Journal of Medicine and Medical Sciences Vol. 4(9) pp. 370-381, September 2013
DOI: http:/dx.doi.org/10.14303/jmms.2013.080
Available online http://www.interesjournals.org/JMMS

Full Length Research Paper

Mathematical-physical prediction of cardiac dynamics using the proportional entropy of dynamic systems

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ABSTRACT

Heart dynamic characterized within the context of dynamical systems theory allows differentiating and predicting normal cardiac states, different levels of disease, as well as evolution towards disease. The purpose of this study is to apply a previously developed methodology to 450 electrocardiographic registers to establish its effectiveness and comparing it with clinical conventional diagnosis. The methodology was applied to 50 normal Holters and 400 Holters with different pathologies. After masking the diagnostic conclusions, the minimum and maximum heart rate and the total number of beats each hour were used to construct an attractor for each Holter in a phase space, by means of which the probability, entropy and their proportions were evaluated in ordered pairs of heart rate. Measures were compared with the physical and mathematical parameters of normality and disease previously settled down. Diagnostic conclusions and dates from medical history of each Holter were unmasked, to calculate sensibility, specificity and coefficient Kappa respect to Gold-standard. This methodology allowed mathematically differentiating the normal, acute and chronic disease dynamics and the evolution among these states. Sensibility and specificity of 100% were obtained and Kappa coefficient was equal to 1, demonstrating its diagnostic utility.

Keywords: Chaotic attractor, Holter, phase space, entropy, probability, cardiac dynamics.

INTRODUCTION

Holter is an ambulatory electrocardiographic test that monitors the heart for 24-48 hours allowing to detect short duration and transient alterations on the electrical cardiac dynamics. The frequent use of Holter is due to its utility for detecting arrhythmias, ischemia, among others, and for evaluating heart rate variability through changes of RR intervals, being frequently used to assess response to treatments (Palma et al., 2000).

Dynamical systems theory represents the dynamical variables of a system in a phase space and its evolution through different kinds of attractors: periodic, punctual or chaotic (Peitgen, 1992). The first two represent predictable dynamics, while the third represents unpredictable dynamics. In the case of chaos theory, there are two types of states: deterministic and stochastic. The first is characterized for being a nonlinear system with loss of accuracy and failure to clarify the long-term behavior, although it is sometimes possible to find statistical regularities (Giron, 2008). Instead, the main characteristic of stochastic chaos is given by a null duration of the statistical memory (Sanchez et al., 2008), for example, the probability is subject to chaotic processes so it is not possible to determine if the underlying phenomenon is likely or unlikely (Calabrese, 1999).

The main feature of cardiac dynamics is its irregular behavior. That's why studies that are developed from physical and mathematical theories claim to predict this phenomenon (Calabrese, 1999; Goldberger et al., 2002; Huikuri et al., 2000; Richman and Moorman, 2000; Myerburg et al., 2001; Ivanov et al., 1999). However, the ability of these methods to predict these phenomena in many cases require further studies in order to be applicable to clinical setting (Perkiömäki et al., 2005; Voss et al., 2009). Instead, diagnostic and predictive methods of cardiac dynamics assessed from Holter have been developed (Rodríguez, 2011b; Rodriguez et al., 2013). Recently, Rodríguez developed a methodology that has proven to be useful in predicting the evolution of cardiac dynamics in the coronary care unit (Rodriguez et al., 2010; Rodriguez, 2011a) and has allowed to differentiate acute, chronic and normal dynamics (Rodríguez, 2010a), from the evaluation of entropy of the occupied spaces probability of ordered pairs of heart rate in the phase space. Statistical comparisons of this method with respect to the Gold Standard has always achieved sensitivity and specificity values of 100%, as well as kappa coefficient of 1 (Rodriguez, 2010a; Rodriguez, 2012a).

The theoretical basis of this methodology is framed in statistical mechanics and the probability theory by its ability to predict the occurrence of a future event in an experiment where each event is content in what is called sample space (Kolmogorov, 1993; Feynman et al., 1998). Carnot was the forerunner of thermodynamics and the first that postulated the concept of entropy. Along the time, entropy has been reformulated (Matveev, 1987) in the context of the gases theory and statistical mechanics and it has recently been reinterpreted within the information theory (Tolman, 1979; Denton, 1990).

The purpose of this investigation is to apply the previously developed methodology for Holter to a greater number of cardiac dynamics, based on entropy proportions (Rodríguez, 2010a) in order to check its predictive power and compared it with conventional clinical diagnosis of Holter.

Definitions

Return Map: type of attractor with two or more dimensions, built in the phase space in which ordered pairs that constitute it are consecutive values in time of a single variable. The Return Map is traditionally performed by the union of the ordered pairs with a continuous line. In this work, following the methodology previously developed (Rodriguez 2010a), we constructed an attractor in which the frequencies of occurrence of each ordered pair for each range of 5 are quantified and located within the attractor (Figures 1, 2 and 3).

Ordered pair of heart rates (*X, Y*): pair of heart rates consecutive in time, represented in the phase space and located in ranges of 5 beats per minute.

Equation 1: Probability of consecutive ordered pairs in range of 5. It represents the quotient between the frequency of the pair (X, Y) occupied in every range and the total of ordered pairs in the whole recording (Feynman et al., 1998; Kolmogorov, 1950).

$$\mathrm{P(X,\ Y)} = \frac{\mathrm{Number\ \ of\ \ ordered\ \ \ pairs\ \ in\ \ X,\ Y}}{\mathrm{Total\ \ of\ \ ordered\ \ \ pairs\ \ in\ the\ \ \ recording}}$$

Where: X and Y are multiples of 5.

Equation 2: Entropy of attractor.Taking into account that the onset of ranges (X, Y) is a non-equiprobable system, the Entropy (S) of an attractor in the phase space is calculated through the sum of the multiplications of the probability found for each range (X, Y) by their respective logarithms:

$$S = k\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times Ln\,P(X,Y)$$

Where: $P(X,Y)$ is the probability for the range (X, Y), ***k*** is Boltzmann constant which value is 1.38x 10^{23}Joules/Kelvin and ***n*** is the total number of frequencies of the recording (Matvéev, 1987; Machta, 1999).

Equation 3: S/k ratio of attractor. It is obtained by taking the equation 2 and dividing it by Boltzmann constant **(*k*):**

$$\frac{S}{k} = \sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times Ln\,P(X,Y)$$

Now, by grouping the terms and taking the ranges (*X*,*Y*) which occurrence frequencies are of unit, tens, hundreds and thousands, the next statement is obtained:

$$\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times Ln\,P(X,Y)$$

$$\Rightarrow \boldsymbol{U} = \sum_{b}\sum_{a} P(a,b)\,x\,Ln\,P(a,b)\text{: (a, b) Units}$$

$$\Rightarrow \boldsymbol{Te} = \sum_{c}\sum_{d} \mathrm{P(c,d)\ x\ Ln\,P(c,d)}\text{: (c, d) Tens}$$

$$\Rightarrow \boldsymbol{H} = \sum_{f}\sum_{e} P(e,f)\,x\,Ln\,P(e,f)\text{: (e, f) Hundreds}$$

$$\Rightarrow \boldsymbol{Th} = \sum_{h}\sum_{g} P(g,h)\,x\,Ln\,P(g,h)\text{: (g, h) Thousands}$$

Equation 4: represents the equation 3 in a synthetic form:

$$\frac{\mathrm{S}}{\mathrm{k}} = \mathrm{U} + \mathrm{Te} + \mathrm{H} + \mathrm{Th} = \mathrm{T}$$

Where: **U** is the sum of probabilities associated to frequencies of the order of units, **Te** is the sum of probabilities associated to frequencies of the order of Tens, **H** is the sum of probabilities associated to frequencies of the order of Hundreds, **Th** is the sum of probabilities associated to frequencies of the order of Thousands, and T is the total sum, which is equal to the S/k ratio.

Equation 5: Entropy proportions. This equation corresponds to proportions between parts and totality of equation 4 and it can be defined as follow:

$$\frac{U}{T},\ \frac{Te}{T},\ \frac{H}{T},\ \frac{Th}{T},\ \frac{H}{Th},\ \ and\ \ \frac{Te}{H}$$

There are defined in three regions: **Region 1**: It contains all the ranges of heart rates that are common to all the normal Holters. **Region 2**: It contains the totality of the occupied ranges by normal Holters, excluding Region 1. **Region 3**: It is the remaining region of the phase space, namely, excluding region 1 and 2.

MATERIALS AND METHODS

450 Holters were analyzed, which had been evaluated from conventional parameters by an expert cardiologist. These Holters were taken from database of previous research realized by Insight Group at the Fundación Cardioinfantil and the Fundación Abood Shiao, where 400 of these were diagnosed as pathological and 50 were considered within normal limits. There were included a wide range of cardiac pathologies, but there is no differentiation between the type or the degree of severity, because the first objective is to determine the capacity of the methodology to differentiate normality and disease. The table 1 shows the clinical diagnosis of 50 of the cases evaluated. The pathological cases of this table were taken at random from the overall sample, so that the fact that there is a greater or lesser number of cases with certain pathology does not mean that there is a greater or lesser number of cases of this disease in the overall sample.

First, the values of maximal and minimum heart rates per hour and the total number of beats per hour were taken for 18 consecutive hours, masking information related with clinical conclusions of Holters. After, with the values of heart rates and the total number of beats per hour of each Holter, a simulation of the totality of dynamic was performed. Then, an attractor was constructed in the phase space, in which occurrence frequency of ordered pairs of heart rates was plotted in ranges of 5 beats/min (see figures 1, 2 and 3). Afterwards, each ordered pair was considered as an event and for each region was evaluated the probability of each event respect to the totality (see equation 1). By this way, the entropy (see equation 2) and the S/k ratio (see equation 3) of each total attractor was evaluated too.

With the results of the S/k relation, the terms associated to the ranges (*X*, *Y*) which probabilities were related with frequencies of occupied spaces in the order of units (from 1 to 9), tens (from 10 to 99), hundreds (from 100 to 999) and thousands (from 1000 to 9999) were grouped and added for each region (see equation 4) (Rodríguez, 2010a). Next, entropy proportions for each region were calculated (see equation 5).

For each Holter, the number of proportions outside normal limits –defined in previous studies - in any of the three regions was quantified (Rodríguez, 2010a). According to the diagnosis developed if the number is two or more the dynamics is abnormal, otherwise it is normal.

With the purpose of quantifying the severity degree of chronic and acute states of each cardiac dynamic, subtractions were performed between the values of proportions that were out of normal limits of the evaluated dynamic and the extreme values of normality. For instance, if the value was greater than normality limit, the superior limit of normality was subtracted of this value, while if the value was less than the inferior normality limit, this value was subtracted from this limit. These subtractions were added so that **Th** grouped the subtractions of proportions related to occurrence frequencies of the order of thousands, **H** grouped the

Figure 1. Numerical attractor corresponding to Holter N7.The region marked in pink corresponds to Region 1, the region marked in green corresponds to Region 2, the white region corresponds to Region 3.

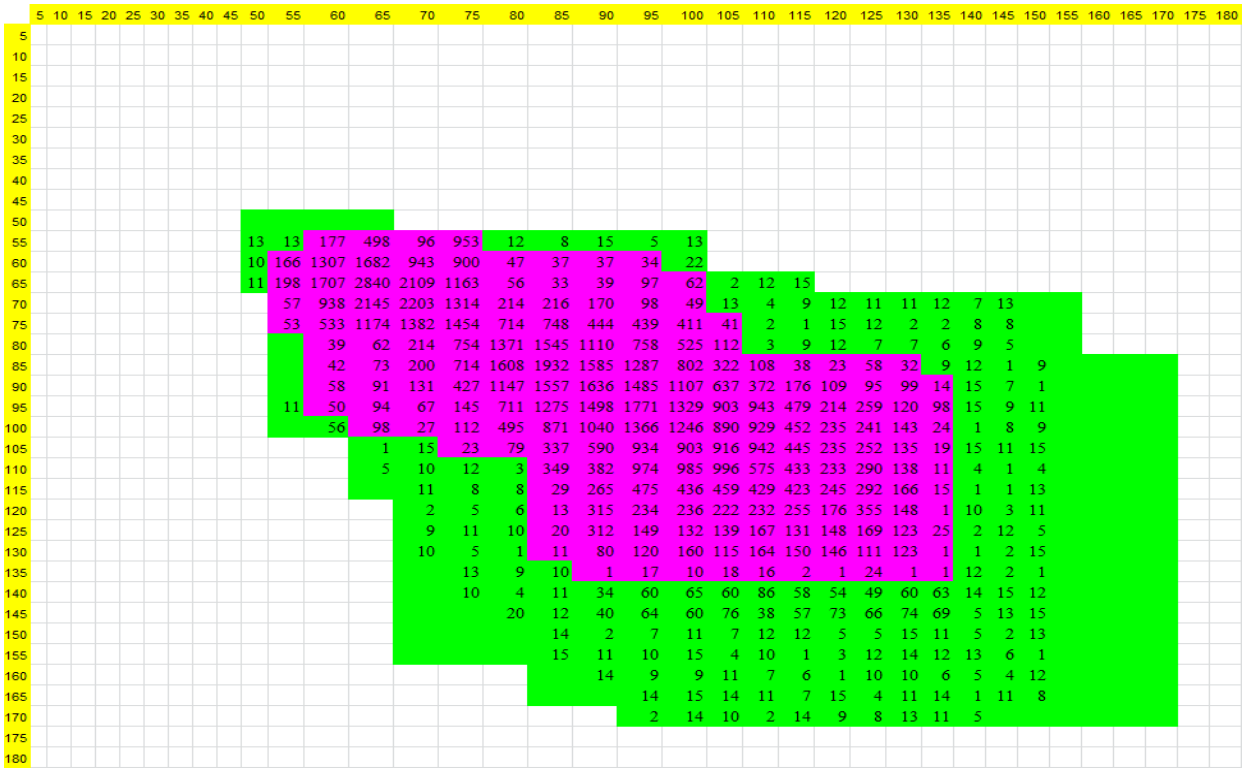
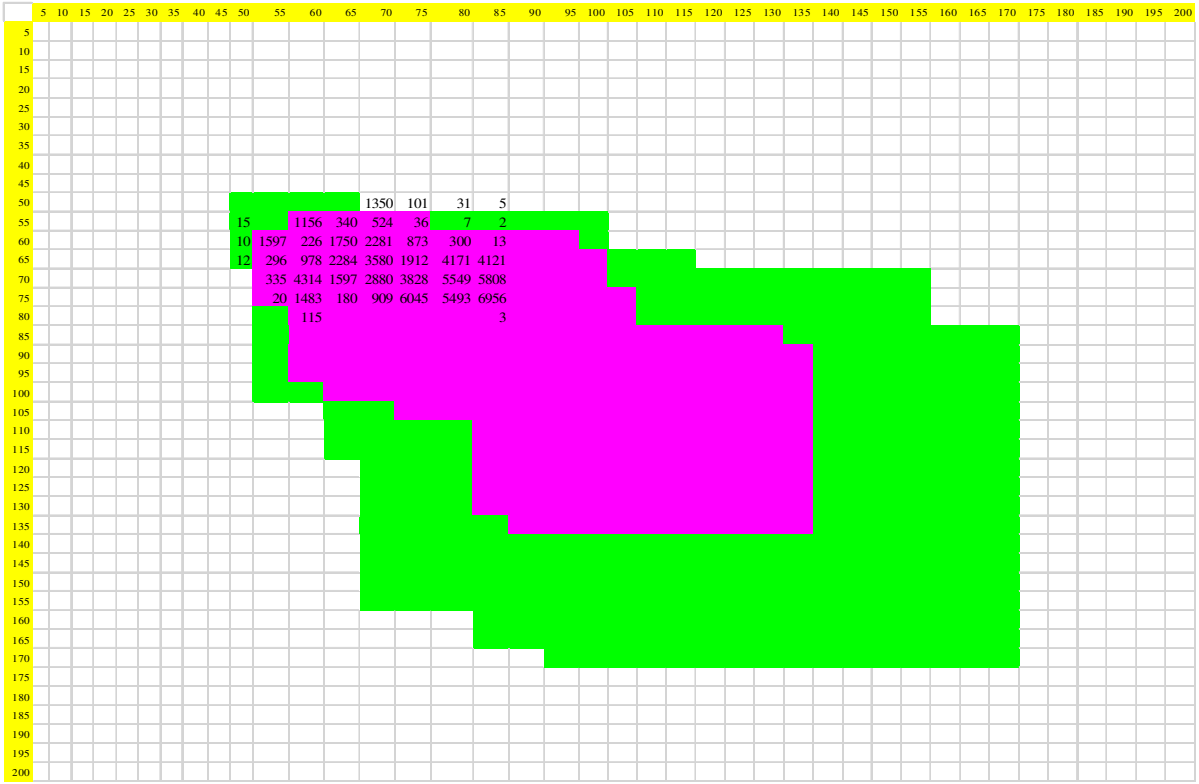


Figure 2. Numerical attractor corresponding to Holter H26 with a diagnostic of Sinus tachycardia (and an inappropriate increase of HR) according to the conventional analysis, and characteristic of a pathological cardiac dynamic in a chronic state.The region marked in pink corresponds to Region 1, the region marked in green corresponds to Region 2, the white region corresponds to Region 3.

Figure 3. Numerical attractor corresponding to Holter H4, with a diagnostic of Acute coronary disease according to the conventional analysis, and characteristic of a pathological cardiac dynamic in acute state.The region marked in pink corresponds to Region 1, the region marked in green corresponds to Region 2, the white region corresponds to Region 3.



hundreds, **Te** grouped the tens and **U** grouped the units (Rodríguez, 2010a). According to the predictions found in the previous work, greater values are associated with more severe levels of disease, starting from the values of Thousands, and following with the values of Hundred, Tens and Units.

The present research was undertaken and it conforms to the provisions of Declaration of Helsinki in 1995, according to World Medical Association. Likewise, it is classified as without risk according resolution 008430 of 1993, of Health Ministry of Colombia, because the applied methodology makes physical calculus from noninvasive test results of clinical practice that have been prescribed, doing the informed consent unnecessary. Privacy, integrity and anonymity of the test were protected, too (Health Ministry of Colombia, 1993).

Statistical Methodology

Conventional diagnosis was unmasked and taken as Gold-standard for comparing it with the mathematical methodology. Specificity and sensibility was calculated through a binary classification where true positives (TP) corresponds to the number of abnormal patients according to both Gold-standard and the mathematical values; false positives (FP) are those that mathematically behave as abnormal but that have been clinically diagnosed as normal; false negatives (FN) are those that have been mathematically diagnosed as normal but which clinical diagnosis corresponds to abnormality, and finally, true negatives (TN) are the number of cardiac recording clinically diagnosed as normal, with mathematical values that corresponds with normality too.

The agreement between physical-mathematical values and conventional clinical diagnosis was calculated with Kappa coefficient through the next equation:

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

Where:**Co** is the number of observed concordances, this is, the number of patients with the same diagnosis according to both the new methodology and with Gold-standard; **To** is the totality of observations, this is, the totality of normal and sick cases; **Ca** is the agreement attributable to chance which is calculated through the next equation:

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

Where $\mathbf{f_1}$ is the number of cases with mathematical values within normality limits; $\mathbf{C_1}$ is the number of patients clinically diagnosed within normality; $\mathbf{f_2}$ is the number of patients with mathematical values associated with abnormality; $\mathbf{C_2}$ is the number of patients clinically diagnosed with any pathology; and **To** is the total number of normal and abnormal cases.

RESULTS

It was found that entropy values varied between 4,255 X 10^{-23} and 7,049 X 10^{-23} for the 450 Holters. For the 10 normal Holters, this value was between 6,497 X 10^{-23} and 7,049 X 10^{-23}. For patients with Holters diagnosed with chronic pathologies, entropy values varied between 5,641 X 10^{-23} and 6,937 X 10^{-23}. For the dynamics with pathologies in acute states, the values of the entropy varied between 4,255 X 10^{-23} and 4,665 X 10^{-23} (see Table 1).

The values of the S/k ratio for the 450 Holter varied between 3,083 and 5,108. For the 50 normal Holters, the values of S/k ratio varied between 4,707 and 5,108. For the patients with chronic pathologies, the values of the S/k ratio varied between 5,6933 and 3,8871; for the dynamics with acute diseases the values of S/k ratio varied between 3,083 and 3,380 (see Table 1).

For normal patients, values of entropy proportions for U/T were between 0 and 0,0135, for D/T were between 0 and 0,1346, for C/T were between 0 and 0,5516, for M/T were between 0 and 0,4487, for C/M were between 0 and 3,4878 and for D/C were between 0 and 3,2834 (See Table 2). All the proportions were inside the normal limits.

For patients with chronic pathologies, the values of entropy proportion U/T were between 0 and 0,0224, for D/T were between 0 and 0,1322, for C/T were between 0 and 0,6660, for M/T were between 0 and 0,6314, for C/M were between 0 and 3,0539 and for D/C were between 0 and 9,6388.

For the dynamics with acute diseases, values of entropy proportions for U/T were between 0 and 0,0031, for D/T were between 0 and 0,0164, for C/T were between 0 and 0,1091, for M/T were between 0 and 0,9016, for C/M were between 0,081 and 0,5600 and for D/C were between 0 and 0,3619.

As the normal dynamics had no entropy proportions outside the normal limits, all the values of the sums of the subtractions of proportions out of normal limits are 0. For the dynamics that corresponds to chronic disease, the sums of the subtractions of proportions out of normal limits related to occurrence frequencies of the order of thousands were between 0 and 0,9978, for hundreds the values varied between 0,0403 and 6,3375, for tens the values oscillated between 0 and 0,0348 and for units the values were between 0 and 0,0256.

For the dynamics with diagnostic of acute disease, the sums of the subtractions of proportions out of normal limits related to occurrence frequencies of the order of thousands were between 1,3197 and 1,8554, for hundreds the values varied between 0,4509 and 3,0865, for tens the values oscillated between 0,0232 and 0,0378 and for units the values were between 0,00006 and 0,0029.

The cardiac dynamics that presented the higher values in the sums of subtractions of the order of thousands, belonged in all the dynamics to patients with acute diseases, while for the chronic dynamics, lower values of thousands were found. This result evidences that the severity of cardiac dynamics is quantified by means of this measure (See Table 1). This fact is also evidenced analyzing the chronic dynamics: the values in the sums of the subtractions of the order of Thousands for the dynamics with chronic disease were lesser than the values of the dynamics with acute diseases, showing values equal to or lesser than 0,9978 in all the dynamics, while the acute dynamics showed always values higher than 1,3197. Besides it was observed that the higher values of the order of Hundreds belong to chronic dynamics, and in all the chronic dynamics this value is higher than the value of Thousands (with the only exception of patient H12). For instance, the Holter H26 (See figure 2) presents values of the order of Thousands equals to zero while the values of the order of Hundreds corresponds to 2,4253. The patient H19, presented a value of 6,3375 of the order of Hundreds, and a value of 0 of the order of Thousands. This fact confirm that the sums of the subtractions of proportions out of normal limits evaluated in order –first the values of Thousands, next the values of Hundreds, etc.- allows to quantify the level of severity of the disease regardless of its etiology.

DISCUSSION

This is the first study which confirms the predictive power of the methodology previously developed in a population of 450 Holters, differentiating physically and mathematically normality from disease in the cardiac dynamics. This methodology developed from calculation of entropy proportions and the analysis of occurrence of dynamic ordered pairs of chaotic attractors in phase space, achieved predicting the evolution towards a worsening of the cardiac system, since it is based on mathematic and geometric order of universal space of chaotic attractors, without requiring individual variables such as age, gender and other variables defined in epidemiological studies. The statistical analysis in this article was done as part of the requirements of the current medical literature.

Table 1. Measures corresponding to 50 of the measured Holter, 10 normal (N) and 40 with different pathologies (H), where the eight first (Holters H1 to H8) correspond to acute diseases, while the remaining 32 (H9 to H40) correspond to chronic pathologies. The Holters of this table were chosen at random from the complete sample of 450 Holter, in order to represent all cases studied, except for the cases that presented the limit values for each measure, which were selected to be included. Sum: corresponds to the sum of subtractions of entropy proportions respect to normality limits, grouped by Units (U), Tens (Te), Hundreds (H) and Thousands (Th). Those are the values that quantify the level of severity of the cardiac dynamic.

Holter	Conventional Diagnosis	Entropy	S/k	Sum			
				U	D	C	M
N1	Normal	7,049E-23	-5,1082	0	0	0	0
N2	Normal	6,497E-23	-4,7076	0	0	0	0
N3	Normal	6,521E-23	-4,7256	0	0	0	0
N4	Normal	6,532E-23	-4,7331	0	0	0	0
N5	Normal	6,526E-23	-4,7292	0	0	0	0
N6	Normal	6,528E-23	-4,7303	0	0	0	0
N7	Normal	6,636E-23	-4,8089	0	0	0	0
N8	Normal	6,531E-23	-4,7325	0	0	0	0
N9	Normal	6,646E-23	-4,8159	0	0	0	0
N10	Normal	6,622E-23	-4,7983	0	0	0	0
H1	Acute myocardial infarction	4,665E-23	-3,3802	0,0003	0,0332	2,8392	1,6092
H2	Acute myocardial infarction	4,562E-23	-3,3061	0,0006	0,0351	2,9781	1,3433
H3	Acute coronary disease	4,569E-23	-3,3112	0,0008	0,0350	2,8313	1,3419
H4	Acute coronary disease	4,640E-23	-3,3620	0,0012	0,0338	2,8508	1,3197
H5	Acutecoronary disease	4,544E-23	-3,2928	0,0029	0,0232	3,0866	1,5086
H6	Acute coronary disease	4,349E-23	-3,1511	0,0012	0,0343	0,4509	1,8554
H7	Acute coronary disease	4,255E-23	-3,0835	0,0002	0,0377	0,7967	1,4135
H8	Acute coronary disease	4,583E-23	-3,3211	0,0001	0,0378	3,0581	1,6591
H9	Palpitations, chest pain	6,398E-23	-4,6359	0,0256	0,0294	2,5654	0,8129
H10	Palpitations	6,787E-23	-4,9182	0,0001	0,0010	2,0362	0
H11	Arrhythmia	6,695E-23	-4,8518	0	0,0246	0,0922	0
H12	Coronary disease	6,004E-23	-4,3508	0	0,0013	0,1986	0,5416
H13	Coronary disease	6,138E-23	-4,4476	0	0	1,5951	0,6638
H14	Syncope	6,109E-23	-4,4270	0	0	2,9360	0,3313
H15	Arrhythmia	6,506E-23	-4,7144	0	0,0037	0,2200	0
H16	Arrhythmia	5,925E-23	-4,2933	0	0,0180	2,1965	0,3843
H17	Arrhythmia	6,442E-23	-4,6681	0,0002	0,0017	0,3994	0,1240
H18	Arrhythmia	6,385E-23	-4,6272	0,0010	0,0104	2,2671	0,4899
H19	Arrhythmia. Atrial ectopy	6,147E-23	-4,4544	0,0011	0,0078	6,3375	0
H20	Tachycardia	6,408E-23	-4,6437	0,0012	0,0006	4,9962	0,1043
H21	Atrial Tachycardia	5,866E-23	-4,2504	0,0006	0,0023	0,6036	0
H22	Tachycardia, decrease of the variability of the HR	6,114E-23	-4,4302	0,0001	0,0137	1,5298	0
H23	Tachycardia and palpitations	6,776E-23	-4,9101	0	0,0188	1,7348	0
H24	Sinus tachycardiain appropriate	5,967E-23	-4,3236	0	0,0182	0,0404	0
H25	Blow systolic, sinus tachycardia	5,641E-23	-4,0876	0	0,0222	2,5373	0,4428
H26	Increased HR inappropriate, sinus tachycardia.	6,937E-23	-5,0268	0	0,0114	2,4253	0
H27	Pacemaker	6,582E-23	-4,7694	0	0,0220	1,0967	0,5783
H28	Pacemaker	6,031E-23	-4,3702	0,0007	0	0,6180	0,5887

Table 1 cont.

H29	Pacemaker	6,730E-23	-4,8766	0	0,0139	1,1064	0,5301
H30	Ventricular and atrial extrasystoles	6,001E-23	-4,3482	0,0008	0,0030	0,8658	0
H31	Atrial flutter	5,774E-23	-4,1837	0	0,0022	2,1983	0,4192
H32	Atrial fibrillation	5,996E-23	-4,3446	0,0004	0,0188	1,5473	0,0319
H33	Atrial fibrillation disorder intraventricular conduction. Atrial frequent extrasystolia	6,206E-23	-4,4967	0,0104	0,0076	0,7240	0
H34	Cardiac Arrhythmia	6,771E-23	-4,9065	0,0010	0,0349	0,9912	0
H35	WPW Syndrome	6,404E-23	-4,6405	0	0,0076	1,1490	0,2438
H36	Cardiac Arrhythmia	6,441E-23	-4,6673	0,0043	0,0230	2,0241	0
H37	Chestpain. Moderate decrease in heart rate variability.	6,117E-23	-4,4323	0,0004	0	0,6625	0,3742
H38	Dizziness, ventricular ectopy with trigeminy	6,254E-23	-4,5316	0	0	1,3507	0
H39	Fatigue	6,135E-23	-4,4460	0	0	0,3923	0,3677
H40	CIA, dizziness, chest pain	6,383E-23	-4,6257	0,0014	0,0330	3,4334	0,9978

Table 2. Entropy proportions (see definitions) of each region for the 50 Holters described in table 1, 10 normal (N) and 40 with different pathologies (H), where the eight first (Holters H1 to H8) correspond to acute diseases, while the remaining 32 (H9 to H40) correspond to chronic pathologies.

Holter	Region 1						Region 2						Region 3					
	U/T	D/T	C/T	M/T	C/M	D/C	U/T	D/T	C/T	M/T	C/M	D/C	U/T	D/T	C/T	M/T	C/M	D/C
N1	0,0002	0,0869	0,5516	0,1582	3,4878	0,1576	0,0083	0,1346	0,0410	0,0192		3,2834	0	0	0	0	0	0
N2	0,0009	0,0399	0,4918	0,4487	1,0961	0,0812	0,0057	0,0130	0	0			0	0	0	0		
N3	0	0,0869	0,4831	0,3141	1,5379	0,1799	0,0077	0,0804	0,0278	0			0	0	0	0		
N4	0	0,0874	0,4838	0,3125	1,5481	0,1806	0,0083	0,0821	0,0259	0			0	0	0	0		
N5	0	0,0888	0,4836	0,3131	1,5445	0,1835	0,0106	0,0762	0,0277	0			0	0	0	0		
N6	0,0002	0,0904	0,4792	0,3127	1,5324	0,1886	0,0083	0,0811	0,0281	0		2,8914	0	0	0	0		
N7	0,0002	0,0395	0,4841	0,4263	1,1356	0,0817	0,0085	0,0413	0	0			0	0	0	0		
N8	0	0,0897	0,4826	0,3116	1,5490	0,1858	0,0081	0,0780	0,0302	0		2,5866	0	0	0	0		
N9	0,0002	0,0396	0,4899	0,4190	1,1693	0,0808	0,0135	0,0379	0	0			0	0	0	0		
N10	0	0,0394	0,4942	0,4230	1,1683	0,0798	0,0084	0,0351	0	0			0	0	0	0		
Holter	**U/T**	**D/T**	**C/T**	**M/T**	**C/M**	**D/C**	**U/T**	**D/T**	**C/T**	**M/T**	**C/M**	**D/C**	**U/T**	**D/T**	**C/T**	**M/T**	**C/M**	**D/C**
H1	0,0005	0,0067	0,0690	0,8193	0,0843	0,0972	0,0006	0,0006	0,0107	0,0000		0,0545	0,0000	0,0000	0,0194	0,0731	0,2662	0,0000
H2	0,0007	0,0045	0,0800	0,8976	0,0891	0,0562	0,0005	0,0015	0,0118	0,0000		0,1271	0,0001	0,0006	0,0028	0,0000		0,2147
H3	0,0009	0,0044	0,0792	0,8955	0,0884	0,0552	0,0007	0,0016	0,0119	0,0000		0,1367	0,0001	0,0004	0,0052	0,0000		0,0731
H4	0,0011	0,0055	0,0884	0,8848	0,0999	0,0626	0,0006	0,0016	0,0130	0,0000		0,1217	0,0002	0,0004	0,0042	0,0000		0,0953
H5	0,0031	0,0164	0,0558	0,6883	0,0810	0,2938	0,0000	0,0016	0,0528	0,1452		0,0310	0,0001	0,0007	0,0063	0,0297	0,2113	0,1085
H6	0,0014	0,0062	0,0988	0,8503	0,1162	0,0624	0,0010	0,0005	0,0000	0,0000			0,0001	0,0005	0,0148	0,0265	0,5600	0,0341
H7	0,0001	0,0024	0,1091	0,8585	0,1271	0,0223	0,0004	0,0014	0,0000	0,0000			0,0002	0,0011	0,0029	0,0238	0,1233	0,3619
H8	0,0000	0,0032	0,0656	0,9016	0,0728	0,0491	0,0000	0,0000	0,0117	0,0000		0,0000	0,0001	0,0006	0,0038	0,0135	0,2819	0,1450
H9	0,0059	0,0122	0,4937	0,3724	1,3256	0,0247	0,0224	0,0186	0,0446	0,0155	2,8715	0,4159	0,0060	0,0027	0,0059	0		0,4549
H10	0	0,0382	0,5457	0,3624	1,5056	0,0700	0,0004	0,0161	0,0369	0		0,4354	0,0001	0,0003	0	0		
H11	0	0,0143	0,5874	0,3404	1,7259	0,0244	0	0,0415	0,0164	0		2,5362	0	0	0	0		

Table 2 cont.

H12	0	0,0729	0,3207	0,5697	0,5630	0,2273	0,0004	0,0269	0,0081	0		3,3002	0	0,0013	0	0	
H13	0	0,0405	0,3173	0,6314	0,5025	0,1277	0,0003	0,0053	0,0051	0		1,0309	0	0	0	0	
H14	0,0001	0,0568	0,3847	0,5268	0,7304	0,1476	0	0,0272	0,0044	0		6,1395	0	0	0	0	
H15	0	0,0592	0,4529	0,4310	1,0509	0,1307	0,0022	0,0355	0,0156	0		2,2704	0	0,0037	0	0	
H16	0,0002	0,0209	0,4059	0,5662	0,7168	0,0516	0,0003	0,0017	0,0047	0		0,3701	0	0	0	0	
H17	0	0,0462	0,4259	0,4788	0,8897	0,1085	0,0041	0,0292	0,0138	0		2,1179	0,0002	0,0017	0	0	
H18	0,0002	0,0815	0,3051	0,5303	0,5753	0,2673	0,0033	0,0574	0,0108	0		5,3141	0,0010	0,0104	0	0	
H19	0	0,0598	0,4887	0,3802	1,2853	0,1223	0,0009	0,0556	0,0058	0		9,6388	0,0011	0,0078	0	0	
H20	0,0013	0,0456	0,3817	0,4206	0,9074	0,1195	0,0018	0,1322	0,0161	0		8,1967	0,0001	0,0006	0	0	
H21	0,0004	0,0723	0,4707	0,4100	1,1481	0,1536	0,0013	0,0339	0,0087	0		3,8931	0,0004	0,0023	0	0	
H22	0,0003	0,0253	0,4997	0,4637	1,0776	0,0505	0,0003	0,0053	0,0055	0		0,9612	0	0	0	0	
H23	0	0,0206	0,6660	0,2333	2,8543	0,0310	0,0011	0,0369	0,0415	0		0,8907	0	0,0005	0	0	
H24	0	0,0207	0,5131	0,4054	1,2658	0,0403	0,0026	0,0582	0	0			0	0	0	0	
H25	0,0002	0,0177	0,3905	0,5805	0,6726	0,0453	0	0,0005	0,0106	0		0,0509	0	0	0	0	
H26	0,0002	0,0276	0,4912	0,3258	1,5076	0,0562	0	0,0207	0,1346	0		0,1537	0	0	0	0	
H27	0	0,0191	0,3263	0,5934	0,5500	0,0586	0	0,0358	0,0232	0		1,5423	0	0,0022	0	0	
H28	0,0009	0,0420	0,3244	0,5971	0,5433	0,1294	0,0016	0,0227	0,0114	0		2,0009	0	0	0	0	
H29	0	0,0251	0,3306	0,5726	0,5774	0,0758	0,0010	0,0572	0,0135	0		4,2510	0	0	0	0	
H30	0	0,0855	0,5045	0,3631	1,3893	0,1696	0,0004	0,0344	0,0083	0		4,1670	0,0008	0,0030	0	0	
H31	0	0,0945	0,3435	0,5310	0,6468	0,2750	0,0020	0,0244	0,0046	0		5,2759	0	0	0	0	
H32	0,0002	0,0228	0,4661	0,4757	0,9799	0,0490	0,0004	0,0155	0,0162	0		0,9616	0,0004	0,0027	0	0	
H33	0,0070	0,0485	0,5529	0,3218	1,7182	0,0878	0,0041	0,0436	0,0108	0		4,0240	0,0036	0,0076	0	0	
H34	0	0,0057	0,5118	0,3468	1,4755	0,0112	0,0003	0,0807	0,0520	0		1,5502	0,0010	0,0017	0	0	
H35	0,0002	0,0314	0,4248	0,5223	0,8134	0,0739	0	0,0173	0,0040	0		4,3858	0	0	0	0	
H36	0,0019	0,0272	0,5190	0,3516	1,4761	0,0524	0,0007	0,0279	0,0578	0		0,4819	0,0026	0,0112	0	0	
H37	0,0006	0,0447	0,3823	0,5431	0,7038	0,1169	0,0002	0,0191	0,0101	0		1,8985	0	0	0	0	
H38	0,0002	0,0420	0,4972	0,4471	1,1119	0,0844	0,0004	0,0069	0,0062	0		1,1101	0	0	0	0	
H39	0	0,0538	0,3810	0,5393	0,7065	0,1413	0,0003	0,0175	0,0081	0		2,1700	0	0	0	0	
H40	0,0014	0,0227	0,5316	0,2997	1,7735	0,0428	0,0008	0,0219	0,0685	0,0224	3,0539	0,3198	0,0002	0,0168	0,0139	0	1,2129

In this paper, no distinction is made regarding the specific mathematical response of each pathology studied, since the objective was to determine if the method allowed the differentiation between normality and disease, regardless of the specific pathology. For this reason we included patients with multiple symptomatology and pathologies with different severity, including arrhythmias, Acute myocardial infarction, Palpitations, Chest pain, CIA, Blow systolic, or sinus tachycardia, among others. Indeed, one of the advantages of the applied method is that it allows objective and reproducible quantification of the level of severity of cardiac dynamics regardless of its etiology, as evidenced by the fact that cases with more serious diseases, such as AMI, presented the higher values in the sums of subtractions of the order of Thousands. This can be seen in Figures 1, 2 and 3, respectively representing a normal dynamic, a dynamic with a pathology in a chronic state and a dynamic with a pathology in an acute state. These figures reveal a progressive decrease of the spatial occupation of the numerical attractor as there is a higher level of severity of the disease. This was already observed in a previous work in which the attractors were built in the traditional way, with a line linking each ordered pair (X, Y) with the next point (Rodríguez et al., 2008). Thus it was possible to differentiate normality and chronic disease from acute disease, based in the differences in the occupied spaces of the attractor in the Box Counting space (Rodríguez et al.,2008)

However, to establish differences of clinical application between normal, chronic and acute disease was necessary to build the new type of attractor that is used in this work, a numerical attractor, and to evaluate it by means of the proportions of entropy (Rodriguez, 2010a). By quantifying the changes associated with states near or far from normality, this measure serves as an early warning indicator of cases that may tend to more acute conditions, as it was demonstrated in applications of this method to CCU patients (Rodriguez et al., 2010a; Rodriguez, 2011a) and confirmed in the present work. Based on the general result obtained in this work, which demonstrates the method's ability to detect disease states as opposed to normal, and quantifies the severity of their disease state, in future studies will be made new applications where specific pathologies will be analyzed in order to establish possible new implications.

Although in the current medical literature the heart rate variability from RR changes is being studied as a diagnostic parameter and a predictor ofcardiac dynamic in the context of physical and mathematical theories (Huikuri et al., 2000, Peng et al.,1995; Porta et al., 2001; Guzzetti et al, 2005; Maestri et al., 2007; Khoo 2008; Ivanov et al., 1999), it has been shown that cardiac dynamics has a chaotic or irregular behavior (Denton et al., 1990), contradicting the conventional homeostatic conception whose normality and disease diagnosis corresponds to regularity and irregularity, respectively.

Goldberger et al (2002) developed a concept of health – disease applied to cardiac physiology, in the framework of dynamical systems theory, where health state is in the intermediate range between extreme irregularity and extreme regularity. The latter states have correspondence, then, with a pathological behavior. From this perspective, predictive measures of mortality with fractal dimensions of the heart rate have been developed in patients diagnosed with acute myocardial infarction (AMI) with ejection fraction less than 35%, finding more reliable predictors factors of death (Huikuri et al., 2000) than those proposed from conventional approaches.

On one hand, the nonlinear dynamic methods have shown that when they are applied to the study of dynamic behavior of heart rate, they achieve an innovative approach of this phenomenon by nonlinear analysis of time series of cardiac dynamics. However, these methods lack of enough sensitivity and specificity to distinguish between chaotic dynamic and random noise (Wu et al., 2009). Likewise, other methods have proved to be poor indicators of cardiac dynamic nonlinearity. In general, it is considered that these methodologies are subject to further studies (Perkiömäki et al., 2005) that allow clarifying what methods should be applied under certain standardized conditions (Voss et al., 2009).

The methodology developed in this paper is applicable to each particular case in clinical setting as a diagnostic aid method of prevention and of intervention assessment. The entropy considered in this study is a measure of the underlying order of geometric attractor that shows the self-organization of probability distributions. It allows a theoretical analysis of the whole phenomenon.

Prigogine raised the concept of "temporal window" referring to the discontinuous information in time which is accessible for evaluation of certain phenomena and based on which it is not possible establishing causal relationships. In this sense, the numerical attractors are temporal windows (Fernandez, 1990) described in a finite and bounded space. These attractors allow establishing intrinsic geometric states which reveal numerical differences between normality and abnormality, thus permitting the establishment of predictions of clinical application from an acausal perspective. Within this view, the evolution of cardiac dynamics represents the succession of temporal windows as observed in cases where different Holters corresponded to the same patient but at different times. Furthermore, this methodology has predicted mathematically, in other studies, the evolution of patients in the Coronary Care Unit (Rodriguez et al., 2010a; Rodriguez, 2011a), suggesting that the predictions obtained are helpful in a clinical level for assessing the recovery of patients who have undergone to pharmacological and/or surgical interventions. Thus, it has been confirmed not only the capacity of methodology for differentiating normality from disease, as evidenced in a blind study with 300 Holter in which the comparison with the Gold Standard presented 100% in sensitivity and specificity, as well as a Kappa coefficient of 1 (Rodríguez, 2012a), but its ability for quantifying the degree of severity of the dynamics and clinically predicting its evolution (Rodriguez et al., 2010a; Rodriguez, 2011a)

Within the same context, other methodologies have been developed in cardiology. For instance, through an exponential law, a study was able to achieve the determination of all possible cardiac dynamics, including the normal ones and those with acute disease as well as evolution between these two states (Rodriguez, 2011b).This work was confirmed clinically as a diagnostic aid tool (Rodriguez et al., 2013). Also, there are similar works in the fields of infectious diseases (Rodriguez et al., 2012b), immunology (Rodriguez et al., 2009), molecular biology (Rodriguez et al., 2010b) and erythrocyte morphology (Correa et al., 2012). In the area of epidemics, a predictive methodology for malaria outbreaks in 820 municipalities was recently developed with a success of 99.86% (Rodríguez, 2010b). These works, likewise as the present investigation, demonstrate the relevance of the use of physical and mathematical theories for solving problems in all medical fields.

ACKNOWLEDGEMENTS

This Research is part of the results of CIAS-1169 project, which was funded by Research Fund of Universidad Militar Nueva Granada.

Thanks to the Universidad Militar Nueva Granada, especially to the Research Fund, who financed this work and the School of Basic and applied Science, for their support to our work. Especial thanks to Dr. Martha Bahamón, Academic Vice-Rector, to Dr. Fernando Cantor, Research Vice-Rector, to Dr. Ericsson Coy, Director of Research Center of School of Basic and Applied Sciences, to Alejandro Castro, Chief of Department of Scientific Research and to Henry Acuña for their constant support and collaboration in our investigations.

We also thank to Fundación Cardio Infantil, especially to Dr. Rodolfo Dennis and Dr. Gabriel Salazar for their support to our research. Similarly, we thank to Fundación Fundación Abood SHAIO, especially to Dr. Andrés León, Research Director of Clínica Shaio, for his support to our work.

To Research Center of Clínica del Country, for its support to our investigations; to Doctors Tito Tulio Roa, Director of Medical Education; Jorge Ospina, Medical Director, Alfonso Correa, Director of Research Center, Adriana Lizbeth Ortiz, epidemiologist and to Silvia Ortiz, Chief Nurse of Research Center.

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How to cite this article: Rodríguez J, Prieto S, Domínguez D, Melo M, Mendoza F, Correa C, Soracipa Y, Pinilla L, Pardo J, Ramírez N (2013). Mathematical-physical prediction of cardiac dynamics using the proportional entropy of dynamic systems. J. Med. Med. Sci. 4(9):370-381