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Application of the chaotic power law to the study of cardiac dynamics in patients with arrhythmias

Aplicación de la ley exponencial caótica al estudio de la dinámica cardíaca de pacientes con arritmias

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| Summary |

Background. An exponential law for chaotic cardiac dynamics, found previously, allows the quantification of the differences between normal cardiac dynamics and those with acute diseases, as well as the cardiac dynamics of the evolution between these states.

Objective. To confirm the clinical applicability of the developed methodology through the mathematical law for cardiac dynamics in dynamics with arrhythmias.

Materials and methods. 60 Holter electrocardiograms were analyzed, 10 corresponded to normal subjects, and 50 to subjects with different arrhythmias. For each Holter, an attractor was performed, and its fractal dimension and spatial occupancy were measured. A mathematical evaluation was applied in order to differentiate normal dynamics from pathological ones. Sensitivity, specificity and the Kappa coefficient were calculated.

Results. The mathematical evaluation differentiated occupation spaces, normal dynamics, acute illness dynamics, and evolution between these states. The sensitivity and specificity values were 100%, and the Kappa coefficient was 1.

Conclusions. The clinical applicability of the methodology for cases with arrhythmia was shown. It is also applicable for the detection of changes in dynamics that are not classified clinically as pathological.

Keywords: Fractals; Nonlinear Dynamics; Diagnosis; Arrhythmias, Cardiac; (MeSH).

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Resumen

Antecedentes. Se ha encontrado una ley exponencial para los sistemas dinámicos caóticos cardíacos que logra cuantificar las diferencias entre dinámicas cardíacas normales y aquellas con enfermedad aguda, así como la evolución entre estos estados.

Objetivo. Confirmar la aplicabilidad clínica de la metodología desarrollada a partir de la ley matemática para la dinámica cardiaca en dinámicas con arritmia.

Materiales y métodos. Se analizaron 60 holter, 10 correspondían a sujetos normales y 50 con diferentes tipos de arritmias. Para cada holter se construyó un atractor, se midió su dimensión fractal y ocupación espacial. Se aplicó la evaluación matemática para diferenciar dinámicas cardíacas normales de enfermas y en proceso de evolución. Se calculó la sensibilidad, especificidad y coeficiente Kappa.

Resultados. La evaluación matemática diferenció los espacios de ocupación, normalidad, enfermedad aguda y evolución entre estos estados. Los valores de sensibilidad y especificidad fueron de 100% y el coeficiente Kappa fue de 1.

Conclusiones. Se evidenció la aplicabilidad clínica de la metodología para casos con arritmias, siendo capaz de detectar cambios en la dinámica que no son clasificados como patológicos clínicamente.

Palabras clave: Fractales; Dinámicas no Lineales; Diagnóstico; Arritmias Cardíacas (DeCS).

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Introduction

From the temporary changes of the dynamic variables of a system, it is possible to determine its behavior. Predicting this behavior is the central problem of dynamical systems (1,2). In this theory, dynamical variables that are called attractors are put into graphic representations in the phase space (3). If they are completely irregular, they are chaotic attractors that can be studied with fractal geometry. Fractal geometry studies irregular objects of nature (4-6) rather than regular geometric objects that are studied by Euclidean geometry.

There are several types of fractals. One of them, called the wild fractals, involves the super-positioning of its parts. To calculate its degree of irregularity —the fractal dimension— the box-counting method is generally used (7). This method allows us to observe the spatial distribution of a particular object in different scales through the use of overlapping grids of different sizes.

According to the World Health Organization, cardiovascular diseases (CVD) represent 1.9% of yearly deaths in the Americas. CVDs are known as non-communicable diseases. Among these are included myocardial infarction and stroke. It is estimated that one in four people suffer from this disease category and that, by 2030, approximately 23.6 million people could die from this condition (8). One of the CVDs with the greatest incidence is arrhythmia (9), being associated with 50% of CVD deaths. According to medical literature, they can be divided into three categories: passive arrhythmias, automatic or ectopic arrhythmias, and re-entry arrhythmias (10).

The most important diagnostic test for identifying significant —but of transitory, sudden, asymptomatic presentation— alterations in cardiac rhythm is the Holter test (11). This test allows for the visualization of the RR interval, with which interpretations regarding the variability of the heart rate (12), the appearance of non-mortal post-infarction arrhythmic events (13), and arrhythmias as a means of cardiovascular deterioration in the context of sepsis (14) can be made.

A new interpretation of the concept of normality-disease has developed from the dynamical systems theory. In this new interpretation, an unhealthy dynamic would be either very regular or highly random (15-19) and a normal dynamic would be placed in between these two extremes. From this conception, measurements that seek to obtain better analyses of cardiac dynamics have been developed (20-23). However, it is still debatable which of these methods should be applied and under which conditions (24). In some cases, more than one study may be required to ascertain their applicability (25).

The opportune diagnosis and treatment of arrhythmic cardiac conditions are of much relevance given their association with acute illnesses (26,26). The establishment of a measurement that allows for the quantification of the differences between arrhythmias that evolve into acute illnesses and arrhythmias that do not evolve into acute illnesses could help us to understand what type of intervention would be most appropriate. It could also help to give some patients priority care (28). New methodologies (29,30) have been developed from mathematical laws and theories that have allowed us to make objective quantifications and predictions regarding cardiac dynamics.

An example of this is a methodology for the mathematical evaluation of the Holter test for which a power law (30) for chaotic cardiac dynamics was found. In this study, through the quantification of the occupancy space of attractors generated from the Holter values of the heart rates, normality was differentiated from acute illness and the evolution between these states.

Based on the evaluation method found previously (30), this investigation sought to analyze cardiac dynamics associated with arrhythmias in order to test its evaluation capacity and its clinical applicability and as a diagnostic aid.

Materials and methods

Definitions

Heart rate map delay: a diagram in which each heart rate is plotted as a function of the previous heart rate.

Box-counting of fractal dimensions (D) (7):

Equation 1

$$D = \frac{LogN(2^{-(K+1)}) - LogN(2^{-K})}{Log\,2^{k+1} - Log\,2^{k}} = Log_2 \frac{N(2^{-(k+1)})}{N(2^{-k})}$$

$N(2^{-k})$ is a function of the degree of partitions of the grid k. It corresponds to the number of boxes occupied by the object in the grid with partitions 2^{-k}.

Power law of the chaotic cardiac dynamic: by renaming the values of the function $N(2^{-k})$ as Kp for the grid with the smallest partitions, and Kg for the grid with the biggest partitions, equation 1 takes on the following form (30):

Equation 2

$$D = Log_2 \frac{N(2^{-(k+1)})}{N(2^{-k})} = Log_2 \frac{K_p}{K_g}$$

By solving for *Kp*, an exponential relationship between the occupied spaces and the fractal dimension (D) (30) is obtained:

Equation 3

$$K_p = K_g 2^D$$

Population

A total of 60 Holter electrocardiograms of at least 21 hours were taken. Of these, 10 corresponded to cases diagnosed as normal by an expert cardiologist. The other 50 cases corresponded to cases diagnosed with different types of arrhythmias suffered by individuals with more than 21 years of age. All of the electrocardiograms were taken with the same brand of Holter monitor, and are therefore standardized.

Procedure

The maximum and minimum values of the heart rates, along with the total number of beats per hour, were taken for the analysis of the electrocardiographic records. Later, these values were processed by a previously developed program (30) that generates a sequence of the heart rates obtained through the Holter test by using an equiprobable algorithm. After, the sequences were plotted in the phase space through the use of a delay map (see definitions), making in this way the chaotic attractor of the cardiac dynamics (Figures 1 and 2).

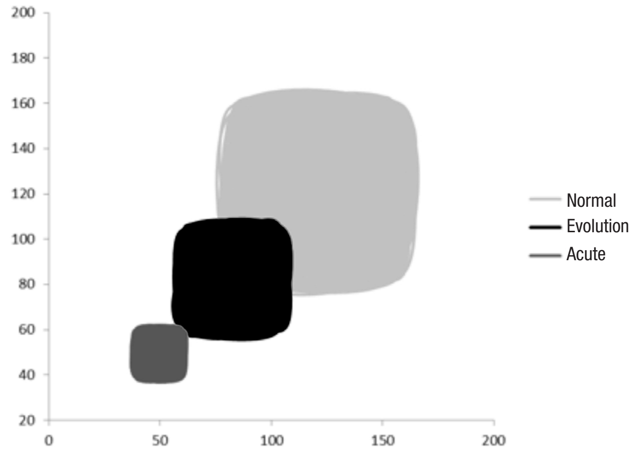

Figure 1. Attractors of the cardiac dynamic.

Note: Examples of normal, chronic, and acute dynamics. The occupancy spaces of these attractors are, for the acute case, Kp=35 and Kg=15, and, for the chronic case, Kp=124 and Kg=36. The example of the normal case corresponds to Holter 10 in Table 1.

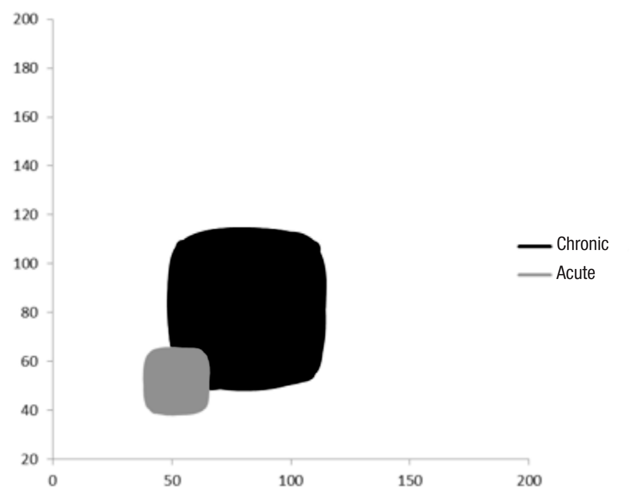

Figure 2. Attractors for two dynamics.

Note: Acute and chronic dynamics with occupancy spaces of Kp=187 and Kg=58, and Kp=41 and Kg=15 respectively. The acute dynamic is of a case of acute myocardial infarction and the chronic case represents an arrhythmia case.

Later, we proceeded to calculate the fractal dimension with the Box-counting method (Equation 1), overlaying two grids in order to quantify the spaces occupied by each attractor. The physical and mathematical evaluation of each of the Holter electrocardiograms was established according to the previously developed methodology (30). In this way, a Holter electrocardiogram is associated with the physical-mathematical characteristics of acute disease when the Kp occupancy spaces of their chaotic attractors are inferior to 73. A physical-mathematical diagnosis of normality will be established when Kp occupancy spaces with values greater than 200 are found. A state of evolution toward disease would be considered when occupancy spaces have a value of between 73 and 200. Later, we looked for consistencies or divergences when we compared the physical-mathematical diagnosis to the conventional diagnosis.

Statistical analysis

The clinical confirmation of the results found upon applying this methodology was compared to the conventional clinical diagnosis, as a gold standard test. These measurements were made with a binary classification, in which true positives (TP) represent cases evaluated conventionally and mathematically as being pathological; false positives (FP) represent cases that were diagnosed conventionally by an expert as being normal, but that mathematically had disease values; false negatives (FN) represent cases that were evaluated mathematically as within the normal limits, but that had a conventional diagnosis of disease; and, lastly, true negatives (TN) represent cases that were diagnosed both mathematically and conventionally as normal. Finally, we proceeded to evaluate the consistency between the conventional and physical-mathematical diagnoses through the Kappa coefficient equation (31):

Equation 4

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

Where *Co* represents the number of consistencies observed, corresponding to the number of patients with the same diagnoses from both the mathematical methodology and the gold standard. *To* represents the totality of cases. *Ca* corresponds to the number of consistencies attributable to chance, calculated through the following equation (31):

Equation 5

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

Where f_1 is equal to the number of cases with mathematical values of normality, C_1 represents the number of cases diagnosed as normal by the clinical expert, f_2 equals the number of cases mathematically evaluated as being of disease, C_2 equals the number of cases diagnosed as having a pathology in the clinical environment, and *To* refers to the total number of cases.

Ethical aspects

This study is declared to be a minimum risk investigation in accordance with Resolution 8430 of 1993 of the Colombian Ministry of Health, since it involves physical and mathematical calculations on exam reports, and non-invasive paraclinical procedures that have been previously prescribed according to conventionally established protocols. The anonymity and integrity of the participants was also protected. The study complied with the ethical principles of the Helsinki Declaration from the World Medical Association.

Results

The values of the fractal dimensions of the attractors corresponding to each cardiac dynamic were between 0.7464 and 1.9875. The spaces occupied by the Kp grid were between 30 and 336, with the Kg values were between 8 and 183. The dynamics that were mathematically evaluated as acute, with spatial occupancy values of between 33 and 68 in Kp grid were 14. Dynamics evaluated as cases that were evolving towards disease amounted to 36, with occupancy values on the Kp grid of between 99 and 197 (Table 1). All Holter cardiograms classified as normal showed Kp occupancy values of more than 200, which corresponds to a mathematical evaluation of normality (Table 1).

Table 1. Age, conventional diagnosis, and measurements of the cases studied.

No.	Age	Conventional diagnosis	VE	SVE	KP	KG	FD	Dx
1	38	Normal.			252	118	1.0946	N
2	29	Normal.	8		324	133	1.2846	N
3	44	Normal.	3	2	324	90	1.8480	N
4	39	Normal.	1		244	69	1.8222	N
5	35	Normal.			307	86	1.8358	N
6	67	Normal.	2		200	62	1.6897	N
7	35	Normal.	1		301	133	1.1783	N
8	44	Normal.		4	307	183	0.7464	N
9	45	Normal.		1	252	89	1.5015	N

10	32	Normal.		2	336	96	1.8074	N
11	71	Atrial fibrillation with high average ventricular response.	143	309	154	42	1.8745	E
12	38	Dilated ischemic cardiomyopathy.		195	137	72	0.9281	E
13	76	Ischemic cardiopathy.	814	48	65	28	1.2150	A
14	43	Primary dilated cardiomyopathy.	55		101	45	1.1664	E
15	83	Acute heart failure.			36	11	1.7105	A
16	30	Tachyarrhythmia – Systolic murmur.	62	143	151	49	1.6237	E
17	27	Arrhythmia, HR variability is slightly reduced. Study within normality.	719		119	62	0.9406	E
18		Acute myocardial infarction.		2	41	13	1.6571	A
19	56	Dilated ischemic cardiomyopathy. Dilated cardiopathy.	24	1602	163	69	1.2402	E
20	72	Frequent polymorphic ventricular extrasystole with pairs and short, isolated episodes of bigeminy and trigeminy. Episodes of atrial fibrillation with rapid ventricular response.			33	9	1.8745	A
21	51	Tachycardia with a slight tendency toward sinus tachycardia.			135	47	1.5222	E
22	49	Arrhythmia control. The QTC interval is normal. Study: within bounds of normality.	1590	57	142	46	1.6262	E
23		Acute ischemic stroke.			51	16	1.6724	A
24	48	Atrial fibrillation, infrequent monomorphic ventricular extrasystole, infrequent and isolated and occasionally blocked atrial extrasystole, and occasionally blocked.	433		115	29	1.9875	E
25	62	Ischemic dilated cardiomyopathy.			150	46	1.7053	E
26	48	Acute myocardial infarction.			39	12	1.7004	A
27	53	Intermittent left bundle branch block dependent on HR increase.	808		143	45	1.6680	E
28	68	Palpitations, asthenia, arrhythmia, moderate reduction in HR variability.			99	40	1.3074	E
29	54	Atrial fibrillation, heart failure.			43	12	1.8413	A
30	38	Syncope. Study: within bounds of normality		1063	197	54	1.8672	E

Note: VE: Ventricular ectopies, SVE: Supraventricular Ectopy, Kp and Kg: Spaces occupied by the attractor for each of the grids, FD: Fractal dimension. Dx: Mathematical evaluation: N: Normal, E: Evolution, A: Acute.

Sensitivity and specificity values of 100% were found, along with a Kappa coefficient of 1. The methodology differentiates adequately the cases of normality, cases of acute pathologies, and cases that are evolving toward a case of acute arrhythmia. For the Holters that were clinically classified as within normal limits, but that presented alterations in the heart rhythm, the spatial occupancy was between 38 and 65 for the Kg grid, and between 115 and 197 for the *Kp* grid (Table 1). This corresponds to a mathematical assessment of evolution, which shows the capability of the mathematical methodology to evaluate slight changes in the cardiac dynamic that are not taken into account in clinical conclusions.

By comparing the occupancy spaces between normal attractors, in evolution attractors, and acute disease attractors, it was possible to observe the reduction in the size of the attractor in the phase spaces (Figures 1 and 2) as the dynamic evolves toward an acute state. As could be observed in Figures 1 and 2, the attractors corresponding to an acute dynamic occupy less space than those corresponding to chronic or normal dynamics. It can be seen that their heart rates are in a narrower range than the range in which the heart rates of chronic and normal dynamics are found. This could correspond to the difference in spatial occupancy of the different dynamics.

Discussion

This is the first study in which a mathematical law of chaotic cardiac dynamics has been applied to the analysis and assessment of 60 Holter records with normal and arrhythmic dynamics. By quantifying the occupancy spaces to the attractors of the dynamics, objective and reproducible differences between the studied dynamics were found. The quantification of the arrhythmic dynamics also let us observe that the methodology is able to quantitatively evaluate the degree of abnormality in the cardiac dynamic in such a way that the dynamics classified clinically as being within the bounds of normality were evaluated as being in evolution toward disease by the mathematical methodology. This shows the capacity of the methodology for quantifying changes in the dynamic that were omitted by the conventional clinical classification. This makes the methodology a useful diagnostic aid in clinical practice.

In a previous study (30) with the power law of chaotic cardiac dynamics it was possible to deduce all of the possible cardiac attractors by their spatial occupancy values in the box-counting space. In accordance with this spatial distribution, normal cardiac dynamics were differentiated from those related to acute pathological states, while those that were in intermediate values between these first two states corresponded to cases of evolution toward disease or normality.

Fractal geometry has been applied in different fields of medicine to differentiate normality from a disease state (32-35). However, isolated fractal dimensions have proven non-conclusive for achieving this differentiation (36-37). For this reason, different concepts have been developed in search of this differentiation (38,39). In the same way, isolated fractal dimensions have been shown to be insufficient for differentiating normality and disease in cardiac dynamics, something that has been evidenced by the application of the mathematical law (30, 41, 42). In this way, the occupancy spaces of the attractor allow us to establish a differential diagnosis for each particular case, independently of the statistical and epidemiological methodologies that describe population behaviors.

Analyzing physiological dynamics through linear methods, the chaos theory, and fractal analysis has contributed to the development of new methodologies for its study (17-23). From here, important considerations have been made, including a new conception of normality and disease (15), as well as better predictors of mortality and new indexes for quantifying the complexity of the dynamics studied. Nevertheless, it is necessary to perform more studies to ascertain their clinical applicability (24,25).

The methodology was applied to cases with diagnoses of arrhythmia, finding that all possible variants of arrhythmias can be evaluated quantitatively with the methodology. This shows the degree of evolution toward acute disease, meaning that the methodology is also capable of showing slight changes in the cardiac dynamic that are not classified clinically as pathological. The maximum level of consistency (Kappa coefficient) between the physical-mathematical diagnosis and the gold standard was obtained. Furthermore, the sensitivity and specificity was 100%. This shows that the methodology is capable of differentiating normal dynamics from dynamics with arrhythmias objectively and quantitatively.

Today, in clinical practice, methodologies based on statistical and population analyses that relate causes and effects have been applied generally without allow for affirmations about specific cases. This study leans on the method of theoretical physics in which, based on abstractions and inductions about the phenomenon that are observed with physical-mathematical theories and laws, the phenomenon is described to that point at which it is applicable to all cases and to any case in particular. Furthermore, it allows us to evaluate the phenomenon independently of the risk factors or statistical variables.

This methodology, thanks to its simplicity, could be implemented through software attached to the Holter devices or used in the analysis of the Holter data. This would allow for the automatic mathematical evaluation of the data, which would be an aid in daily clinical practice.

In other areas of medicine, generalizations have been obtained that allow for the prediction of a specific phenomenon, like the field of morphometry (38,39), infectology (43), and epidemiology (44). In the field of molecular biology and immunology, a theory was developed that enables the prediction of the phenomena involving the union of peptides to class 2 HLA based on entropy and probability (45). Elsewhere, applications have been found in the field of cardiology (46) for the intensive care unit (47,48).

Conclusions

The mathematical law of chaotic cardiac dynamics applied in this study to normal and arrhythmic dynamics allowed for the quantification in an objective and reproducible way of the occupancy spaces of the attractors. From this quantification, quantitative differences between the dynamics studied could be ascertained.

The application of the mathematical law for the particular study of cases with arrhythmia was able to assess different degrees of abnormality in the cardiac dynamics. This showed the capacity of the methodology to quantify changes in the dynamics that could be perceived in the conventional clinical classification. Thus, this methodology represents a useful tool for aiding diagnosis in clinical practice.

Conflict of interests

None declared by the authors.

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