaotic process, making it impossible to establish if the underlying phenomenon is probable or improbable, so, there is a null duration of the statistical memory (Sánchez et al., 2008; Calabrese, 1999).

The study of cardiac behavior based on dynamic system theory resulted in a new definition of normality

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and disease (Goldberger et al., 2002). Diagnostic methodologies of clinical application recently raised, show a self-organization of the cardiac dynamic system; they start with the distribution of the attractor's occupation probability, evaluate it according to their order of magnitude in the context of non-equally probable entropy, and predict the differences among normality, chronic and acute disease, and the evolution of those states (Rodríguez, 2010a). These studies show that measuring the heart rate variability is not enough to establish diagnostic predictions and that is necessary to implement measures that account for the self-organization of the system. In this line of study, Rodríguez et al. built a new assessment methodology for Holter based on the probability theory applied to a range of occurrences of the heart rate (maximum and minimum) and the number of beats per hour, making a clinical differentiation between normality and disease (Rodríguez et al., 2012a).

The Holter is among the most used noninvasive tests on clinic. This diagnostic aid has been developed in order to obtain more data from the variability of the cardiac function on extended periods, usually 24 to 48 hours. It has been useful in the evaluation of symptomatic and asymptomatic cardiac arrhythmias, cardiac risk and response to treatments, among others (Charria and Sánchez, 2007; Pineda et al., 2002). Based on the Holter's data, the dynamic systems theory and fractal geometry, a new methodology that allows studying the occupation spaces of the attractor in the fractal space of Box Counting has been built. This methodology allows differentiating between normality and chronic with respect to acute disease, and it has been applied to 150 Holters, statistically confirming its clinic applicability (Rodríguez et al., 2011a). Based on this work, Rodríguez recently developed a law of geometric exponential nature with clinic application for the Holter (Rodríguez, 2011b).

The exponential law allows deducting all the discrete cardiac chaotic attractors and the mathematical values associated to the states of normality, disease, and the evolution between them, through the assessment of fractal occupation spaces. This work has been developed in order to assess all the possible cardiac dynamics through the construction of attractors into a delay map, in the Box counting's fractal space. This study found that the occupation spaces' values (Kp) that are greater than 200 correspond to normal Holters, the Holters from acute cases are in the order of tens, and the evolution cases present values among them. Furthermore, by plotting the values of the ratio of occupied spaces (Kp/Kg) to the fractal dimension, an exponential behavior of the variables was found. The occupation values of normality and acute disease evaluated in the context of the exponential law restricted a physical and mathematical space in which all the possible dynamics of evolution were present. This result mathematically demonstrated that the developed simulations include the real behavior of all the possible cardiac dynamics, making the use of all the information about heart rates unnecessary.

The purpose of the present study is to confirm, with 115 adult Holters, the clinical application of the previously (Rodríguez, 2011b) developed methodology based on the exponential law described above and to compare the physical-mathematical results with the conventional diagnostic by applying statistical measurements.

Definitions

Delay Map

Specific type of attractor that represents graphically the dynamics of a system, locating ordered pairs of values of a dynamic variable consecutive in time, in a space of two or more dimensions.

Box-Counting fractal dimension

$$D = \frac{LogN(2^{-(j+1)}) - LogN(2^{-j})}{Log2^{j+1} - Log2^{j}} = Log_2 \frac{N(2^{-(j+1)})}{N(2^{-j})}$$

Where:
D: Fractal Dimension.
N: Number of boxes occupied by the object.
j: Grade of division of grid.

MATERIALS AND METHODS

Based on the previously developed methodology (Rodríguez, 2010a), 115 cardiac dynamics were analyzed using Holters from outpatients and continuous cardiac records of patients in the Coronary Care Unit (CCU), chosen from cardiology service of the Fundación Cardio Infantil. All patients included were older than 20 years. The maximum and minimum heart rates and the total value of beats per hour were taken during the ambulatory electrocardiographic monitoring in 21 hours. 15 Holters with normal dynamics and 100 with different pathologies were analyzed for the study, using a program that generates the sequence of heart rates in the defined range by an algorithm equally probable. The attractor of each dynamic was later built on a delay map in which a two dimensional space for each frequency was printed against one another. Afterwards, the squares occupied by the attractor were measured and its fractal dimension was calculated using the simplified method of Box-Counting, where only two grids are used (one is double the size of the other). Therefore, the respective equation can be rewritten as follows:

$$D = \log_2 \frac{K_p}{K_g}$$

Where K_p the number of is squares in the small grid and K_g is the number of squares in the large grid.

Starting from the Box-Counting equation the terms that evaluate the occupancy of the attractor are cleared and a relationship is deduced from the fractal dimension.

$$K_p = K_g 2^{DF}$$

Where Kp: Spaces occupied by the attractor in the small grid. Kg: Spaces occupied by the attractor in the large grid. DF: Fractal Dimension

Predictions will be conducted in the following equation:

$$K_g = \frac{K_p}{2^{DF}}$$

Based on this equation, the physical-mathematical diagnosis of patients was determined, comparing it with the limit values obtained in the studied methodology[16], where patients that had acute illness were among those with minimum space occupation, being less than 73, while normal individuals revealed the maximum values of space occupation, being greater than 200. The dynamics in evolution between normality and disease were between those values.

Statistical Analysis

The clinical information was unmasked and the obtained mathematical results were compared with the indications and conclusions of the evaluated patient's Holter in order to confirm the numerical values for the limits that the exponential law determines to predict normality and disease in the developed methodology. They were compared with conventional diagnosis in order to confirm their clinical applicability and discrepancies and / or agreements with the conventional method.

Later conventional analysis was taken as Gold-Standard, comparing this result with the mathematical methodology, calculating specificity and sensitivity. These measurements were performed through a binary classification where true positives (TP) are the number of patients diagnosed within the limits of abnormality (including evolution and acute disease) and had the same mathematical values for the diagnosis. False positives (FP) are the number of Holters that behave mathematically as studies within abnormality and whose clinical diagnosis is normal. False negatives (FN) are the number of Holters clinically diagnosed as abnormal but whose mathematical values correspond to normality. Finally, true negatives (TN) are defined as the number of Holters clinically diagnosed as normal and whose mathematical values also correspond to normality.

In order to evaluate the correlation between the physical-mathematical values and the conventional clinical diagnosis, Kappa coefficient was calculated by the following formula:

$$K = \frac{Co - Ca}{To - Ca}$$

Where:

Co: observed number of matches, i.e. number of patients with the same diagnosis according to the new proposed methodology and the Gold Standard.

To: Total number of observations, i.e. all normal and abnormal cases.

Ca: Matches due to chance, which is calculated according to the following formula:

$$Ca = [(f_1 x C_1)/To] + [(f_2 x C_2)/To]$$

Where f1 is the number of patients with mathematical values within normal limits, C1 is the number of patients clinically diagnosed within normality, f2 is the number of patients showing mathematical values associated to abnormality, C2 is the number of patients clinically diagnosed as abnormal and To is the total number of normal and abnormal cases.

The present work follows the established norms on articles 11 and 13 at 008430 of 1993 resolution of Colombia's Health Ministry, due to the methodology is applied to results of non invasive medically prescribed exams of the clinical practice, protecting the integrity and anonymity of participants; in that sense, there was not necessary informed consents.

RESULTS

For the 115 Holters studied, the fractal dimensions of the attractors varied between 1.485 and 1.968. The spaces occupied by the grid Kp varied between 45 and 450, and the ones occupied by the grid Kg ranged between 14 and 123 (Table 1). All patients with studies within the normal range presented Kp occupancy greater than 200, while cases with any pathology had Kp occupancy below this value, confirming the limits for normality and abnormality obtained in the previous work (Rodríguez, 2011 b).

When comparing the physical-mathematical diagnosis established by applying the methodology with the diagnosis established conventionally by an expert cardiologist, and after realizing statistical analysis, a sensitivity and specificity of 1 was found. Positive predictive and negative predictive values were both 1, and the Kappa coefficient found was also 1. This result implies that all the studied dynamics were properly differentiated.

Table 1. Conventional diagnosis and diagnostic mathematical measures found for 20 of the studied Holters.

No.	Age	Kp	Kg	Kp/Kg	DF	Indications and conclusions of the study conventionally evaluated
1	46	450	123	3,659	1,871	Normal
2	35	375	103	3,641	1,864	Normal
3	27	350	99	3,535	1,822	Normal
4	41	327	91	3,593	1,845	Normal
5	39	315	88	3,58	1,84	Normal
6	55	289	80	3,613	1,853	Normal
7	62	248	68	3,647	1,867	Normal
8	53	245	69	3,551	1,828	Normal
9	58	225	62	3,629	1,86	Normal
10	76	150	40	3,75	1,907	Arrhythmia / First-degree AV block, frequent atrial extrasystoles, some of them with AV block, frequent ventricular extrasystoles with duplets and bigeminisms, nonsustained ventricular tachycardia.
11	79	141	45	3,133	1,648	Tachycardia / Complete right bundle branch block, rare supraventricular extrasystoles, 3 uncommon monomorphic ventricular extrasystoles
12	62	128	41	3,122	1,642	Tachycardia / First-degree AV block occurring predominantly at night, rare supraventricular extrasystoles, uncommon ventricular extrasystoles with episodes of duplets.
13	65	113	36	3,139	1,65	Arrhythmia. / Second-degree AV block: Mobitz type II occurring predominantly at night between 1:06 and 1:43, rare supraventricular extrasystoles, very frequent monomorphic ventricular extrasystoles with episodes of bigeminism, slight decrease in heart rate variability.
14	33	93	31	3	1,585	Sinus tachycardia, decrease in heart rate variability.
15	51	90	23	3,913	1,968	Control / Frequent monomorphic ventricular extrasystoles without repetitive phenomena.
16	62	89	29	3,069	1,618	Control / Diagnosis: Non – ST elevation myocardial infarction, KILLIP class I, Ischemic heart disease LVEF 60%, Severe 3-vessel coronary disease
17	59	84	30	2,8	1,485	Control. / Frequent ventricular extrasystoles with bigeminism. Nonsustained ventricular tachycardia. Slight decrease in heart rate variability.
18	62	84	30	2,8	1,485	Decrease in heart rate variability.
19	79	71	21	3,381	1,757	Syncope. / Uncommon atrial extrasystoles. Nonsustained atrial tachycardia. Ventricular extrasystoles of several uncommon morphologies without repetitive phenomena.
20	64	45	14	3,214	1,684	Control / Occasional ventricular extrasystoles of two morphologies. Rare supraventricular extrasystoles.

DISCUSSION

This is the first work in which a clinical confirmation for the diagnostic methodology based on an exponential law is obtained. Differentiation between normality and disease was achieved in 115 cases, including 15 with normal diagnosis and 100 with different pathologies, using the space occupation of the cardiac chaotic attractor in the general space of the Box Counting.

The physical-mathematical methodology designed to evaluate the cardiac dynamic was compared with the conventional diagnosis done by an expert cardiologist, taken as Gold Standard. Values of 100% were obtained for sensibility and specificity, and a Kappa coefficient of 1, corresponding to the largest possible match, was achieved. The method's ability to differentiate between normality and disease in any individual over 20 years, regardless of cardiac pathologies was confirmed, as well as its applicability to clinically detect cardiac alterations. Also, given that it can predict evolution towards disease when the attractor's space occupation diminishes, it can be used as a predictive method to take preventive measures.

It was confirmed that the study based on the analysis of fractal dimensions alone is not diagnostic, as observed with the overlapped values comparing between health and illness. Thus, it has been necessary to create new perspectives through new concepts in cardiology and other areas in order to differentiate between normality and disease. In the Cardiology area, for example, studies with coronary arteries in an experimental model of restenosis allowed the creation of a new physical-mathematical differentiation between normality and restenosis (Rodríguez et al., 2010 b). In the Oncology area, a diagnostic method to quantitatively differentiate normal cells from preneoplasic and neoplasic cells in the cervical squamous epithelium was developed (Rodríguez et al., 2010 c). In these studies, the concept of Intrinsic

Mathematical Harmony (IMH) was applied to fractal dimension measurements in order to objectively establish the relationship between the component parts of arteries and cells. These types of investigations allow setting generalizations of the total possible number of coronary arteries' (Rodríguez et al., 2010 b) and the total number of cervical squamous epithelium cells' prototypes for normality and disease (Rodríguez et al., 2010c).

Although the fractal dimension does not allow establishing the differentiation between normality and disease for the cardiac dynamic, the space occupation by the attractor in the Box Counting Space, where the attractors respond to an exponential law, allows establishing a differential diagnosis for each particular case, regardless of statistical and epidemiological methods. This law allowed deducting all the possible discrete fractal attractors and their occupation spaces and also making predictions based on a physical-mathematical self-organization that defines finite limits in which any dynamic can be found in the general space of Box Counting (Rodríguez, 2011b).

In this paper, the predictions of the previously developed law were confirmed, and the evaluated Holters were found within the limits established in the previous induction. The simulations were performed within physiological and clinical ranges measured, making unnecessary to have all the heart beats in order to obtain cardiac dynamics.

These results confirm the diagnostic capacity of the methodology at a clinical level. The mathematical limits delimited and confirmed in the present study may be useful to program pacemakers as well as to evaluate the clinical efficacy of medications or specific treatments. Later studies based on the established law will allow establishing diagnostic methods in individuals younger than 21 years. In the same way, applications of this work may be very helpful to make precise diagnosis in patients with arrhythmia and useful for the adequate assessment of patients whose poor health must be overlooked from the conventional approach.

Methodologies for clinical diagnosis based on the use of physical and mathematical theories such as dynamic systems have allowed developing diagnosis based on entropy proportions that differentiate normality, chronic and acute disease, as well as evolution between these states. The predictive capacity of this methodology was confirmed when it was applied to the follow-up of patients in the Coronary Care Unit, confirming its clinical applicability and showing its capacity to alert about evolution of the cardiac system to acute states without presenting clinical symptoms (Rodríguez et al., 2011d). This demonstrates the methodology is useful to evaluate the impact of pharmacological or surgical interventions, as well as the implementation of preventive measures (Rodríguez 2011d,e; 2012a).

Physical and mathematical theories applied to other areas of medicine have allowed the development of other diagnostic or predictive methodologies, such as a diagnostic method for fetal monitoring based on Zipf-Mandelbrot's law (Rodríguez, 2006). In the field of public health a predictive method for malaria outbreaks was developed and applied to 820 municipalities in Colombia in periods of three weeks with an accuracy of 99.86% (Rodríguez J, 2010d). In the same way, a predictive methodology for lymphocyte CD4 count based on the complete blood count and set theory has been developed, useful in a clinical setting for HIV seropositive patients' follow-up, making unnecessary the flow cytometry and allowing reducing global costs for this pandemic (Rodríguez et al., 2012b).

Following the line of thought of modern physics, where statistical mechanics predictions (Feynman et al., 1987 a), quantic mechanics (Feynman et al., 1987 b), or chaos theory (Crutchfield et al., 1990), are based on a causeless thought, the law confirmed in this work reveals a causeless physical-mathematical order that underlies the chaotic cardiac dynamic and allows its prediction. This suggests that this law is applicable to any chaotic process, ignoring considerations like the initial conditions and avoiding the problems of unpredictability of chaos theory. From this perspective it is possible to achieve generalizations of all physiological phenomena (Rodríguez et al., 2010 b, c; 2011 b), establishing a physical basis for the study of physiology.

ACKNOWLEDGMENTS

Especially to the Research Fund of Universidad Militar Nueva Granada, for funding the project CIAS-934,from which this paper is a result. Special thanks to the Department of Basic Sciences, the Dean Fernando Cantor, Dr. Jairo Bautista and Dr. Ericsson Coy, Director of the Research Center, for their constant support and collaboration in our investigations. We also thank Dr. Martha Bahamón, Academic Vice- Chancellor, Dr. Jacqueline Blanco, Vice-Chancellor for Research, Dr. Juan Miguel Estrada, Dean of the Faculty of Medicine, Dr. Esperanza Fajardo, Director of the Research Center in Medicine, to the Engineer Mario Castro, and Dr. Henry Acuña, for their constant support to the Insight group researches.

To Dr. Sami Viskin from the Tel Aviv Sourasky Medical Center in Tel Aviv - Israel, for unconditionally supporting our investigations. To the Fundación Cardio Infantil, especially to Dr. Rodolfo Dennis and Dr. Gabriel Salazar for their support to our investigations.

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