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Research Article
Clinical Application of a Cardiac Diagnostic Method Based on Dynamic Systems Theory

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Abstract
Background: A new methodology based on dynamical systems theory has been developed to differentiate normal cardiac dynamic from acute illness by calculating the space occupation of chaotic geometric attractors in the phase space. **Objective:** The purpose of this study was to apply this methodology to confirm its clinical applicability and the relation between the measures and the appearance of arrhythmic electrical storms. **Methodology:** There were analyzed 200 holters. The minimum and maximal heart rate and the number of beats per hour were selected. Then, a simulation for constructing the attractor of each cardiac dynamic in the phase space was made. Fractal dimension and space occupation of the attractors with the two grids were calculated according to the box-counting method and the differentiating parameters of normality and acute disease were applied. Sensibility, specificity and kappa coefficient were calculated for evaluating diagnostic concordance. Fractal dimension for normal holters was between 1,621 and 1,970 and between 1,268 and 1,784 for holters with arrhythmic electrical storm. It was not possible to identify differences between groups with mathematical values of fractal dimension. **Results:** However, space occupation of normal dynamic attractors was always greater than 200 with the 5 beats min^{-1} grid and space occupation of cases with arrhythmia was between 31 and 60, close to space occupation of cases with acute myocardial infarction, which was between 19 and 23. **Conclusion:** This study confirmed the clinical applicability of the methodology. It detects when a cardiac dynamic exhibits a progressive diminution of spatial occupation, which is useful to distinguish the cases with arrhythmic electrical storm from cases with chronic arrhythmias or normal dynamic. These findings could be useful to predict appearance of arrhythmic electrical storms.

Key words: Fractals, nonlinear system, heart rate, arrhythmia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Dynamic systems theory study show that how systems evolve through time by the analysis of their dynamic variables. Systems and their evolutionary states are represented on phase space by geometrical attractors. These ones can be punctual or cyclic if they describe predictable dynamics or chaotic if they describe unpredictable dynamics[1]. Chaotic attractors can only be correctly characterized from fractal geometry. Two types of chaos can be distinguished: Deterministic or not lineal; in which it is unlikely to establish long-term predictions about evolution due to its irregular character[2] and stochastic chaos with an un-deterministic character[3], in which it is not possible to make predictions about its behavior due to the invalid duration of statistical memory in this kind of systems[4].

Recent studies in cardiology have focused on heart rate variability analysis starting from RR interval on electrocardiography through time, showing that it could be a useful measure to establish associations with pathologies as Acute Myocardial Infarction (AMI)[5], arrhythmias[6,7], heart failure[8] and sepsis[9-11]. Although, those studies have certainly obtained notable results, some of them are limited because they are based on methodologies that search causal correlations, establish general statements and make inferences in large populations but cannot consider particular behaviors.

Another difficulty in these approaches on heart dynamics is the regularity and periodicity conception based on classic homeostasis notions[12]. From no-lineal dynamic systems, Goldberger *et al.*[13] have designed new research methodologies, demonstrating that those cardiac behaviors which are characterized by a regular, cyclic and stable pattern are really related to pathological dynamics, in the same way those patterns that exhibit an extremely randomized behavior. Between these two extremes, there is an intermediate range that, from these new conceptions is related to normality or health state. This contradicts conventional homeostatic conceptions. One of the study in this field and from this new perspective used fractal geometry to find reliable mortality predictors using information from RR interval dynamic in patients with ejection fraction lower than 35% after an AMI[14]. This study and others based on similar conceptions have been done; nevertheless other studies are required before the result of those researches can be introduced in the clinical practice[15].

Some scientific approaches based on logical procedures followed in exact sciences, as physics and mathematics have led to generalizations or universalizations, represented in laws, principles and theories, which are applicable to each particular case. A study of Rodriguez[16], achieved a deduction of an exponential chaotic law of the cardiac dynamic on the generalized space of box counting context, getting a differentiation of normal dynamics from others with acute disease or in progress to disease and by mathematical permutations, finding all the normal and abnormal cardiac dynamic prototypes in the universe.

Holter has been an exam of diagnostic utility for its ability to identify fine changes, sudden appearance and short duration of cardiac electrophysiological dynamics. In the same way, it has been useful to assess RR interval variability[17]. In this study, a new methodology for holter assessment was developed[18], on the theoretical basis of dynamic systems and fractal geometry, which allowed to differentiate acute pathological dynamics from chronic pathological and normal, by quantifying space occupation of chaotic attractors for each cardiac dynamic. In this study it was demonstrated that acute pathological dynamic attractors occupied the third part of box counting space compared to normal dynamic attractors. Later, this methodology was applied to 150 holter registers, confirming its clinical application in differentiating normal dynamics from acute pathological ones[19].

This study aimed to apply the previous method[18] of holter assessment, based on dynamic system and fractal geometry, to confirm its clinical applicability and its ability to predict acute pathological dynamics that could be related to the appearance of arrhythmic electrical storms.

MATERIALS AND METHODS

Definitions

Delay map: It is a 2-3 dimension space which is drawn the attractor by ordered pairs of a consecutive variable in time of a dynamic system. Each HR value is plotted as function of the previous value.

Fractal: Corresponds to an irregular object itself.

Fractal dimension: It is the measure that determines an object irregularity. In this study, there was used box counting fractal dimension.

Box counting fractal dimension:

$$D = \frac{\text{Log}N_1(2^{-(K+1)}) - \text{Log}N_2(2^{-K})}{\text{Log}2^{k+1} - \text{Log}2^{k}} = \text{Log}_2 \frac{N_1(2^{-(k+1)})}{N_2(2^{-k})}$$

where, N_1 is the number of squares occupied by the object on partition grille K, N_2 is the number of squares occupied by the object on partition grille K+1, K is the partition grade of the grille 1 and K+1 is the grade of partition of the grille 2 and D is the fractal dimension.

Subjects: There were 200 holters analyzed. Thirty of them had a cardiologist and/or an electrophysiologist diagnosis of normality and 170 records were diagnosed with different pathologies including AMI and arrhythmias, even cases with arrhythmic electrical storm. There were holters included in the study with a minimal record time of 18 h and those from patients over 21 years old.

Mathematical analysis: Maximal and minimal heart rate values and total heart beats were taken every hour. Information was introduced into a program which generated a simulation of the dynamic, beat by beat, on the right range for every hour registration. With these data, there were drawn ordered pairs of heart rate to construct the chaotic attractor of the dynamics. Later, it was calculated fractal dimension by overlapping two grilles, calculating the space occupation of the attractor following the box counting method and using the equation defined previously.

Finally, there were applied differentiation patterns of normality and acute disease found on previous study[18], which indicate that if spaces occupied by the attractor in the first grille are less than 100, this is a case of acute disease and if they are over 200 this is a case of normality or chronic disease.

This study agreed to ethical principles of Helsinki Declaration from World Medical Association and is supported by scientific, technical and administrative standards for health research from Health Ministry of Colombia. According to Resolution 8430 of 1993, this study is classified as minimum risk research because it makes calculations on exams previously prescripted without a direct intervention on patients.

Statistical analysis: For patients diagnosed as normal and with different acute arrhythmias, according to conventional medical analysis, diagnosis established by a clinical expert was taken as Gold-Standard, comparing this result with mathematical methodology by calculating specificity and sensibility.

Statistical analysis consists in a binary classification where True Positives (TP) is the number of patients diagnosed as abnormal by the clinical expert and also by mathematical methodology, False Positives (FP) is the number of holters that mathematically were on limits of abnormality but its clinical diagnosis was normal, False Negatives (FN) is the number of holters clinically diagnosed as normal but with mathematical values that indicated acute arrhythmia and finally True Negatives (TN) defined as the number of holters clinically diagnosed as normal and with mathematical values that also indicate normality.

Kappa coefficient assesses correspondence between physical-mathematical values and clinical conventional diagnosis through this equation:

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

where, Co is number of concordances observed, it means, number of patients with the same diagnosis according to the new methodology proposed and with Gold Standard, To is totality of observations, it means, the totality of normal and acute arrhythmia cases and Ca is concordances attributable to randomness, which are calculated according to the next equation:

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

where, f_1 is the number of patients that present mathematical values on normality limits, f_2 is the number of patients that have mathematical values associated to acute arrhythmia, C_2 is the number of patients clinically diagnosed with acute arrhythmia and C_1 is the number of patients clinically diagnosed as normal.

RESULTS

All fractal dimensions of analyzed holter recordings were between 1,268 and 1,970. Specifically, for those who had a normal diagnostic by conventional medical interpretation, fractal dimensions were between 1,621 and 1,970. Within abnormal recordings, 16 had AMI and 13 had electrical storms. For holters with different arrhythmias, fractal dimensions were between 1,528 and 1,952, with Arrhythmic Electrical Storm (AES) fractal dimensions were between 1,268 y 1,784 and with AMI were between 1,354 y 1,441 (Table 1).

Number of occupied spaces with 5 beats min^{-1} grid (Kp) ranged between 19 and 464; for 10 beats min^{-1} grid (Kg) ranged between 7 and 126 (Fig. 1). Holter recordings classified as normal had a space occupation with Kp-grid between 203 and 464 and with Kg-grid had an occupation between 66 and 126. For patients with different arrhythmias, the occupation spaces with Kp-grid were between 67 and 245, with Kg-grid were between 19 and 69. For patients with AES, occupation

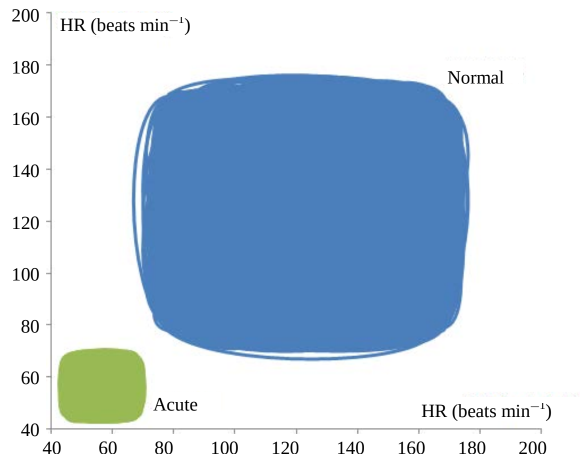

Fig. 1: Examples of attractors, an acute dynamic and normal dynamic, HR: Heart rate

Table 1: Selection of 16 holter recordings

Kp	Kg	FD	Diagnosis
464	126	1,881	Normal
337	86	1,970	Normal
285	74	1,945	Normal
245	66	1,892	Normal
203	66	1,621	Normal
245	65	1,914	Arrhythmia and ventricular and supraventricular ectopia
225	69	1,705	Mildly decreased HR variability
168	53	1,664	Arrhythmia, chest pain, ventricular, supra ventricular ectopia, bigeminy and trigeminy
147	38	1,952	Auricular fibrilation
124	43	1,528	Ventricular extrasystole, trigeminy and decreased HR variability
67	19	1,818	Bradicardy, ventricular and supraventricular ectopia and trigeminy
60	18	1,737	AES, auricular fibrilation/flutter, ventricular extrasystole and supraventricular ectopia
53	22	1,268	AES, ventricular and supraventricular extrasystole, bi and trigeminy
31	9	1,784	AES, ventricular and supraventricular extrasystole, bi and trigeminy and tachycardia
23	9	1,354	AMI
19	7	1,441	AMI

Kp: 5 beats min^{-1} grid, Kg: 10 beats min^{-1} grid, FD: Fractal dimension, holder recording show the maximal and minimum values of spatial occupation in the Kp-grid, of which 5 are normal, 6 have different pathologies including arrhythmias, 3 with Arrhythmic Electrical Storm (AES) and 2 with Acute Myocardial Infarction (AMI)

spaces with Kp-grid were between 31 and 60 and with Kg-grid were between 9 and 22. Patients who had diagnosis of AMI had space occupations with Kp-grid between 19 and 23 and with Kg-grid between 7 and 9 (Table 1).

Fractal dimension values do not allow to differentiate any of the groups, unlike space occupation values, as found in a previous study by Rodriguez *et al.*[18]. The cases with AES (e.g., cases 12-14) and AMI (e.g., cases 15 and 16) had occupation spaces less than 100 with the Kp-grid. For normal cases, it was always observed a space occupation in Kp-grid greater than 200. Reported cases with different arrhythmias had space occupations in Kp-grid that were both in acute disease region and normality region, which may indicate the presence of chronic disease or progression to this condition (Table 1).

Sensitivity and specificity were 100% and kappa coefficient was equal to one, which showed the diagnostic capacity of the mathematic methodology developed and the agreement between conventional and physical-mathematical diagnosis.

DISCUSSION

This is the first study in which a new methodology for evaluating cardiac dynamic through space occupation of attractors in box counting space, is tested in 200 holters. This methodology allows to establish differences between normal and acute sick cases, with a sensitivity and specificity of 100% when compared with diagnostic conclusion established by conventional clinic interpretation. Likewise, it allows to identify cardiac recordings with mathematical results related to a clearly acute dynamic as AMI and AES, through space occupation analysis.

In the case of chronic arrhythmias, the diminution of space occupation in time would identify critical cases, such as AES; this condition until now is a serious, unpredictable, malignant and hemodynamically destabilizing syndrome, which is frequent in patients after an AMI and also in people who are using implantable automatic cardioverter-defibrillators. This syndrome can be involved in the generation of sudden cardiac death[20,21]. However, further studies are required in this particular topic to improve diagnosis.

In a previously study about fractal measures, complexity and their relation to heart rate variability, Perkiomaki *et al.*[22] showed several methodologies for assessing cardiac dynamic. However, it is declare that there is still not enough evidence of the clinical application of these methods. This methodology allows quantifying, in an objective and reproducible way, a particular cardiac dynamic and is especially sensitive to detect when the cardiac system is evolving towards a significant diminution of space occupation resulting in acute critical illness. Also, it could be applied to assess the effect of specific pharmacological and surgical interventions on cardiac dynamic, regardless causal correlation and epidemiological variables such as age, comorbidities and risk factors.

Unlike these methodologies, this study shows, from a causeless perspective, that cases with acute critical disease as AES can be distinguished from normal cases. Nevertheless, the applied methodology does not yet allow differentiating normal cases from the chronic ones, as in previous studies[18,19]. Such limitations have been solved through the development of a diagnostic methodology[23,24] based on probability theory and non-equiprobable entropy proportions of chaotic attractors in the context of non-linear dynamical systems theory.

This methodology is framed in reasoning ways from modern physical theories as chaos theory and[1,25,26], quantum mechanics[27] that do not consider all cause-consequence relations, simplifying the approach to the studied phenomenon.

Generally, it is considered that a retrospective analysis can be limiting because the information collected may not be enough or necessary to do the job, also because the reason why it was collected does not necessarily match the study and there may be gaps. However, in this case, this is a mathematical and objective methodology that does not take into account factors such as the purpose for which the information was taken or others factors; the information required for the work performed is numerical information (maximum and minimum heart rates) which are obtained from an electronic device. In this method, regardless of the purpose for which the information was collected, the same information and results are obtained.

Just like this methodology based on physical and mathematical theories has been useful in cardiology; in other areas of medicine, there have been obtained results of clinical and investigative impact with the application of new conceptions derived from exact sciences. In the area of adult cardiology, from similar conceptions but based on a chaotic exponential law of cardiac dynamics, a methodology which allows to assess the dynamic of different types of arrhythmia was developed, making easier the identification of progressive cases or acute arrhythmias in 115 cardiac dynamics[28,29]. In the area of cellular morphometry, it was developed a diagnostic methodology for cervix cells through the use of fractal and Euclidean geometry[30]. In the area of perinatology, with dynamical systems theory and application of Boltzmann-Gibbs entropy law, it was possible to differentiate normality from disease in fetal monitoring (cardiotocographic recordings), as well as the evolution towards disease, establishing itself as a predictive tool[31]. Also mortality predictions in the Intensive Care Unit (ICU) have been developed through dynamical system and set theories[32], the application of probability and entropy has been useful in molecular biology to predict binding of *Plasmodium falciparum* peptides to HLA class II[33] and in the prediction of malaria outbreaks in Colombia[34]. Finally, in the field of immunology, application of set theory has been useful to predict the value of CD4 cells from leukocyte and total lymphocytes counts of complete blood count[35]. Other methodologies developed for different areas as cellular and arterial morphometry[36-39], allowed objective and reproducible results, useful as diagnostic tools.

CONCLUSION

Normal dynamics differs quantitatively from acute through spatial occupation of chaotic attractors of each dynamic. The methodology is applicable to each particular case, regardless statistical population parameters. The space occupied by the attractors of normal cardiac dynamics is 3-8 times the space occupied by the attractors of acute dynamics, while respect to chronic could become double.

SIGNIFICANT STATEMENTS

The physical and mathematical perspective, used to understand the cardiac dynamic has proved to be a helpful tool in diagnosis for its objective and reproducible results. In this study we apply a methodology, based on this perspective and dynamical systems theory, according to which cardiac dynamics are represented by chaotic attractors. Space occupation of those attractors in the phase space is calculated to differentiate normality from acute illness. The importance of this methodology lies in its ability to establish mathematical parameters that could lead to better and more objective decisions in medicine. Heart disease is the main cause of death in the world. Improving treatments, interventions and diagnosis tools could help to decrease the number of deaths worldwide.

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