PROPORTIONAL ENTROPY OF NORMAL AND ARRHYTHMIC HEART DYNAMICS IN INTENSIVE CARE UNITS

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Abstract:

Antecedents: Based on probability theory and proportions of the non-equiprobable entropy in the context of dynamics systems theory we developed a method for evaluating heart dynamics. Objective: to confirm the clinical applicability of the proposed diagnostic method on patients with different types of arrhythmia by comparing the degree of worsening of a patient's condition with variations in their entropy proportion values, computed based on Holter measures extracted from the patient. Methods: we analyzed 80 Holter taken from patients in ICUs with a diagnosis of arrhythmia, and 20 normal Holters. The clinical conclusions based on the Holter registers were masked, and the highest and lowest heart rates were recorded, together with the total number of beats per hour. Using these values, the numeric attractors for each dynamic were constructed. The probability, entropy and S/k ratio were computed, and entropy ratios were evaluated, establishing a mathematical diagnosis and measuring severity. Results: we showed that the method presented can discriminate between normal and abnormal dynamics, achieving high sensitivity and specificity values, and showing that it is possible to establish quantitatively the degree of worsening of a dynamic. Conclusions: the methods developed here are of use in clinical practice, being able to make predictions based on correlations between the degree of severity of arrhythmias and physical-mathematical variables.

Keywords: diagnosis; entropy; probability; arrhythmia.

Introducción

Theories such as dynamic systems theory, probability and entropy have been used to evaluate and diagnose heart functioning. The physical theory that describes the state and evolution of dynamic systems is dynamic systems theory [1, 2]; the evolution of a system can be represented geometrically in abstract spaces termed latency maps, in which the attractors of a system (which might represent predictable dynamics, yielding punctual or cyclic attractors, or unpredictable dynamics, represented by chaotic attractors [2, 3]) can be observed.

Chaos is classified as deterministic or stochastic. Deterministic systems have properties like non-linear behavior, loss of accuracy when making predictions, inability to make long-term predictions, and knowledge of the behavior of trajectories and their statistical properties, when regularities of this kind exist [4]. Stochastic systems are characterized by a null length of the statistical memory [5], and subjection to a chaotic process precludes determining whether a phenomenon is likely or unlikely to occur [6].

Dynamical systems theory and fractal geometry constitute the foundation over which diagnostic physical-mathematical laws with clinical applications could be developed for heart functioning as a dynamical system, which can discriminate between normal conditions, acute illness and the evolution between

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these states, and whose application to patients with arrhythmia made it possible to establish how serious their condition was, and to identify mild cases which were evolving towards pathological dynamics, which had been under-diagnosed until these developments took place [7].

The mathematical language that provides the foundation for modern physics is based on probability theory. It is based on measures that quantify the likelihood of an event taking place in the future [8]. The concept of entropy has been reinterpreted in other contexts, such as the kinetics of gases, statistical mechanics and information theory [9-11]. In medicine, it has been the basis over which measures like approximate entropy have been developed, making it possible to describe changes in the complexity of different systems [12-14]. However, its clinical applicability is still under study [13].

Within the context of dynamical systems, probability theory and entropy ratios, Rodriguez developed the mathematical diagnosis of heart dynamics using Holter measures, discriminating between normality, chronic conditions, acute conditions, and transitions between these states. It is a mathematical induction based on the lowest and highest heart rates each hour and the number of heart beats per hour of ten Holter measurements. Using these, we carried out computational simulations in order to construct numeric attractors that represented the patients' dynamics by quantifying the frequency with which ordered pairs containing each heart rate were found [15].

Its diagnostic efficacy and clinical applicability have been attested in numerous works, including a blind study of diagnostic correlation comparing it to conventional diagnosis that gathered data from 450 normal and ill patients (suffering from varied diseases) and found 100% sensitivity and specificity metrics and a Kappa value of one [16]. Additionally, several clinical implementations in ICUs [17], which predicted when heart conditions worsened and predicted the impact of specific pharmacological and surgical interventions on heart dynamics.

Arrhythmia is included among the most frequent cardiovascular conditions, and is associated to 50% of deaths from cardiovascular origin [18]. Arrhythmias are considered alterations of the heart rhythm of different origin [19], and according to the medical literature are grouped into three classes: passive, ectopic and re-entry arrhythmia. The conventional diagnosis of arrhythmia is regarded as a complex task and relies on several variables that must be recovered from the patient's clinical history and the study of an electrocardiogram [20], which makes it difficult to achieve an objective diagnosis with a single procedure.

The goal of the present work is to apply this method to normal cases and cases of arrhythmia in ICUs as a means to quantify how serious the condition of a patient is and how much his or her state has deteriorated, in order to determine whether whether there is a correlation between the degree of physical-mathematical worsening and the amount of clinically reported arrhythmia-related events.

Methods

Definitions

Latency map: specific attractor representing the dynamics and evolution of a system graphically by placing ordered pairs of consecutive values of a variable on a space of two or more dimensions.

Heart rate ordered pair: each pair of consecutive heart rates, denoted (X, Y) is placed on the latency map in cells corresponding to value spans of length five.

Equation 1: Probability of span (X, Y)

$$P(X,Y) = \frac{Number\ of\ ordered\ pairs\ within\ range\ X,Y}{Total\ number\ of\ ordered\ pairs\ on\ the\ measure}$$

Equation 2, Entropy of an attractor: non-equiprobable system constructed using the (X, Y) span. The occupation entropy of an attractor on a phase space is computed using the following equation:

$$S = -K\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y) \times \mathrm{LnP}(X,Y)$$

Equation 3 is deduced from equation 1 by clearing the Boltzmann constant:

Equation 3, S/K ratio:

$$\frac{S}{K} = -\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y) \times \mathrm{LnP}(X,Y)$$

Where S is entropy and P(X, Y) is the probaility of each span (X, Y). Equation 3 can be rewritten in the following way:

Equation 3(a):

$$\sum_{U} P(U) \times \mathrm{LnP}(U): \quad \text{Unidades } (U) \rightarrow (1-9)$$

$$\sum_{D} P(D) \times \mathrm{LnP}(D): \quad \text{Decenas } (D) \rightarrow (10-99)$$

$$\sum_{C} P(C) \times \mathrm{LnP}(C): \quad \text{Centenas } (C) \rightarrow (100-999)$$

$$\sum_{M} P(M) \times \mathrm{LnP}(M): \quad \text{Miles } (M) \rightarrow (1000-9999)$$

$$\frac{S}{K} = \{\{\{$$

Which upon simplification results in:

Ecuación 4: $\frac{S}{K} = T = U + D + C + M\,;$ where T= $\frac{S}{K}$

The rations between the parts (U, D, C, M) and the total (T), which corresponds to the relation S/k.

$$UT\,;DT\,;CM\,;MT\,;CM\ y\ DC$$

Areas

Area 1: it contains all the heart rate spans common to all normal Holter measures. **Area 2**: it contains all the spans occurring in normal Holters but one. Area **3:** it contains all the heart rates that were not included in any normal measure (that is, it comprises the rest of the latency map).

Data collection and analysis

100 Holter measures taken from patients aged 21 or older were analyzed. 80 were from the ICU of Hospital Universitario Mayor and had been diagnosed with arrhythmia and 20 corresponded to normal subjects, and were extracted from the Insight group database. 5 normal Holters correspond to patients who were examined upon request due to presenting certain symptoms and whose results were found to be within the normal parameters, while the remaining 15 correspond to control cases, and were taken from subjects without a history of cardiovascular disease and without symptoms. The diagnostic interpretation of Holter registers was carried out by expert cardiologists or electrophysiologists following the conventional clinical evaluation procedures.

The clinical information and conclusions registered for every Holter measure were masked (table 1). The only unmasked data were the hourly values of minimal and maximal frequencies and the number of heart beats. Using these values, the consecutive values of heart rates were computed with a software implementation of the method developed by Rodriguez [15]. After that, these values were used to graphically represent a numerical attractor on a latency map, which consists of the number of frequencies of the ordered pairs of consecutive heart rates in cells spanning five beats per minute that were found on the attractor, instead of the points connected by a continuous line that represent conventional chaotic attractors. Then, for we computed the probability of the ordered pairs grouped on the same area, for each record in the cells of the phase space. Later, we evaluated the entropy of each attractor (equation 2) and calculated the ratio S/k (equation 3).

We then grouped the values found for each of the addends depending on their value on equation 3(a), which correspond to the probabilities associated to occupation frequencies in the thousands, hundreds, tens and units. Computing these sums makes it possible to evaluate the proportions relating each addend

to the rest of the values, which corresponds to the ratio S/k, as well as the ratios between hundreds and thousands and the ratio from tens to hundreds for each area.

The criterion with which it was decided whether a Holter value was normal or not (previously established by Rodriguez [15, 16]) was followed by analyzing the number of proportions (in any of the three areas) outside the limit of normality. According to this criterion, if there are two or more values outside the normal range, the patient's dynamic is abnormal; else, the dynamic is normal.

In order to quantify the degree of severity of pathological dynamics, we evaluated quantitatively the distance between the patient's dynamic and normality, by substracting the values of the proportions outside normal parameters and the outer normal values. That is, if a value is higher than the interval within which normal values lie, the highest normal value is substracted from it. If the value is lower than the lowest normal value, the it is substracted from the normal value. Then, the results of the substractions are added, grouping them by their order of magnitude (thousands, hundreds, tens or units).

To quantify a more severe or acute state of the dynamics, one must analyze the value of the grouped substractions. A study carried out in ICUs showed that higher values of the thousands correlate with severe clinical decay or acute states (e.g. a heart attack) and a decrease in these values corresponded to satisfactory clinical developments in patients who underwent a surgical intervention [15].

Statistical Analysis

In order to carry out the statistical analysis we included the 15 normal Holter measures and the 80 Holter from arrhythmic patients in ICUs. The clinical conclusions dervied from the Holter measure were unmasked and the diagnosis at which practitioners arrived was considered the Gold Standard against which the physical-mathematical diagnosis should be compared. We then computed our method's sensitivity, specificity, number of false negatives and false positives using a 2*2 contingency table. We then evaluated our method using the Kappa coefficients and the diagnostic agreement between the gold standard and the methods results.

Results

We found that the entropy values of the 100 attractors varied between 4.92E-23 and 7.84E-23; the 15 normal Holters varied between 6.47E-23 and 7.01E-23, and the remaining 5 Holters with some kind of symptoms varied between 6.42E-23 and 6.98E-23, and ICU Holter values ranged from 4.92E-23 yto 7.84E-23. The entropy proportions of normal Holters for area 1 ranged between 0 and 2.671; for area 2, between 0 and 3.166 and for region 3 they adopted values of 0 in all cases. The entropy of area 1 in ICU Holters was between 0 and 6.354; for area 2 between 0 and 2.603 and for region 3 between 0 and 4.408 (see Table 2). All normal Holters without any symptoms had entropy values within the previously established normality limits [15], while normal Holters with symptoms included in four cases two or more values outside the normality limits. ICU Holters included at least two proportions outside the normality limit in all cases (thus being diagnosed as abonrmal, according to the definition of normality and anormality introduced above).

	SEX	AGE	DIAGNOSIS	CONCLUSIONS
N1	F	35	Control case	Average HR 75; min HR 57 at 04:34; max HR 136 at 16:01. Test within normal limits.
N2	M	26	Control case	Average HR 72; min HR 59 at 02:53; max HR 141 at 12:17. Test within normal limits.
N3	M	49	Syncope	Average HR 84; min HR 60 at 05:41; max HR 156 at 20:40. Test within normal limits.
1	F	84	Bradiarritmia	Sinus rhythm. Average HR 63 bpm, min HR 50, max HR 100. No ventricular arrhythmia. Sporadic atrial ectopic beats, with some duplets and salves of three and four.

2	F	58	arrhythmia	Attrial fibrillation with uncontrolled ventricular response: Average HR 103, min HR 67 bpm, max HR 153 bpm. 37 monomorph ventricular ectopic beats, 2 duplets.
3	M	74	arrhythmia	Sinus rhythm. Average HR 65 bpm, min HR 46 bpm, max HR 96 bpm. 28911 monomorph ventricular ectopies, 78 episodes of unsustained ventricular tachycardia, frequent duplets (4637), 871 bigeminy events and 292 trigeminy events. Wide QRS with image favoring right branch blockage.
4	M	80	Ahrrythmia study	Sinus rhythm. Average HR 63 bpm, min HR 51 bpm, max HR. 55 monomorph ventricular ectopic beats with some duplets (3), prematurity index > 1 and two ventricular tachycardia events. Atrial ectopic beats (38 ESV) and two ventricular tachycardia events. Atrial ectopia (38 ESV), 3 seconds atrial fibrillation. Slightly diminished RR variability with a SDNN value of 89.
5	M	78	Ahrrythmia study	Sinus rhythm Average HR 78 bpm, min HR 64 bpm, max HR. 550 dimorph ventricular ectopic beats, duplets y trigeminism. Atrial ectopic beats (422 ESV) con duplets and atrial tachycardia salves. Diminished RR variability with a SDNN value of 70 ms.
6	M	33	Syncope	Vagal tone. Average HR 66 bpm, min HR 43 bpm, max HR 127. QRS with morphology favouring right branch blockage.
7	F	83	Myocardial infarction	Sinus rhythm. Average HR 60 bpm, min HR 41 bpm max HR 90 bpm. 3060 monomorph ventricular ectopic beats, isolated, intersparsed, unsustained ventricular tachycardia. 34 ventricular duplets, trigeminy envents. Isolated arterial ectopic beats. RR variability was preserved.
8	F	75	Sick sinus syndrome	Sinus rhythm, Average HR, fue de 50 bpm, min HR 26 bpm, max HR de 92 bpm. Ritmos de escape de la union, 3622 ectopias ventriculares dimorfas, 28 dupletas bidireccionales, 157 bigeminismo y 194 trigeminismo.
9	F	75	Syncope	Sinus rhythm. HR 67 bpm, min HR 47 bpm, max HR 125 bpm. 1234 monomorph ventricular beats, 7 duplets y 7 trigeminism events. Union rythms favouring sick sinus syndrome. AV block episodes.
10	M	60	Ischemic cardiopathy. Trifasicular block.	Sinus rhythm. Average HR 68 bpm, min HR 51 bpmHRmax 98 bpm. 6228 ectopias ventriculares monomorfas, 10 duplas, 5 de eventos de bigeminismo y 236 de eventos de trigeminismo, Bloqueo AV de primer grado con un PR de hasta 280 ms. Variabilidad RR ligeramente disminuida con un SDNN de 98 ms.
11	F	87	Sincope	Sinus rhythm . Average HR 68 bpm, min HR 54 bpm , max HR 92. ectopias ventriculares monomorfas escasas, un episodio de taquicardia ventricular. Variabilidad RR severamente disminuida con un SDNN de 61 ms.
12	F	71	Atrial fibrillation	fibrilacion atrial permanente con respuesta ventricular controlada: HRprom 81 bpm, min HR 47 bpm, HRmax 151 bpm. Ectopias ventriculares muy poco frecuentes. un evento de taquicardia ventricular.
13	M	68	Bradycardia	Sinus rhythm con tendencia a la bradicardia: HRprom 50, min HR 41 bpm, HRmax 69 bpm. 235 ectopias ventriculares monomorfas aisladas. Ocasionales ectopias atriales con algunas dupletas y una salva de taquicardia atrial. Variabilidad RR ligeramente disminuida con un SDNN de 95 ms.
14	F	78	Syncope	Sinus rhythm. HRprom 64 bpm, min HR 48 bpm, HRmax 112 bpm. 1678 Ectopias ventriculares monomorfas con una dupleta, Ocasionales ectopias atriales (306 ESV) aisaldas, algunas dupletas. bloqueo de rama izquierda permanente. Variabilidad RR disminuida con un SDNN de 89 ms
15	F	80	Tachychardia	Sinus rhythm. HRprom 99 bpm, min HR 64 bpm, HRmax 139 bpm. 5569 Ectopias ventriculares dimorfas con algunas dupletas (95), y un episodio de taquicardia ventricular polimorfica, 83 de eventos de bigeminismo y 44 de eventos de trigeminismo. Variabilidad RR disminuida con un SDNN de 71 ms.

16	M	81	Myocardial infarction	Sinus rhythm.HRprom 91 bpm, min HR 70 bpm, HRmax 122 bpm. 1751 ectopias ventriculares monomorfas, 7 dupletas y 52 trigeminismo. numerosas ectopias atriales (5323 ESV), dupletas. Variabilidad RR severamente disminuida con un SDNN de 47 ms.
17	M	72	Heart failure	Sinus rhythm.Average HR 87 bpm, HR 66, max HR 104. 3501 Ectopias ventriculares Dimorfas, 2 bigeminismo y 38 trigeminismos, algunas dupletas, dos Taquicardia ventricular lenta. Variabilidad RR severamente disminuida con un SDNN de 44 ms
18	M	82	Lypothimia	fibrilacion Atrial. HRprom 60 bpm, min HR 31 bpm,HRmax 103 bpm. 2210 ectopias ventriculares monomorfas, 3 taquicardia ventricular y 132 dupletas, 1 bigeminismo y 7 trigeminismo
19	F	79	Syncope	Sinus rhythm.Average HR 96 bpm, min HR 81, max HR 126. Variabilidad RR severamente disminuida con un SDNN de 46 ms
20	F	85	Chest pain	Sinus rhythm. Average HR 74 bpm, min HR 56 bpm, max HR 142. 1133 ectopias ventriculares monomorfas, con algunas dupletas
21	F	66	Chagas disease	Base rhythm on auricular fibrillation with delayed response. Very frequent polymorph ventricular extrasystole, with duplets. Intraventricular conduction disturbances due to branch block.

Tabla 1. Consideraciones clínicas desde los parámetros convencionales para 24 de las dinámicas estudiadas

N1, N2: dinámicas normales sin sintomatologías, y **N3**: dinámica normal con sintomatologías.

When analyzing the proportion substractions outside the normal range, grouped and added based on the order of magnitude of their corresponding frequency, it was found that, since normal Holters always had values within the normality limits, all their values are zero, while normal Holter values with some symptoms had zero values for the thousands, 0 for the hundreds, 1.651 for the tens and unit values between 0 and 0.426. By comparison, the thousands values for ICU Holters were between 0 and 3.905, the hundreds values were between 0.317 and 5.873, the tens values were between 0 and 0.001 and the units were between 0 and 0.077.

		NORMALES			HOLTER DE UCI CON ARRITMIAS CARDIACAS																				
		SS		CS																					
		N1	N2	N3	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	S/k	4,741	5,03	4,872	4,694	5,456	5,052	4,219	4,808	4,964	4,85	5,212	4,87	4,17	3,79	5,683	3,566	4,805	4,724	4,595	4,115	5,105	3,836	5,059	4,555
	Entropía	6,50	6,90	6,70	6,50	7,50	7,00	5,80	6,60	6,90	6,70	7,20	6,70	5,80	5,20	7,80	4,90	6,60	6,50	6,30	5,70	7,00	5,30	7,00	6,30
Region 1	U/T	0	0	0	0,002	0	0,003	0,001	0	0,002	0	0	0	0	0	0	0,032	0,002	0	0,001	0	0	0	0	0
	D/T	0,088	0,092	0,005	0,024	0,009	0,025	0,069	0,056	0,026	0,023	0,01	0,044	0,011	0,057	0,019	0,022	0,053	0,016	0,022	0,011	0,034	0,011	0,063	0,025
	C/T	0,483	0,551	0,477	0,408	0,695	0,785	0,219	0,418	0,393	0,653	0,413	0,278	0,261	0,217	0,672	0,059	0,264	0,246	0,176	0,18	0,553	0,185	0,448	0,199
	M/T	0,309	0,176	0,428	0,45	0	0	0,648	0,432	0,415	0,103	0	0,459	0,692	0,702	0	0,275	0,534	0,713	0,73	0,798	0	0,803	0,374	0
	C/M	1,566	3,12	1,114	0,905			0,339	0,968	0,946	6,354		0,605	0,376	0,309		0,212	0,494	0,344	0,242	0,225		0,231	1,2	
	D/C	0,183	0,167	0,011	0,059	0,012	0,032	0,314	0,134	0,067	0,035	0,024	0,16	0,041	0,263	0,028	0,377	0,2	0,066	0,125	0,061	0,062	0,061	0,141	0,128
Regionn 2	U/T	0,008	0,008	0,001	0,001	0,001	0,001	0	0,001	0,001	0	0	0	0	0	0,002	0,033	0,013	0	0	0	0	0	0,001	0
	D/T	0,084	0,132	0,042	0,023	0,034	0,011	0,028	0,055	0,017	0,009	0,003	0,025	0,002	0,022	0,065	0,004	0,058	0,014	0,005	0,003	0,017	0	0,025	0,005
	C/T	0,027	0,04	0,047	0,069	0,261	0,116	0,026	0,031	0,096	0,139	0,098	0,09	0,034	0	0,165	0	0,047	0,01	0,048	0,008	0,127	0	0,071	0,111
	M/T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,341	0	0	0,018	0	0	0	0	0
	C/M																0			2,603					
	D/C		3,29	0,892	0,333	0,132	0,098	1,07	1,769	0,177	0,063	0,032	0,282	0,059		0,395		1,235	1,393	0,1	0,449	0,133		0,357	0,049
Region 3	U/T	0	0	0	0,001	0	0,001	0,001	0	0	0,001	0,002	0,001	0	0	0	0,022	0,003	0	0	0	0,001	0	0,001	0
	D/T	0	0	0	0,01	0	0,019	0,007	0,007	0,015	0,015	0,034	0,024	0	0,001	0,016	0,015	0,021	0	0	0	0,026	0	0,017	0,032
	C/T	0	0	0	0,012	0	0,039	0	0	0,035	0,058	0,439	0,078	0	0	0,061	0,075	0,005	0	0	0	0,241	0	0	0,627
	M/T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,124	0	0	0	0	0	0	0	0
	C/M																0,603								
	D/C				0,851		0,499			0,412	0,26	0,078	0,314			0,265	0,2	4,408				0,107			0,051
SUMA	U	0	0	0	0,003	0	0,004	0,002	0	0,002	0,001	0,002	0,001	0	0	0	0,077	0,01	0	0	0	0,001	0	0,001	0
	D	0	0	0,034	0,025	0,03	0,033	0,007	0,007	0,027	0,031	0,063	0,024	0,028	0,001	0,036	0,032	0,021	0,023	0,017	0,028	0,03	0,029	0,017	0,046
	C	0	0	1,651	3,116	2,761	3,257	1,778	0,756	2,889	2,961	3,129	2,824	2,664	0,338	2,688	0,886	5,873	1,319	2,674	2,334	2,782	0,317	2,168	3,444
	M			0	0,107	0,153	0,153	0,844	0,043	0,066	2,797	0,153	0,407	0,851	0,928	0,153	3,905	0,575	0,904	1,568	1,108	0,153	1,107	0	0,153

Table 2. S/k ratio, entropy and its proportions for each area taken from 24 of the dynamics surveyed

SS: asymptomatic, normal dynamics **CS**: symptomatic normal dynamics, Entropy proportions for each area; **U/T**: Units/ total, **D/T**: Tens/ Total, **C/T**: Hundreds/ Total, **M/T**: Thousands/ Total, **C/M**: Hundreds/Thousands, **D/C**: Tens/ Hundreds

Theory predicts that heart dynamics with higher results for the addition of the substractions grouped in the thousands correspond to the most acute conditions, according to clinical observations, while lower values correspond to less severe conditions, which was verified with clinical observations (see Table 1 and Table 2).

As a result of the statistical analysis, it was determined that the specificity and sensitivity values of the evaluated Holters was 100%, when comparing the mathematical diagnosis to the gold standard, much like the agreement between the mathematical diangosis and the conventional clinical diagnosis, which was established by a Kappa coefficient of 1.

Discussion

This is the first work to confirm the diagnostic and predictive capability of the heart dynamics methodology based on the probability and proportion of entropy in normal cases and cases with arrhythmia obtained from patients in ICU. This is also the first work to find correlations between the degree of intensification of arrhythmia-related dynamics and the values computed with these mathematical tools, and to show a correlation between the intensification predictions and conventional clinical diagnoses.

Statistical analysis showed that this method is able to discriminate normal and arrhythmic dynamics objectively based on quantitative methods. It was also confirmed that arrhythmic dynamics exhibiting higher values on the substractions of the thousands corresponded to ICU patients in critical or acute states, adding further support to previous finding, which applied the methods presented here to ICU patient Holters [17]. We carried out a statistical analysis of diagnostic agreement both in order to meet the standards of current medical research, and to make use of its ability to analyze arrhythmia.

For instance, the seventh Holter, whose values were 2.797 on the thousands and 2.961 on the hundreds, corresponds to a patient who suffered myocardial infarction, presenting numerous arrhythmic events, including 3060 monomorph ventricular ectopic beats. It is worth mentioning that although he presented a mathematical value indicative of severely acute states, his RR variability was preserved, which highlights the unreliability of variability measures to predict acute states. By comparison, the fifth Holter, whose values on the thousands were 0.043 (significantly lower than those of the previous Holter), had significantly milder clinical symptoms (550 dimorph ventricular ectopic beats and 422 ESV), despite displaying typical signs of arrhythmia following the conventional evaluation (see Table 1 and Table 2). Both dynamics corresponded to acute clinical pictures from the point of view of traditional diagnosis techniques, but the second case was much less severe than the first, which is in agreement with the mathematical scoring, since the values on the thousands are higher in the seventh Holter than in the fifth, confirming the methods predictions (See Table 1 and Table 2).

Based on this methodology, the orders of magnitude of the values on the thousands allow us to determine the degree of severity of the dynamics, and the values in the hundreds, tens and units also account for the differences between them. For example, dynamics 12 and 21 had both values of 0.153 on the thousands, but the values on the hundreds is 2.688 in number 12, while the value for 21 is 3.444- Theory predicts that the clinical state of 12 is less severe than that of 21, a prediction that was confirmed when comparing the Holter conclusions, where 12 reports permanent atrial fibrillation with controlled ventricular response and infrequent ventricular ectopic beats and a ventricular tachycardia event. By comparison, 21 corresponds to a case of Chagas disease, with symptoms of higher severity, like conduction disturbances due to branch block, with a base rhythm on auricular fibrillation and delayed response, which includes very frequent polymorph ventricular extrasystole with duplets (see Table 1 and Table 2).

Dynamics 1 presented, among all the patients surveyed, the highest value on the thousands, denoting a severely acute process; however, the conclusions of the conventional Holter analysis reveal only a state of bradycardia, without pointing out the existence of a state of increasing severity. This case serves as an example to illustrate the way in which the physical-mathematical evaluation of the total self-organization of the system allows us to predict progress towards acute states that are not detectable by means of the conventional procedures.

Additionally, the analysis of the Holter measures classified as normal taken from patients who previously displayed symptoms, which in all cases were diagnosed as normal. This result highlights the capability of our method to establish metrics that warn us about mild disturbances that are underdiagnosed, and might give rise to pathological states, and might require a more careful clinical follow-through. It becomes

apparent that they presented values of zero on the thousands in all cases, indicating their subclinical nature, as compared to the ICU Holter measures.

Based on the theory of non-linear dynamic systems it has been demonstrated that the behavior that is characteristic of normality contradicts the classical premise of homeostatic regularity [22], by showing that pathological dynamics are characterized by excessively regular or chaotic behaviors, while normality is to be found between these two [23]. From this perspective, several metrics for the description and prediction of abnormal events in cardiological dynamic systems have been established [24-26]. However, despite the progress achieved, its clinical applicability is not yet firmly established [26].

The study of heart dynamics from a strictly physical-mathematical point of view makes the use of the statistical considerations that serve as their foundation unnecessary, providing insight on how a quantitative value makes it possible to draw distinctions between one and another arrhythmia, even when they display very similar overt characteristics form the conventional clinical point of view, which makes it a useful practical tool in clinical decision making.

This new approach proposes evaluating informational entropy in a geometrical context, which makes it possible to visualize an underlying acausal physical order of a predictive nature, aside from the randomness and chance normally associated to chaos theory and non-linear dynamic systems. The acausal context has been the foundation for physical theories such as chaos theory [3, 9-15, 27], quantum mechanics [28] and statistical mechanics [10-11]. Works in other areas of medicine have developed methodologies based on probability and entropy, which reveal and establish forms of self-organization in different systems, be them immunology [29], epidemics prediction [30], and fetal heart dyamics [31]. Other physical and mathematical theories have achieved predictive diagnostic results in other areas of medicine, such as cell morphology [32], arterial morphology [33], infectology [34], and have established mortality predictions in ICUs [35], showing that by applying physical and mathematical theories it is possible to find regularities in phenomena that are perceived as random or non deterministic, and that there exist physical-mathematical orderings that underlie different medical phenomena, whose formulation allows us to improve diagnostic methods and current predictive tools.

Conclusions

The diagnostic and predictive capacity of our heart dynamics evaluation methods based on probability and proportional entropy was confirmed, and the method quantified successfully the degree of worsening of arrhythmic heart dynamics, showing that there is a correlation between the physical-mathematical predictions of intensification and the conventional clinical diagnosis.

Dedication

To our children.

To Master Paramahamsa Hariharananda, Master Paramahamsa Prajnanananda and Master Bhadrayu Pandya.

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