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Mathematical physical diagnosis of neonatal cardiac dynamics based on dynamic systems and fractal geometry: Clinical validation study

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Abstract. A mathematical evaluation of neonatal cardiac dynamics was developed. The purpose of this study is to confirm the diagnostic capacity of this methodology to differentiate normal neonatal cardiac and cardiac pathologies through a blind study. For this, 80 Holter records were taken, 10 with evaluation within the limits of normality and 70 with different cardiac pathologies. The conventional evaluations were masked, and the maximum and minimum heart rates were taken every hour and the number of beats/hours, during 21 hours. These values were used to generate the neonatal cardiac attractor, then their fractal dimension was calculated, their occupation spaces were quantified in the fractal space of Box-Counting, determining their physic mathematical diagnosis. The spaces of occupation of neonatal chaotic cardiac attractors measured according to the number of frames occupied by the Box Counting method, differentiate states of normality from acute pathologies, achieving a sensitivity and specificity of 100%, as well as a kappa coefficient of 1. The This study confirms the diagnostic capacity of the methodology developed, from which it is possible to establish geometric differences between the chaotic attractors of normal neonatal cardiac dynamics and with disease.

1. Introduction

Dynamical systems theory analyzes the different geometric configurations that can generate attractors in a system as it evolves, additionally show information of predictable or unpredictable character of the system [1]. The space where the attractor is generated is called phase space, which can have more than two degrees of freedom. The attractors most studied are the chaotic attractors, which are characterized by their irregularity, which can be evaluated by fractal geometry [1,2].

The acquisition of electrical signals from the heart by electrocardiograms in neonates requires a process of acclimatization prior to the registration of the newborn [3]. In analogy to how it has proceeded with the registration of the ECG in adult, it is necessary to analyze the time [4] and the moment that guarantees the recording of heart rate variability (HRV). Neonatal heart rate records greater than 3 minutes are considered reliable [4]. However, there are few clinical studies performed in neonates, children and adolescents [5]. The causes may be due to the fact that the measurement of HRV requires multiple methodological processes, accompanied by a series of disagreements with these guidelines, when reproducing these methodologies and the significant comparisons of HRV results in different studies [5].

In light of these results, other types of studies in the neonatology area has been proposed in the context of mathematics and theoretical physics. The scope of these predictive and diagnostic methodologies [6-9] can be seen in adult chaotic cardiac dynamics studies based in the heart rate (HR) values of continuous and ambulatory ECG records. Within these results, it is worth highlighting the first predictions of mortality in patients admitted to the Post-Surgical Care Unit [10]. Among these methodologies is a law of exponential geometric character, through which it is possible to deduce all the possible discrete cardiac attractors, and the mathematical values associated with the states of normality-disease and the evolution between the two, through the evaluation of fractal occupation spaces [8,9].

Establish differences in four different behavioral states of the normal newborn (active awake, awake still, asleep in REM sleep and still asleep) [11] was possible through of a mathematical methodology. Also, empirical values of cardiac dynamics were taken at three moments before the sepsis episode to generate a neonatal chaotic attractor representative of each state, differentiating in a geometric manner the episodes prior to neonatal sepsis [12]. Subsequently, this type of measure was applied to the development of a diagnostic method of neonatal cardiac dynamics, finding that the space occupied by the attractor is smaller as it approaches the acute state revealing the clinical condition of the neonate [13-14].

After the foregoing, the purpose of this paper is to apply the methodology described above, to confirm its diagnostic capacity at the clinical level, through a blind study that includes normal cases and with different cardiac pathologies.

2. Methodology

2.1. Definitions

2.1.1. Delay map. In the present study, is a space of two dimensions that generates a type of attractor, whose geometric configuration shows the dynamics of the system, from the location of consecutive ordered pairs of the values the neonatal heart rate, in analogy even point with coordinates on the x and y (x, y) axis, which were consecutively linked with a line.

2.1.2. Fractal dimension. To find the fractal dimension of the neonatal chaotic cardiac attractor, Box-Counting definition was applied, which is calculated with the Equation (1),

$$D = \frac{Log N_1(2^{-(K+1)}) - Log N_2(2^{-K})}{Log 2^{k+1} - Log 2^{k}} = Log_2 \frac{N_1(2^{-(k+1)})}{N_2(2^{-k})} \tag{1}$$

Where: N1 is the number of squares containing the object contour, with the partition grid K; N2 the number of frames containing the object's outline with the partition grid K+1; K is to the degree of partition of grid 1; K+1 corresponds to the degree of partition of the grid 2 and D is the fractal dimension.

- Grid large frames (Kg): corresponds to a grid whose dimension is 5 beats/minute.
- Grid small squares (Kp): corresponds to a grid whose dimension is 10 beats/minute.

2.2. Process

Holter records were taken from newborns from 0 to 10 days old, from previous research databases of the Insight Group, each evaluated by an expert specialist.

The indications and the conventional diagnosis of each Holter were masked for the realization of the blind study. Based on the previously developed methodology [10], from the neonates Holter, the maximum and minimum of values HR were taken, recorded each hour for 21 hours, as well as the total number of beats per hour. These values systematized, in order to generate a sequence of values the HR by means of a random algorithm, taking as limits the maximum and minimum values established in each Holter, then the attractor of each dynamic was constructed in a map of delay (see definitions). In each generated attractor, two grids were superimposed, one of 5 and 10 beats/minute respectively, and the squares occupied by the attractor for each of them were counted. From these values, the fractal dimension was calculated with the simplified Box-Counting method (Equation 1).

2.3. Statistic analysis
To evaluate the reproducibility and clinical applicability of the methodology, clinical evaluation of each Holter registers was unmasked, in order to evaluate the diagnostic agreement between the mathematical method and the conventional evaluation. For this, sensitivity and specificity were calculated, with respect to conventional diagnosis by means of a binary classification, VP: corresponds to the number of neonates with clinical evaluation of acute disease and that are within the mathematical values corresponding to the same evaluation, FP: number of Holter records that mathematically behave as acute disease studies and whose clinical evaluation is within normal limits. FN: corresponds to the number of Holter records whose mathematical values to normality, but whose clinical evaluation corresponds to patients with acute disease. VN: corresponds to the number of Holter records clinically evaluated as normal and whose mathematical values correspond to normality.

The diagnostic agreement between the physic mathematical diagnoses and the conventional clinical evaluation was evaluated by establishing the Kappa coefficient through the following formula:

$$K=\frac{Co-Ca}{To-Ca} \quad \Rightarrow Ca=[(f_1 x C_1)/To]+[(f_2 x C_2)/To] \tag{2}$$

Being, Co: the number of matches observed, that is, number of patients with the same diagnosis according to the proposed new methodology and the Gold Standard; To: the totality of cases evaluated, including normal and with acute disease; Ca: Matches attributable to chance, whose variables are:

- f_1: is the number of neonates with mathematical values within the limits of normality.
- C_1: is the number of neonates diagnosed clinically within normality.
- f_2: the number of neonates with mathematical values associated with acute illness.
- C_2: the number of neonates diagnosed clinically with acute disease.
- T_0: the total number of normal neonates and with acute disease.

2.4. Ethical aspects
The present study satisfy ethical, scientific, technical and administrative norms for the investigation in health, based on the resolution No. 008430 of 1993 [24], specifically in the title 11 referring to the investigation in human beings, when being included in the category of research without risk, because physical calculations are made on the results of non-invasive clinical practice exams, coming from previous research, protecting the integrity and anonymity of the participants. In addition, this work is based on the ethical principles for medical research in humans of the Declaration of Helsinki of the World Medical Association, the Nuremberg Code and the Belmont report.

3. Results
The mathematical evaluation of some normal and pathological neonatal Holter can be seen in Table 1. The fractal dimension value of the normal cardiac attractors varied between 1.18587 and 1.82491, with each attractor occupying a space that varied between 101 and 146 frames with the grid Kg and between 273 and 417 on the grid Kp (see Table 1).

The pathological cardiac attractors (Figure 1) presented a fractal dimension that varied between 1.6781 and 1.9587, occupying between 45 and 91 squares with the Kg grid and 144 and 321 squares with the Kp grid (see Table 1).

The blind study conducted in the present study showed a sensitivity and a specificity of 100% as well as a kappa coefficient of 1.

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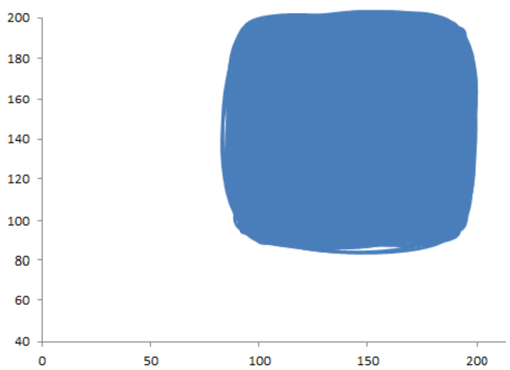
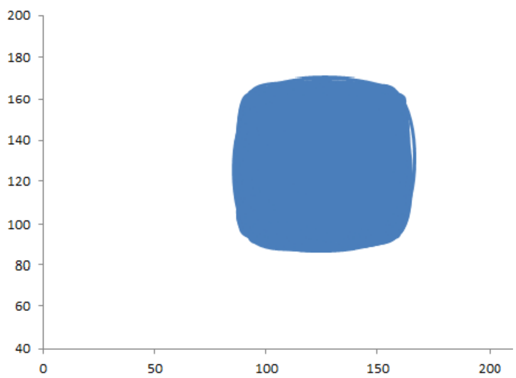
Table 1. Mathematical evaluation of 20 of the Holter of neonates evaluated, Kp and Kg, are the values of occupied space by attractor in each grid respectively. Df: fractal dimension.

No.	Mathematical Diagnosis	Kp	Kg	DF
1	Normal	417	136	1.6164
2	Pathological	158	49	1.6891
3	Normal	375	137	1.4527
4	Pathological	208	58	1.8425
5	Pathological	241	62	1.9587
6	Normal	273	120	1.1859
7	Pathological	187	51	1.8745
8	Pathological	316	84	1.9115
9	Normal	295	113	1.3844
10	Normal	282	107	1.3981
11	Normal	350	101	1.7930
12	Pathological	144	45	1.6781
13	Normal	371	146	1.3455
14	Pathological	321	91	1.8186
15	Pathological	285	89	1.6791
16	Normal	361	138	1.3873
17	Pathological	289	80	1.8530
18	Normal	317	112	1.5010
19	Normal	372	105	1.8249
20	Pathological	277	80	1.7918



(a)



(b)

Figure 1. Attractor for normal dynamic (a), and pathological dynamic (b).

4. Discussion

This is the first work that confirms the reproducibility and clinical applicability of the diagnostic methodology designed to evaluate neonatal cardiac dynamics from 80 Holter records. As has been done in other studies, the spaces occupied by the normal and abnormal cardiac neonatal chaotic attractors are completely differentiable, as well as their states of evolution towards one of these two states in the context of the theory of dynamic systems and fractal geometry. In mathematical terms, the distance from normality of the neonatal chaotic cardiac dynamic is given by the decrease of the Kg grid values. This evaluation of cardiac dynamics, simplifies any statistical study, leaving only the information relevant to the specialist, whose timely action can prevent adverse situations.

Additionally, the context in which the present methodology was developed reveals that regardless of whether the cardiac dynamic is adult or neonatal, it has the capacity to establish more direct quantitative differences, reflected in effective diagnosis. The generalized space of Box Counting, in which the spaces occupied by the attractors is quantified, gives this methodology a universal character, as they have been done in other works developed in physics [14]. The simplicity of the methodology lies in the fact that it is not based on the studies carried out because of the HRV. Studies conducted on the basis of neonatal HRV have detected some adverse changes that imply mortality risk for neonates such as sepsis [13,15], however, controversies between the guidelines of these methodologies previously applied in adult cardiac dynamics. Reduce the confidence of applying the study in the clinic, but not before having gone through further studies in a greater number of infants.

In the medical literature other works have been found that, being supported by theoretical physical and mathematical bases, such as the study developed in the behavioral states of the neonate, since it is possible to characterize the reason for heart rate patterns [16]. The study found that measurements of the standard deviation of the RR intervals (SDNN) tend to increase from S1 to S4 (S1 being the still sleeping state, S2 active sleeping, S3 awake still and S4 awake active), while the mean deviation quadratic of successive differences (RMSSD) tends to decrease. This study reveals that HRV measures can help to identify all behavioral states with the exception of S4 [17]. The behavioral states of the neonate associated with the HR patterns were the source for the development of a new methodology, which analyzed this relationship from the context of the fractal geometry and the dynamic systems of the attractors generated for the four behavioral states, establishing more objective differences due to the spaces occupied by the attractors in the generalized space of Box Counting [18].

Another study developed from the perspective of the dynamical systems theory and fractal geometry, in relation to the implications of the behavior of cardiac dynamics due to episodes of sepsis and analogous to these [13], achieved through the spaces occupied by the attractors of 6 and 3 hours before the outcome of sepsis, establishing predictions based on the quantification of the space occupied by the attractors, as well as the totality of possible normal neonatal cardiac dynamics and with sepsis or analogous behavior to it, contributing to the improvement of measures previous [13].

The perspective that sustains the present investigation can be observed in other studies, in which new diagnostic and predictive methodologies have been designed, applied for example to evaluate the arterial and cellular structures [19,20]. Likewise, methodologies have been developed for immunology [21], the prediction of epidemics [22] and CD4 T lymphocytes in patients with HIV/AIDS [23]. These results show that this type of research can provide solutions in all fields of medicine, taking this discipline to the predictive level of physics.

5. Conclusions

In the present work, a confirmation of the diagnostic capacity of a mathematical methodology based on the theory of dynamic systems and fractal geometry for the evaluation of neonatal cardiac dynamics was made, based on the analysis of 80 holter registers. A sensitivity and specificity of 100% was achieved as well as kappa 1 coefficient with respect to the conventional diagnosis, which was taken as Gold standard, it was also confirmed that neonatal cardiac attractors tend to decrease in size as the dynamics evolve to more acute states, confirming the previous results.

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