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Evaluation of cardiac dynamics by a mathematical law in 16 hours: application to 400 cases

Javier Oswaldo Rodríguez Velásquez[1*], Guillermo Orlando Trout Guardiola[2], Signed Esperanza Prieto Bohórquez[1], Ribká Soracipa Muñoz[1], Jairo Javier Jattin Balcázar[1] and Ediltrudis Ramos de la Cruz[3]

[1]Insight Group, Insight Research Group SAS, Calle 53 sur 79 C 13 BL G AP 504, Bogotá, Colombia. [2]Centro de Investigaciones Clínicas del Magdalena, Universidad del Magdalena, Santa Marta, Colombia. [3]Ciencias del Cuidado en Enfermería, Universidad del Magdalena, Santa Marta, Colombia. *Author for correspondence. E-mail: grupoinsight2025@gmail.com

ABSTRACT. To corroborate the clinical application of an exponential mathematical law based on dynamic systems by reducing its evaluation time to 16 hours through a diagnostic concordance study with respect to the clinical conventional diagnosis. A blind study was carried out with 400 cardiac dynamics with continuous electrocardiographic recordings and Holter records, of which 150 correspond to normal patients and 250 to patients with cardiac alterations. For this, chaotic attractors of cardiac dynamics were constructed with which the fractal dimension and its spatial occupation in the generalized Box-Counting space were calculated. For normal cases, occupancy spaces between 85 and 354 were found for the Kp grid and between 45 and 342 for cases with pathologies in 16 hours, differentiating through this parameter from normality of disease. The sensitivity and specificity were 100% and the kappa coefficient was 1 when making the comparison between the diagnosis using the physical-mathematical methodology in 16 hours and the Gold Standard. The results demonstrated that by reducing its evaluation time, the exponential mathematical law diagnosed cardiac dynamics in 16 hours with the same precision as in 21 hours, corroborating its clinical applicability.

Keywords: diagnosis; fractals; chaos law; dynamical systems; Holter.

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Introduction

Multiple works have been developed within the framework of the theory of nonlinear dynamics and fractal geometry. The first dynamic system studied in depth was the solar system (Feynman, Leighton, & Sands, 1987). The theory of dynamic systems studies the state and evolution of systems over time, through the analysis of their variables (Devaney, 1992). The geometric space where these systems are represented is known as phase space, whose geometric figure is the attractor. By means of attractors, the trajectories of the systems and their tendency to evolve over time are described (Peitgen, Jurgens, & Saupe, 1992). Geometric trajectories can be predictable, unpredictable (Mood, Graybill, & Boes, 1974) or chaotic. The chaotic systems are characterized by their unpredictability and highly irregular trajectories, so their quantification is performed through fractal geometry (Mandelbrot, 2000a) and the Box-Counting method (Mandelbrot, 2000b). This theoretical approach has been applied to study cardiovascular disease.

The Pan American Health Organization estimated in its Priorities for Cardiovascular Health in the Americas 2011 report that adults under the age of 70 are more likely to suffer cardiovascular events during the next 10 years (Pan American Health Organization [PAHO], 2011). Given the global and worldwide relevance of cardiovascular diseases, new investigations with increasing numbers of cases have been proposed, in which aspects leading to the understanding of cardiac behavior can be evidenced, through the analysis of the variability of the frequency heart rate (HRV) through changes of the RR interval over time (Wolf, Varigos, Hunt, & Sloman, 1978; Nolan et al., 1998; Bayés, 2012). The results from these investigations are interpreted from the pre-established notions of homeostasis (Goldberger, Rigney, & West, 1990), according to which it is established that the body decreases its ability to maintain a constant heart rate in states of rest, and that the variations in heart rate are greater in cases of disease or aging (Goldberger et al., 1990).

HRV measurements have made it possible to interpret cardiac electrical signals from electrocardiographic devices as it provides indices of autonomic function related to cardiovascular risk (Raj, Roach, Koshman, &

Sheldon, 2004; Soares-Miranda et al., 2014). Although promising, these results need further confirmation given their particular nature. On the other hand, research studies have suggested the application of physical-mathematical concepts and techniques to a number of biomedical problems from new perspectives that include non-linear dynamics or other concepts (Walleczek, 1999; Goldberger, 2001) including the analysis and potential diagnosis of cardiovascular disease based on electrocardiographic data.

The existence of 'hidden information' stored in electrocardiographic devices has been established. However, the characterization and measurement of this information is not precise and does not allow precise distinctions to be made between normal and abnormal cardiac dynamics (Goldberger et al., 2002). New non-reductionist perspectives in the framework of approaches not limited to the physiological notions of homeostasis, show that either highly regular behaviors as well as those with increased randomness represent diseased cardiac systems, while intermediate states between these extremes are associated with normality (Goldberger et al., 2002). This observation led to the proposal of theoretical approaches that could evaluate cardiac dynamics in a more accurate way.

Considering the above, based on the framework of physical-mathematical perspectives, new studies have been developed in order to evaluate cardiac dynamics through the values of heart rate extracted from continuous and ambulatory electrocardiographic records, allowing the establishment of methodologies with diagnostic and predictive character that allow differentiating between normality, disease and intermediate states (Rodríguez, 2011; Rodríguez et al., 2011; Rodríguez et al., 2013a; Rodríguez et al., 2014a; Rodríguez et al., 2015a; Rodríguez et al., 2016). This perspective gave rise to the advent of an exponential mathematical law that evaluates the behavior of the different cardiac dynamics in 21 hours, within the framework of the theory of dynamical systems and fractal geometry (Rodríguez, 2011). In a previous study, it was observed that along the evolution of cardiac dynamics from normal to diseased states, the spatial occupation in the Box-Counting space progressively decreases (Rodríguez et al., 2011). This was generalized in an exponential mathematical law which initially was used to perform diagnoses in 21 hours (Rodríguez, 2011).

Among the clinical applications of this methodology is the evaluation of cardiac dynamics variations in patients diagnosed with cardiac arrhythmias (Rodríguez et al., 2014a; Rodríguez et al., 2015a). The diagnostic capacity of said mathematical law in the specific case of arrhythmias was corroborated in various studies with different numbers of patients, establishing quantitative differences in the different degrees of exacerbation, and detecting abnormal cardiac dynamics under diagnosed using conventional clinical parameters, which were categorized as dynamics in evolution towards pathological states through mathematical methodology (Rodríguez et al., 2015a).

Considering the above, this work aims to evaluate cardiac dynamics for 16 hours in 400 Holter records based on the mathematical law developed within the framework of the theory of dynamical systems and fractal geometry, with the subsequent evaluation of its diagnostic capacity in the context of a decrease in its evaluation time.

Materials and methods

Definitions

Delay map: Corresponds to the abstract geometric space composed of two or more dimensions, whose ordered pairs of values corresponding to a consecutive dynamic variable in time generates an attractor.

Box-Counting method: Mathematical calculation that allows finding the fractal dimension, with which the degree of irregularity of an object is established, in this case the attractor, carried out by means of the following Equation 1:

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

Where D corresponds to the fractal dimension, N is the number of squares occupied by the object and K represents the degree of partition of the grid.

Equation 1 was simplified, leaving it in terms of two grids called Kp (small squares) and Kg (large squares) as seen below (Equation 2):

$$D = Log_2 \frac{K_p}{K_g} \quad (2)$$

Exponential mathematical law: By clearing Equation 2 to leave it in terms of Kg, the mathematical law is established with which the evaluation of cardiac attractors is carried out in 21 and 16 hours (Equation 3):

$$\Rightarrow K_p = K_g 2^D \ \Rightarrow K_g = \frac{K_p}{2^D} \quad (3)$$

Where D is fractal dimension.

Population

400 continuous and outpatient electrocardiographic Holter records were taken, considering their availability from a database previously compiled by Insight Group from previous research developed between 2019 and 2020. This database consisted of data related regarding the hourly minimum and maximal heart rates as well as the number of heartbeats. These Holter records were at least 21-hour long and were taken from patients over 21 years who had an indication of the cardiac Holter monitoring. The diagnosis of the Holter registries was performed by an expert cardiologist according to the analysis of the correlation between symptoms and electrocardiographic alterations regarding heart rhythm as well as the analysis of morphological alterations of the electrocardiographic waves and HRV alterations. The 400 registries were divided into two groups: 150 corresponded to normal subjects and 250 to patients with acute cardiac pathologies. Given that this research aimed to diagnose abnormal and normal cardiac dynamics, a convenience sampling was developed to choose the cases.

Procedure

Initially, the clinical diagnoses established by the clinical expert were masked. For each continuous and ambulatory electrocardiographic recording, the values of the minimum and maximum heart rate and the total number of beats per hour in 21 hours were taken. Then, from this same record, the values of the minimum and maximum heart rate were taken, and the total number of beats in each hour for 16 hours.

The heart rate values were entered into a previously developed program capable of generating a sequence of heart rates using an equiprobable algorithm with the values obtained for both continuous electrocardiographic recordings and Holter registries (Rodríguez, 2011).

Then, the sequences of heart rate values were plotted on a delay map, with which the chaotic attractor was generated for each of the cardiac dynamics at 16 and 21 hours.

Next, the Box-Counting method (Equation 1) was applied to calculate the fractal dimension of the chaotic attractors through the superposition of two grids: one of 5 heartbeats/ minute (Kp) and 10 heartbeats/minute (Kg), then, the spaces occupied by each attractor in each of the grids were determined. To establish the physical-mathematical diagnosis, Equation 3 was used, and the previously established limits of normality and disease (Rodríguez, 2011) were used, according to which cardiac dynamics with occupation spaces in Kp greater than 200 are categorized as normal, cardiac dynamics with occupancy spaces with values lower than 73 are categorized as with acute disease, while the evolution between states is in the interval between 74 and 199 (Rodríguez, 2011). With these data from the mathematical diagnoses at 16 and 21 hours, a comparison was made with the Gold Standard.

Statistical analysis

Concordances were sought by establishing a comparison between the physical-mathematical diagnosis at 16 and 21 hours and the traditional diagnosis, established according to conventional parameters and taken as the Gold Standard in the context of a blind study; for which, the clinical information from the electrocardiographic records was unmasked, in order to evaluate the methodology with cases of acute disease and normality. Previously, the concordance between the mathematical diagnosis at 16 and 21 hours was evaluated.

Measures were established based on a binary classification, in which the true positives correspond to the cases evaluated both conventionally and mathematically as acute; the false positives correspond to the cases that were diagnosed by the clinical expert as normal, however they exhibited mathematical values compatible with exacerbation; the false negatives correspond to the cases mathematically evaluated as normal but that presented a diagnosis according to conventional parameters compatible with exacerbation; finally, the true negatives were the cases diagnosed both conventionally and mathematically as abnormal. With the above data, the sensitivity and specificity were established.

Finally, we proceeded to evaluate the concordance between the conventional clinical diagnosis and the physical-mathematical methodology using equation 4 of the kappa coefficient (Equation 4):

$$K = \frac{Co - Ca}{To - Ca} \quad (4)$$

Where, Co corresponds to the number of observed concordances, that is, the number of patients with the same diagnosis from the mathematical methodology and the conventional clinical diagnosis, to represents the total number of cases; Ca represents the number of matches attributed to chance that are calculated using Equation 5:

$$Ca = [\left(f_1 x C_1 \frac{)}{To}\right] + [\left(f_2 x C_2 \frac{)}{To}\right] \quad (5)$$

Where f1 corresponds to the number of cases with mathematical normality values; C1 corresponds to the number of cases diagnosed as normal by the clinical expert; f2 corresponds to the number of cases mathematically evaluated as abnormal and C2 represents the number of cases diagnosed as abnormal from conventional clinical parameters; To corresponds to the total number of cases.

Ethical aspects

This study is an investigation with minimal risk, which adheres to the parameters established in resolution 8430 of 1993 of the Ministry of Health of Colombia, since calculations are made based on reports of clinical examinations and diagnostics tests previously prescribed according to conventional medical protocols. It also adheres to the ethical principles enshrined in the Helsinki declaration of the World Medical Association.

Results

The clinical diagnosis of the electrocardiographic recordings can be seen in Table 1. It was found that in the case of the cardiac dynamics evaluated in 21 hours, the fractal dimensions of the cardiac attractors with normal dynamics were found between 0.8048 and 1.9808, while the fractal dimensions of the pathological dynamics were found between 0.9217 and 1.9398. In the case of dynamics evaluated in 16 hours, the fractal dimensions of the normal dynamics were found between 0.8119 and 1.9530, and the fractal dimensions of the pathological dynamics were found between 0.8853 and 1.9923. The values found confirm previously evidenced findings, which indicate that the fractal dimension does not establish distinctions between the different cardiac dynamics, neither for 16 nor for 21 hours. The concordance between the diagnoses established by the mathematical methodology in 16 and 21 hours was confirmed, for all the cases.

Table 1. Information corresponding to the clinical diagnosis of some of the Holter and continuous electrocardiographic records of the present investigation.

Holter No.	Clinical diagnosis
1	Normal
2	Normal
3	Normal
4	Normal
5	Primum CIA
6	Normal
7	Possible dysfunction of the sinus node and with episodes of sustained bradycardia, frequent VE of at least two morphologies with duplets
8	AVNRT
9	MCHO
10	Arrhythmia analysis
11	Arrhythmia analysis
12	Supraventricular and ventricular extrasystoles
13	Normal
14	First degree AV block
15	Syncope, sinus tachycardia
16	Normal
17	Supraventricular tachycardia, dizziness
18	Arrhythmia; intermittent left bundle branch block dependent on heart rate increases
19	Arrhythmia
20	Normal
21	Difficulty breathing, SVT

22	Arrhythmia control
23	Normal
24	Supraventricular Tachycardia, Sinus Rhythm. Decreased RR variability
25	Normal
26	Normal
27	Acute heart failure
28	Normal
29	Normal
30	Post-infarction angina

The cardiac dynamics without alterations, evaluated in 21 hours in the Kp grid, exhibited occupation spaces between 90 and 355, while in the abnormal ones, said occupation spaces were found between 40 and 339. The dynamics without alterations evaluated in 16 hours in the grid Kp exhibited occupancy spaces between 85 and 354, while abnormal values for this parameter were between 45 and 342 (see Table 2).

Table 2. Occupation spaces of the cardiac attractors at 16 and 21 hours of the electrocardiographic recordings in Table 1. Kp, corresponds to the values of the grid of small squares and Kg to the values of the grid of large squares. D is the fractal dimension.

	21 hours			16 hours		
No.	Kp	Kg	D	Kp	Kg	D
1	236	62	1.92844674	238	64	1.89481776
2	332	151	1.13663469	332	153	1.11765159
3	246	71	1.79276739	244	69	1.82221288
4	269	142	0.92171524	266	144	0.88535743
5	188	49	1.93987901	187	47	1.99230561
6	310	86	1.84985965	309	87	1.82851953
7	128	64	1	129	65	0.98885944
8	168	49	1.77760758	166	48	1.79007693
9	157	45	1.80276765	155	47	1.72153555
10	155	56	1.46876948	151	56	1.43104982
11	143	75	0.93105265	147	75	0.97085365
12	170	45	1.91753784	168	46	1.86875547
13	355	147	1.27200287	350	148	1.24175775
14	150	38	1.98089118	151	39	1.95300252
15	194	51	1.9274875	194	51	1.9274875
16	259	134	0.9507191	263	136	0.95145615
17	147	58	1.34169135	152	59	1.36528446
18	145	83	0.80486966	146	81	0.84997456
19	157	89	0.81888732	158	90	0.81192765
20	308	148	1.05733318	312	150	1.05658353
21	155	68	1.18866156	156	69	1.17687776
22	90	30	1.5849625	85	29	1.55140994
23	247	91	1.44057259	246	93	1.40335569
24	158	50	1.65992456	157	51	1.62219541
25	339	116	1.54716047	342	116	1.55987152
26	245	76	1.68871043	242	78	1.63346102
27	49	23	1.09114789	52	21	1.3081223
28	316	126	1.32650082	312	128	1.28540222
29	346	92	1.91106627	354	97	1.867692708
30	40	11	1.86249648	45	15	1.584962501

Regarding the occupation spaces of the Kg grid in 21 hours, it was evidenced that the normal dynamics had values between 30 and 148, while the abnormal ones had values between 11 and 151. The occupation spaces of the dynamics without alterations in the Kg grid in 16 hours presented values between 29 and 150, while in cases of abnormal dynamics these values were found between 15 and 153 (see Table 2). Thus, the mathematical diagnoses of the cardiac dynamics in 16 and 21 hours for all cases coincided.

In Figure 1 the attractors of two dynamics are shown, one normal and the other acute; The difference in size between the two attractors can be observed, thus confirming the results obtained, where the reduction in spatial occupation is indicative of a tendency towards exacerbation.

The sensitivity and specificity values of the order of 100%, and the Kappa coefficient equal to 1 are the results of applying the statistical analysis to the results obtained from the physical-mathematical methodology.

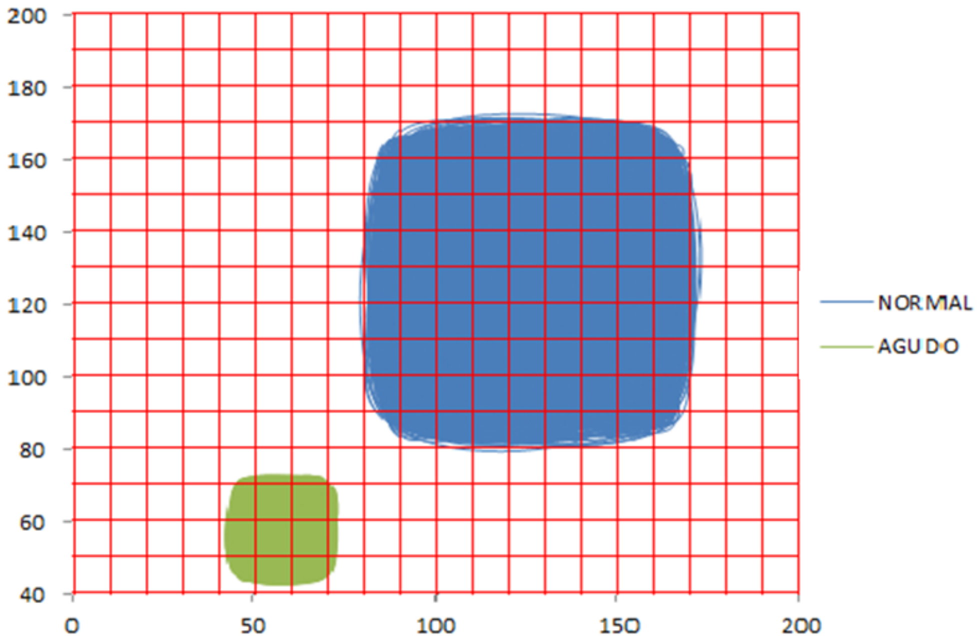

Figure 1. Attractors for two dynamics with the Kg grid superimposed.

The occupation of the attractors was Kp = 354 and Kg = 97, and Kp = 45 and Kg = 15, respectively (Cases No. 29 and 30 of Table 1).

Discussion

This is the first work in which, by quantifying the spatial occupation of cardiac chaotic attractors evaluated within the framework of a mathematical law, the evaluation time is reduced from 21 to 16 hours, with 400 electrocardiographic recordings. It was observed that independent of the heart rate recording system, either through ambulatory or continuous recordings, a quantitative evaluation of normal, acute, and evolving dynamics towards disease can be performed in 16 hours, serving as a clinical diagnostic tool for establish in a timely manner the clinical status of the patient regardless of population and statistical parameters.

The mathematical orders for the different cardiac dynamics, established by the previously developed law (Rodríguez, 2011), showed that without taking into account the considerations regarding the circadian cycle, it is possible to make quantitative distinctions between normal and pathological cardiac dynamics. The present study showed the reproducibility and clinical applicability of the methodology, as well as its ability to establish clear differences between normal and acute dynamics, finding sensitivity and specificity values of the order of 100% and a kappa coefficient with a value of 1 when compared against to the Gold Standard.

It is also worth noting that this methodology was developed based on the framework of the dynamic systems theory which has made it possible to evaluate cardiac dynamics objectively, showing its reproducibility and clinical applicability in previous studies (Rodríguez et al., 2011). Its diagnostic capacity was also confirmed in a study developed to characterize the behavior of cardiac dynamics in patients of the Intensive Care Unit in 16 hours, allowing an evaluation of the cardiac dynamics of these patients in less time independent of their clinical condition (Rodríguez, 2015).

Multiple methods of evaluation of the different physiological signals have been established including cardiac dynamics. Due to its implications, this is one of the areas of greatest interest of research (Walleczek, 1999; Goldberger, 2001; Soares-Miranda et al., 2014). For example, it has been shown that patients with cancer that exhibit higher vagal activity might predict longer survival (Zhou et al., 2016) and that greater components of HRV can be potentially associated with lower lifetime of cardiovascular disease risk (Kubota,Chen, Whitsel, & Folsom, 2017). On the contrary, it has been suggested that lower HRV values could be associated with a higher risk of all-cause death and cardiovascular events (Fang, Wu, & Tsai, 2019). Similarly, it has been described that some HRV parameters are reduced in nonsurviving septic patients in short-term recording (Castilho, Ribeiro, Nobre, Barros, & Sousa, 2018). However, these results should be analyzed with caution considering the heterogeneity between included studies and that major methodological impairments have been detected regarding some components of the HRV analysis (Shaffer & Ginsberg, 2017).

Considering these multiple limitations that have been evidenced the establishment of applicable limits of clinical diagnosis, specifically due to the absence of an algorithm that allows establishing clear differences between normality and disease, HRV analysis might not be yet applicable to any particular case of the universe (Goldberger et al., 2002). On the contrary to the traditional and HRV approaches, the methodology applied on this research established a mathematical law that allows evaluating cardiac dynamics in both 21 and 16 hours of any case independent of causal considerations, taking into account the maximum and minimum values of the heart rate each hour and the number of heartbeats/hour.

Further, this methodology is based on the way of proceeding of theoretical physics, according to which, by means of abstractions and inductions of a certain phenomenon observed in the light of physical-mathematical theories or laws, phenomena can be described in a general way. The generalizations obtained through this method allow its application to particular cases outside of statistical analysis. From this perspective, other diagnoses of cardiac dynamics in adult patients have been developed, including a method based on the proportions of the entropy of the attractors, according to which it is possible to differentiate normality, acute and chronic disease, and evolution between states (Rodríguez et al., 2013a; Rodríguez et al., 2015b). In the same way, a diagnostic methodology of cardiac dynamics applied to the ICU was created, based on the Zipf/Mandelbrot law (Rodríguez et al., 2015c). Likewise, a method based on probability theory has made mathematical distinctions between different cardiac dynamics, even in patients with pacemakers (Rodríguez et al., 2012) or with an established diagnosis of arrhythmia (Rodríguez et al., 2015d).

This physical-mathematical perspective has allowed the establishment of solutions in various fields of medicine. Recently, a methodology capable of predicting mortality in ICU was created based on dynamic systems and set theory (Rodríguez, 2015). Neonatal cardiac dynamics have also been evaluated in patients with sepsis (Rodríguez et al., 2014b). In other areas of medicine, predictions have been established, such as in the area of arterial and cellular morphometry (Rodríguez et al., 2010; Prieto, Rodríguez, Correa, & Soracipa, 2014; Velásquez et al., 2015), in hematology from the simulation of erythrocyte structures (Correa et al., 2012), in infectiology in the prediction of lymphocytes TCD4 based on the theory of sets (Rodríguez et al., 2013b), in the prediction of epidemics of relevance in public health (Rodríguez & Correa, 2009; Rodríguez, 2010), in immunology (Rodríguez, 2013c), among others.

Conclusion

The usefulness of a mathematical methodology based on an exponential chaotic law was demonstrated to diagnose cardiac dynamics independent of clinical and statistical criteria with sensitivity and specificity of 100%.

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