ORIGINAL ARTICLE

Use of the Proportional Entropy Method to Evaluate Electrocardiographic Records

Aplicación del método de entropía proporcional para evaluar registros electrocardiográficos

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ABSTRACT

Background: A new diagnostic methodology developed in the context of dynamic system theory has allowed the assessment of electrocardiographic registries, achieving objective and reproducible diagnoses.
Objective: The purpose of this study was to test the clinical applicability of this methodology based on the probability and the entropy proportions of the attractor through a blinded study compared with the gold standard.
Methods: A total of 650 electrocardiographic registries were analyzed: 150 normal and 500 with different diseases. Numerical attractors were generated from 18-hour registries of heart rate values and probability, entropy and entropy proportions of each attractor were calculated. The physical-mathematical diagnosis was established and the clinical applicability and clinical reproducibility of the mathematical methodology was compared to the conventional clinical diagnosis, calculating sensitivity, specificity and kappa coefficient.
Results: One hundred percent sensitivity and specificity and a kappa coefficient of 1 with regard to the conventional clinical diagnosis confirmed the clinical applicability of the postulated method.
Conclusion: The application of this methodology allowed the quantitative differentiation between normal and abnormal cardiac dynamic states, evidencing self-organization of the geometric dynamic attractor which constitutes a method of diagnostic aid applicable to clinical practice.

Key words: Diagnosis - Nonlinear Dynamics - Entropy - Probability

RESUMEN

Introducción: Una nueva metodología diagnóstica desarrollada en el contexto de la teoría de los sistemas dinámicos ha permitido la evaluación de registros electrocardiográficos, logrando diagnósticos objetivos y reproducibles.
Objetivo: Confirmar la aplicabilidad clínica de la metodología fundamentada en la probabilidad y las proporciones de la entropía del atractor mediante un estudio ciego respecto del patrón oro.
Material y métodos: Se analizaron 650 registros electrocardiográficos, 150 normales y 500 con diferentes patologías, mediante un estudio ciego. Se generaron atractores numéricos a partir de los valores de la frecuencia cardíaca en 18 horas; luego se calcularon la probabilidad, la entropía y las proporciones de la entropía de cada atractor. Se estableció el diagnóstico físico-matemático y se evaluó la aplicabilidad y reproducibilidad clínica de la metodología matemática respecto del diagnóstico clínico convencional, calculando la sensibilidad, la especificidad y el coeficiente kappa.
Resultados: Se confirmó la aplicabilidad clínica del método propuesto al hallar valores de sensibilidad y especificidad del 100% y un coeficiente kappa de 1 respecto del diagnóstico clínico convencional.
Conclusión: La aplicación de la metodología permitió diferenciar cuantitativamente estados de normalidad y anormalidad de las dinámicas cardíacas, evidenciando una autoorganización del atractor dinámico geométrico, que constituye un método de ayuda diagnóstica aplicable a la clínica.

Palabras clave: Diagnóstico - Dinámicas no lineales – Entropía - probabilidad.

Abbreviations

HR	Heart rate	HRV	Heart rate variability

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INTRODUCTION

The study of heart rate variability (HRV) aims to establish patterns that define the different cardiovascular diseases from the electrical signals of the heart. (1) The spectral analysis of HRV provides analytical characteristics of its cyclic variations, but it cannot show the dynamic properties of fluctuations. (2) At present, HRV research focuses on techniques analyzing its time domain (3, 4) and standard frequency. (1)

The dynamical system theory studies the system state and behavior, analyzing its variables as the system progresses in time, based on theoretical physical-mathematical postulations from an acausal perspective. (5, 6) Plotting in the phase space, the behavior of the system is analyzed by its dynamic variables generating different types of attractors. (7) Moreover, there are physical or mathematical phenomena which present a finite number of possible events, whose occurrence is assessed with the probability theory. (8) The concept of entropy was founded upon the study of out of equilibrium systems mainly for the kinetic theory of gases and statistical mechanics. (9-11) Dynamical systems, probability and entropy are some of the mathematical theories applied to the evaluation of cardiac dynamics. (1, 12)

Different types of entropy used in cardiology are defined from the analysis of three, four or six electrocardiographic parameters, with variations in the test cases. (1) Some studies have found that the length of data affects entropy sensitivity. (3, 13, 14) Effectively, HRV data have been tested increasing the number and size of data sample. (1) However, the choice of entropy-associated parameters establishing significant differences between normal and pathological cardiac rhythms, are still subject to study.

In addition, other non-linear types of analysis have emerged, as the Poincaré plot analysis, (15-19) a geometric method able to assess cardiac rhythm variability from the representation of a time series in the Cartesian plane, where the values of each pair of successive elements define a point in the plot. The so-called Poincaré map, (15, 16) also known as the Lorenz map, allows the reconstruction of system attractors based on experimental HRV series to predict cardiac disease and dysfunction.

In the past years, newly developed methodologies have enabled more accurate diagnoses, through mathematical ranges differentiating between normality and disease. (20-23) These methodologies assess heart rate (HR) values independently of the clinical parameters established for HRV. For example, a method was developed based on the attractor entropy probability and proportions (22) to assess electrocardiographic registries. In later studies, (21, 22) the reproducibility and clinical applicability of this methodology has been confirmed, with 100% sensitivity and specificity, and kappa coefficient of 1, with regard to the conventional clinical diagnosis.

The aim of the present work was to confirm the clinical applicability of the method based on proportional entropy, by means of a blinded study of diagnostic concordance with the gold standard in normal and pathological electrocardiographic registries.

METHODS

A total of 650 Holter monitoring studies were evaluated by an expert cardiologist. They were divided into 150 normal registries and 500 with different pathologies. These registries were obtained from subjects >21 years of age and were part of a previous research database from the Insight Group. To apply the proportional entropy method, clinical outcomes were masked for each registry, taking maximum and minimum HR values and the total number of beats every hour, for at least 18 continuous hours. These values were then transferred to a delay map to generate a numerical attractor, where the frequency of HR ordered pairs were plotted in ranges of five beats per minute. Next, the regions were evaluated by means of the occupation probability in relation to the total (see Definitions). The probability calculated for each range of five beats per minute in the phase space, considers each HR pair as an event with Equation1. Then the entropy for each attractor was calculated with Equation 2.

Definitions

A delay map was defined as the geometric space that generates a type of attractor representing graphically the behavior of a system, by positioning ordered pairs of values of a time-consecutive dynamic variable in a space of two or more dimensions. Moreover, the HR pair (X, Y) represents any consecutive combination of two HR in the delay map, positioned in ranges of five beats per minute, according to its coordinates. The probability of the pair of consecutive HR is the ratio between the number of ordered HR pairs occupying that range and the total sum of ordered HR over the entire tracing.

$$P(X,Y) = \frac{\text{Number of ordered pairs found in the X, Y range}}{\text{Total number of ordered pairs in the tracing}} \qquad \text{Equation 1}$$

Cardiac attractor entropy was defined as:

$$S = -k\sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times LnP(X,Y) \qquad \text{Equation 2}$$

where

S is entropy, K is Boltzman's constant (1.38x10-23 Joules/Kelvin), and P(X, Y) is the probability for each (X, Y) range.

The proportions of the cardiac attractor entropy were obtained by algebraically clearing the k constant. This resulted in:

$$\frac{S}{K} = \sum_{x=1}^{n}\sum_{y=1}^{n} P(X,Y)\times LnP(X,Y) \qquad \text{Equation 3}$$

whose sums correspond to:

$$\frac{S}{k} = \begin{cases} \sum_{U} P(U)\times LnP(U) & (1\text{-}9) \Rightarrow \text{U : Units} \\ \sum_{D} P(D)\times LnP(D) & (10\text{-}99) \Rightarrow \text{T : Tens} \\ \sum_{C} P(C)\times LnP(C) & (100\text{-}999) \Rightarrow \text{H : Hundreds} \\ \sum_{M} P(M)\times LnP(M) & (1000\text{-}9999) \Rightarrow \text{Th : Thousands} \end{cases} \qquad \text{Equation 3(a)}$$

Simplifying Equation 2(a) results in:

$$T = U + D + C + M \text{ ,where } \quad T = \frac{S}{k} \qquad \text{Equation 4}$$

and T represent the total with respect to the proportions between parts (U, D, C, M), as well as its parts in relation with other parts of the total.

$$U/T;\ D/T;\ C/M;\ M/T;\ C/M \text{ and } D/C$$

Three regions were established for the cardiac attractor. The first contains all the common HR ranges, which were stored in the Holter monitors and diagnosed as normal. The second corresponds to the total HR ranges occupied by the normal Holter registries, excluding the values of the first region. The third region is the one remaining from the total delay map, i.e. the HR ranges that were not occupied by the normal Holter electrocardiographic registries. (20)

Following entropy calculation with Equation 2, the S/k proportions for each numerical attractor was determined with Equation 3. Then, the proportions between units and total, between tens and total, etcetera, were calculated for each defined region with Equation 4. After these steps, the diagnostic parameters of the previously developed methodology were applied, (20) evaluating if at least two proportions in any of the three regions were outside the limits of normality, which is the parameter discerning normality from abnormality.

Pathological tracings were quantified considering the extreme values of the previously defined normality, (20) which establish that the upper limit of normality must be subtracted from the proportion values above these limits, while values inferior to the lower limit of normality are subtracted from this limit value. Once the value of these differences was obtained, they were added according to the units, tens, hundreds and thousands orders of magnitude, which finally quantified how far or close to normality they were. Thus, higher values corresponded to acute diseases and lower values to less severe diseases.

Statistical analysis

The conventional clinical diagnosis was considered as the gold standard for the statistical analysis. A binary clinical classification was used, taking into account normal and pathological cases, according to the cardiologist's diagnosis, for their later comparison with the mathematical diagnosis. True positives corresponded to cases diagnosed as pathological by both methodologies, false positives as cases mathematically assessed as pathological and as normal by the clinical expert. False negatives were cases mathematically diagnosed as normal and as pathological by the experts, and finally, true negatives were cases diagnosed within normal limits by both methodologies. The kappa coefficient, evaluating the concordance between the physical-mathematical and the conventional diagnosis was also calculated.

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

where:

Co is the number of observed concordances, corresponding to the number of patients with the same diagnosis by the mathematical methodology and the gold standard,

To represents the total number of cases, and

Ca corresponds to the number of random attributable concordances, calculated as:

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

where

f1 is the number of cases with mathematical values of normality,

C1 is the number of cases diagnosed as normal by the clinical expert; f2 represents the number of cases mathematically assessed as disease,

C2 is the number of cases diagnosed from the conventional clinical point of view as having some pathology, and.

To represents the total number of cases.

Ethical considerations

The study represents an investigation with minimum risk, according to Regulation 8430/93 of the Colombian Ministry of Health, as it is the result of physical and mathematical calculations on reports of previously prescribed noninvasive and paraclinical studies, according to conventionally established protocols. The study also complied with the World Medical Association Declaration of Helsinki ethical principles.

RESULTS

The S/k ratios obtained were in the range of -5.108 to -4.709 for the normal registries, and varied between -5,069 and -3,295 for pathological cases (see Tables 1 and 2). In addition, the entropies were between 6.50x10-23 and 7.05x10-23 in normal cases and from 4.55x10-23 to 7.00x10-23 in the dynamics evidencing disease.

The entropy proportions for the group of patients with mathematical diagnosis of normality varied between 0 and 3,488 and for the group of patients with mathematical diagnosis of disease these values ranged between 0 and 26,141. It was seen that at least two of the proportions evaluated for the abnormal attractors, in any of the three areas, were not contained within the limits of normality, corroborating the previously found diagnostic parameter. In the case of pathologies, sums of value subtractions were found outside the limits of normality in the interval between 0.002 and 22,951. With the entropy proportions, it was possible to differentiate normality from disease, as well

Table 1. Types of arrhythmias analyzed and percentage (with respect to total number of registries assessed) of dynamics classified within each type of arrhythmia.

Type of arrhythmia	%
Supraventricular tachyarrhythmia	29.69%
Bradyarrhythmia	20.31%
Ventricular tachyarrhythmia	14.92%
Others (AMI, ischemic heart disease)	12.00%

AMI: Acute myocardial infarction.

as the progression to more severe stages. The former was evidenced in Figure 1, where in the first evaluation parameter, corresponding to the sum of the proportions of thousands outside the limits of normality, these have higher values in acute dynamics and decrease until they disappear for normal dynamics.

Figures 2, 3 and 4 show the electrocardiographic record attractors corresponding to three patients. Figures 2 and 3 evidence that the numerical attractor of acute dynamics (Figure 3) decreases its spatial occupation compared with normal dynamics (Figure 2). In addition, it can be seen that for other pathological dynamics (Figure 4), there is spatial occupation of region 3, also different from normal dynamics, since no values are found in this region for these dynamics.

To assess the diagnostic concordance between both methodologies, the results of clinical conclusions were unblinded showing 100% cardiac dynamics specificity and sensitivity between the mathematical diagnosis and the gold standard. Similarly, the concordance between the physical-mathematical and the conventional diagnoses, determined by the kappa coefficient was equal to 1. These results thus confirm the applicability and clinical reproducibility of the methodology.

DISCUSSION

This is the first study in which the proportional entropy methodology is applied to 650 registries to establish differences between normal and pathological electrocardiographic registries. This method can be applied to any specific case regardless of risk, sex or age factors, as long as patients are over 21 years of age, because the method is independent of causal analysis, following the reasoning contemplated within the framework of modern physics. Additionally, the statistical results corroborated the mathematical pre-

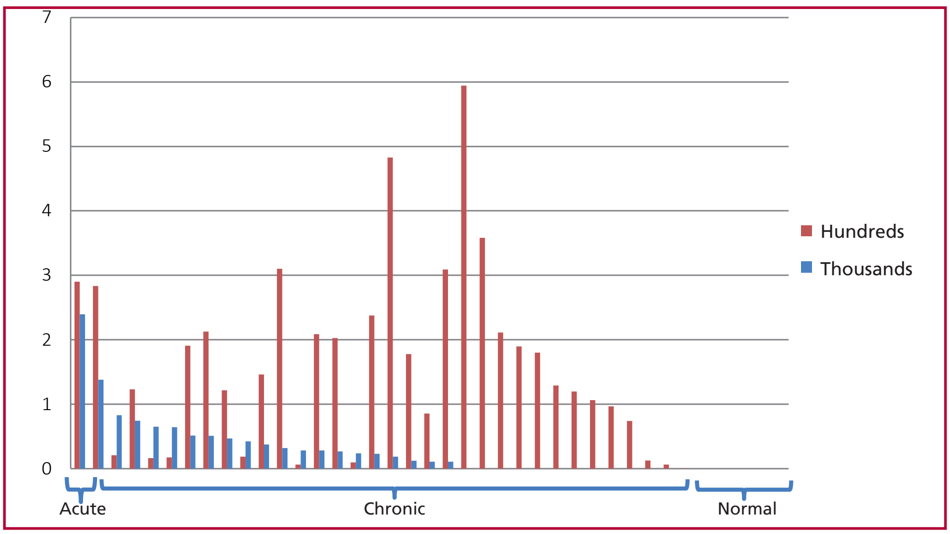

Fig. 1. Distribution plot for hundred and thousand values of sums of proportions outside the limits of normality for some of the Holter monitoring studies assessed. Notice that the thousand values for the acute disease dynamics are much larger than for any other dynamics, whereas for normal dynamics these values are zero.

6	180	203	52	59	11	12	3	9	6									
166	1279	1678	968	475	57	47	54	45	21									
190	1693	2842	2104	1176	36	55	48	70	33	3								
37	956	2127	2198	1340	202	221	166	56	54	1								
42	442	1177	1365	1470	720	750	431	121	121	53	2	15	14	15	5	9		
10	45	53	233	731	1373	1543	1115	761	517	94	10	6	5	7	11	8	2	
13	39	63	203	714	1606	1922	1571	1279	794	319	121	43	21	31	19	5	5	6
4	57	50	150	422	1144	1562	1609	1475	1107	610	358	146	104	110	94	18	5	7
12	54	49	55	162	727	1261	1513	1771	1343	911	624	494	217	172	112	93	14	13
2	39	29	34	113	498	861	1047	1360	1225	894	646	424	215	160	144	456	6	11
		11	4	43	81	327	589	928	922	901	659	448	228	144	126	25	10	6
		10	12	11	3	133	404	632	628	646	552	427	213	147	141	25	4	15
		13	14	7	2	25	170	477	422	444	409	427	247	145	147	12	5	8
			5		1	26	125	232	236	215	219	248	191	171	128		11	14
			5	8	11	17	124	145	145	145	165	136	148	146	118	27	4	8
			7	6	4	26	83	128	153	110	145	138	132	108	134		5	12
			8	14	8	1	103	13	298	10	14	459	12	218	198	11	13	5
						1	13	12	11	8	3	6	10	7	7	12	8	7
						13	2	14	4	6	1	12	5	8	15	15	2	5
												3	14	4	6	1	2	15

Fig. 2. Numerical attractor of a patient with normal ECG.

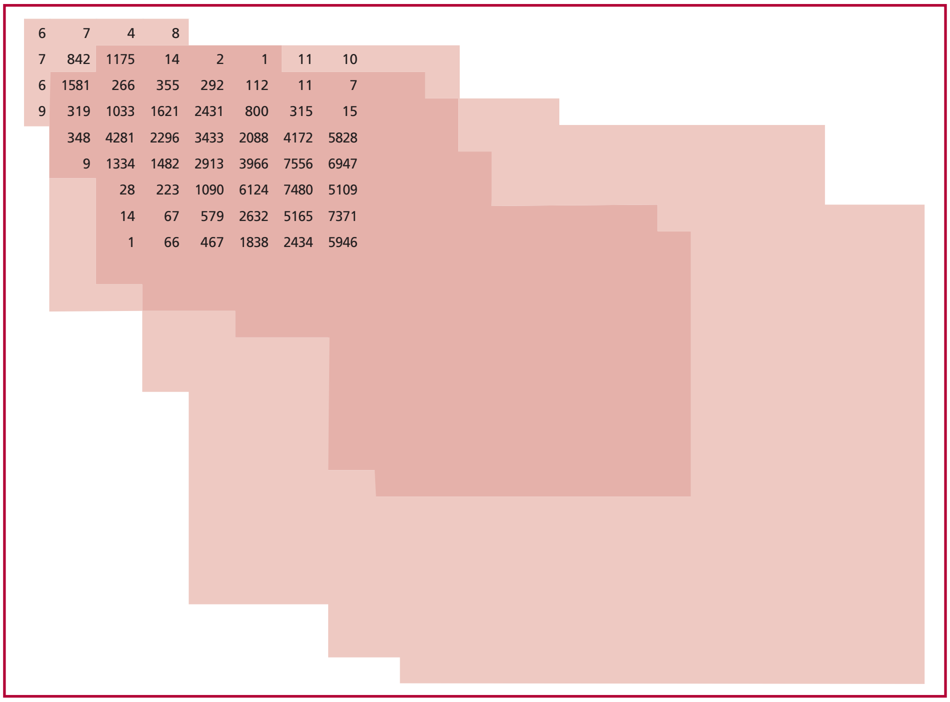

Fig. 3. Numerical attractor of a patient with acute myocardial infarction, and frequent ventricular ectopic beats with bigeminy. Severe decrease of heart rate variability. Fixed repolarization disorder.

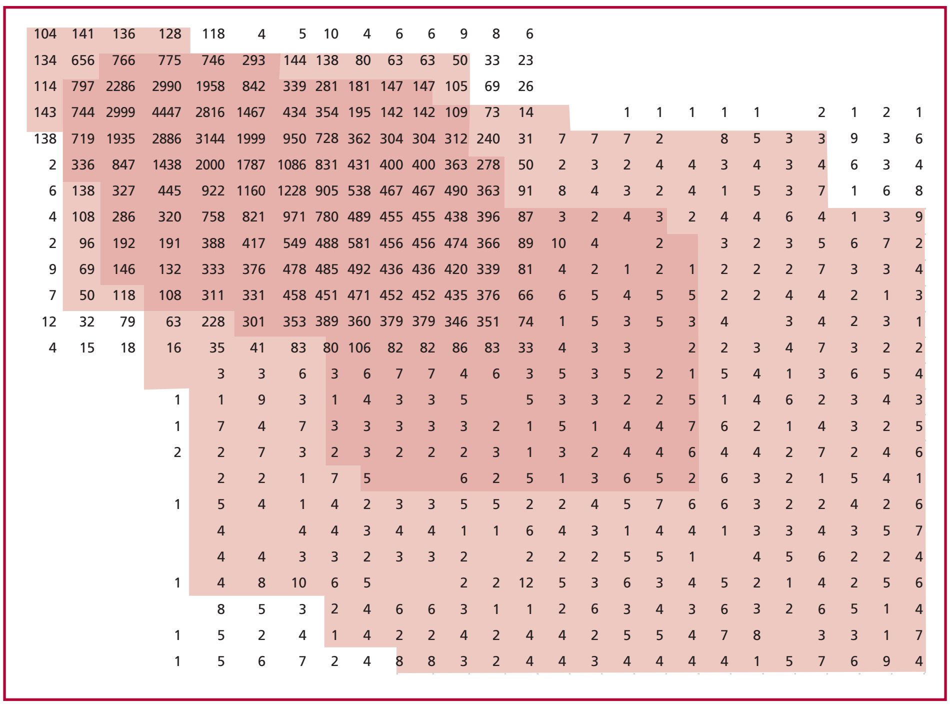

Fig. 4. Numerical attractor of a patient with sinus tachycardia and palpitations.

dictions, with 100% sensitivity and specificity values and kappa coefficient of 1.

Studies which classify the influence of risk factors, such as sex, age or day-night variation in the non-linear HRV parameters (24-30) are usually found in the medical literature. It has been observed, for example, that the circadian cycle changes during the transition phases after getting up and going to bed, increasing during the night, whereas non-linear HR fluctuations decrease with age. Other studies have analyzed HRV from mathematical theories with non-linear systems, developing new methodologies or evaluation indices of cardiac dynamics. (24-31) However, these studies have not yet shown their clinical applicability. (32, 33)

Conversely, the present methodology has exhibited its diagnostic and predictive ability in different population studies, achieving the highest sensitivity and specificity values, (20-22) as corroborated in the present study. This is possible thanks to the acausal perspective validating the method, which allows quantifying the cardiac state independently of its etiology, facilitating its follow-up over time with quantitative values that identify acute processes.

Other methods have been developed with the same acausal reasoning; for example, an assessment of cardiac dynamics was developed quantifying the spaces occupied by attractors, which are measured by means of the box-counting method, during 16 hours in patients admitted to the Postsurgical Intensive Care Unit. It has also been possible to predict in 15 hours cases of mortality through the analysis of other hemodynamic variables of interest in the Intensive Care Unit. (34)

It should be pointed out that the correct interpretation of cardiac behavior must be based on the dynamic assessment of its irregular nature, which when analyzed, for example, within the framework of the dynamical system theory, does not take into account the instances looking for the regularity established by the definition of homeostasis. The first investigations performed by Goldberger et al. (35) in the context of nonlinear dynamical systems, reveal that cardiac dynamics can be understood from three behaviors, the ones excessively random and the regular ones, both associated with pathological cases, and a third behavior intermediate between these two extremes, associated with health. In this same context, more reliable death predictors have been found by means of fractal dimensions in acute myocardial infarction patients, with ejection fraction below 35%. (36) However, the clinical applicability of these two last investigations does not yet reach fully satisfactory levels, requiring additional studies to confirm and in many cases adjust this applicability.

New methods also based on this new acausal perspective have been developed in other fields. Predictions of Intensive Care Unit mortality have been made using the dynamical system principles and set theory, (35) and mathematical differences have been established between normal and abnormal neonatal cardiac dynamics. (37) Moreover, neonatal cardiac dynamics has been analyzed in the context of sepsis predictions, laws, such as the Zipf-Mandelbrot law, have been applied to assess cardiac dynamics in adults, and recently, a mathematical law was developed for cardiac dynamical systems. Also, differences between normal and abnormal morphometries of arterial structure, as well as of cervical cells have been achieved applying geometrical analysis. (39). In addition, infectology predictions have been made particularly in CD4 lymphocytes in HIV patients, (40) and in public health for malaria outbreaks.

Limitations

The impossibility of having Holter monitoring data in the study population during consecutive days limits an improved analysis of the methodology ability to assess the evolution of cardiac dynamics.

Further studies are required to differentiate all types of cardiac arrhythmias using the methodology of the present study.

CONCLUSIONS

The self-organization of the geometric dynamic attractor underlying the methodology enabled the quantitative differentiation of normal and abnormal cardiac dynamic states, thus constituting a diagnostic aid applicable to clinical practice.

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Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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