Diagnostic methodology for the neonatal cardiac system based on dynamic systems

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ABSTRACT

Fractal geometry and nonlinear systems have shown to be useful to diagnose and predict the behavior of cardiac dynamics in adults with promising applications, but studies in neonates are lacking. The objective of this study is to apply a chaotic methodology to diagnose heart dynamics of neonates. 70 electrocardiographic records were taken from newborn patients, 10 normal and 60 pathological. Then, the minimum and maximum heart rates as well as the number of heartbeats/hour were taken for at least 21 hours; a sequence of heart rates was generated and, based on that sequence, chaotic attractors were constructed. Their fractal dimension was calculated as well as their occupation in the Box-Counting space and the mathematical diagnosis was determined based on the limits established in the induction. A blind study was developed for statistical validation against the Gold Standard diagnosis. It was found that the spatial occupation of neonatal cardiac chaotic attractors in the Box-Counting fractal space allowed the differentiation between normality and disease, reaching the highest values of sensitivity, specificity and diagnostic concordance against Gold Standard. Hence, it is concluded that fractal geometry allows

to diagnose and differentiate normal from abnormal heart dynamics of neonates independent of the clinical scenarios, corroborating its utility at clinical level.

Keywords: newborn; heart rate; fractal; nonlinear systems.

Introduction

The dynamical systems theory studies the state and evolution of systems. These can be evaluated through attractors, which represent predictable or unpredictable systems and their evolutionary trends (Devaney, 1992). The trajectory of the systems can be geometrically represented in a delay map. This is an abstract space in which it is possible to define the behavior of a system, giving rise to three types of attractors: punctual, cyclical and chaotic. The latter exhibits an irregular trajectory, which can be measured from fractal geometry since this geometry allows the quantification of irregular objects (Devaney, 1992); (Peitgen, 1992); (Mandelbrot, 2000), and that by their characteristic feature they cannot be evaluated with Euclidean measurements.

Diagnostic methods of neonatal cardiac dynamics have been based on methodologies such as the measurement of heart rate variability (HRV) (Fairchild & O'Shea, 2010; Castro, Hoyos, Londoño y Mercado, 2017). Research has shown a significant decrease of HRV and presence of transient decelerations in the course of neonatal sepsis (Lake, Richman, Griffin & Moorman, 2002; Jerez, Palacios y Castro, 2018). Also, it has been suggested that the normal values of HRV in newborns are not widely available and that this problem can be attributed to the lack of standardization of the different methods (Oliveira et al., 2019). Considering the characteristics of heart rate, it has been possible to predict unfavorable conditions associated with neonatal mortality, such as sepsis (Fairchild & O'Shea, 2010); (Griffin, Lake & Moorman, 2005). The investigations carried out in this respect, have allowed to understand the neonatal cardiac system; however, even its clinical applicability is discussed.

On the other hand, physical-mathematical theories have allowed the development of diagnostic methodologies with clinical applicability (Rodríguez, 2010a); (Rodríguez, 2011). A diagnostic methodology of adult heart dynamics was developed based on the proportions of entropy (Rodríguez, 2010a) and an exponential mathematical law (Rodríguez, 2011) able to differentiate normality of pathological states based on the occupation of the attractors in a fractal space, which its clinical applicability was confirmed in patients with arrhythmias (Rodríguez et al. 2013a) and in a study with 115 electrocardiographic records (Rodríguez et al. 2013b).

In this context, a study (Griffin & Moorman, 2001) was developed, in which, based on information from a normal case, and two states 3 hours and 6 hours prior to the appearance of neonatal sepsis, it was possible to evaluate the mathematical behavior of the cardiac dynamics of neonates with sepsis and with conditions similar to sepsis (Rodríguez et al., 2014a) Then, a diagnostic and predictive methodology for neonatal chaotic cardiac dynamics was developed, through which it is possible to differentiate disease normality, from the spatial occupation of cardiac attractors in the Box-Counting space (Rodríguez et al., 2015a). It was evidenced that as the spatial occupation decreases, the cardiac system approaches clinical deterioration or states of aggravation; likewise, the evolution and severity of the pathologies were evaluated (Rodríguez et al., 2015a). Its clinical usefulness and diagnostic capacity was corroborated in a subsequent study (Rodríguez et al., 2016; Castro, 2018; Arrázola, Valdiris y Bedoya, 2017).

The purpose of the present investigation is to confirm the clinical applicability and to refine the methodology, in the framework of a blind study with 70 normal and 60 abnormal neonatal cardiac dynamics.

Methods

Definitions

Delay map: space where the dynamics of the system are graphically evidenced and consecutive ordered pairs of a specific variable are located, in this case heart rate (HR), as coordinates (x, y), consecutively joining the points to obtain a line.

Fractal dimension of Box Counting: it is calculated with equation:

$$\boldsymbol{D} = -\frac{\boldsymbol{LogN_1}\left(\boldsymbol{2^{-(j+1)}}\right) - \boldsymbol{LogN_2}\left(\boldsymbol{2^{-j}}\right)}{\boldsymbol{Log2^{j+1}} - \boldsymbol{Log2^{j}}} = \boldsymbol{Log_2} - \frac{\boldsymbol{N_1}\left(\boldsymbol{2^{-(j+1)}}\right)}{\boldsymbol{N_2}\left(\boldsymbol{2^{-j}}\right)} \quad Equation\ 1$$

Where: N1 corresponds to the number of frames containing the object's outline with the partition grid k; N2 corresponds to the number of frames that the contour of the object contains with the partition grid (k + 1); k corresponds to the degree of partition of grid 1; - (k + 1) corresponds to the degree of partition of grid 2; and D corresponds to the fractal dimension.

Population

A total of 70 neonatal electrocardiographic records were analyzed from Insight group's previous research databases, 10 normal and 60 pathological, evaluated by an expert electrophysiologist.

Procedure

The maximum and minimum values of heart rate of the electrocardiographic records selected for the induction and the total number of heartbeats/hour during each hour for a minimum of 21 hours were taken. These values were introduced in a previously developed software and a pseudo-random sequence was generated from a pseudo equiprobable algorithm. Next, the delay maps and the attractors were constructed. Then, two grids of 5 and 10 heartbeats/minute were superimposed to account for the squares occupied by the attractors in each one. Subsequently, the fractal dimension was calculated with the Box-Counting method, using Equation 1 for this. These results were evaluated according to the previously established normality / disease limits, thus determining its mathematical diagnosis.

Statistical analysis

The mathematical methodology and the conventional clinical diagnosis, taken the latter as the clinical Gold Standard, were compared. For this, the clinical results of the records not included in the induction were unmasked. Sensitivity and specificity were calculated from a binary classification, in which the true positives corresponded to the electrocardiographic records diagnosed as abnormal by the mathematical method and the conventional clinical diagnosis, the false positives corresponded to the electrocardiographic records with mathematical behavior of abnormality and clinical diagnosis of normality, the false negatives corresponded to the electrocardiographic records clinically diagnosed as abnormal and with mathematical results indicating normality, and the true negatives represented the electrocardiographic records diagnosed as normal by both the mathematical method and the conventional clinical diagnosis.

The agreement between the mathematical and the conventional clinical diagnosis with the Kappa coefficient was evaluated by means of the following formula:

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

Where:

Co: represents the number of matches observed, that is, the number of patients with the same diagnosis according to the mathematical methodology and the Gold Standard.

To: total of cases studied, both normal and pathological.

Ca: concordances attributable to chance, calculated with the following equation:

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

Where,

f1: represents the number of cases that present mathematical values suggesting normality.

C1: are patients diagnosed as normal by the clinical expert

f2: is the number of cases with mathematical values associated with abnormality. C2: are patients with a conventional clinical diagnosis of disease.

To: represents the total of normal and pathological cases.

Ethical aspects

The present study complies with the ethical, scientific, technical and administrative norms for health research, set in resolution No. 008430 of 1993, specifically in title 11, regarding research in human beings; it is included in the category of minimum risk research, since mathematical calculations are made based on the results of non-invasive clinical practice exams, protecting the integrity and anonymity of the subjects. Additionally, the work is subject to 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.

Results

The fractal dimensions of the normal registers presented values between 1.704 and 1.959, occupying between 168 and 302 frames with the grid Kg (10 heartbeats/min), and between 653 and 1047 in the grid Kp (5 heartbeats/min) (table 1). The pathological records presented a fractal dimension that varied between 1.611 and 1.9118, occupying between 55 and 95 frames with the grid Kg, and between 168 and 314 frames with the grid Kp.

After unmasking the conventional diagnoses, we selected the cases that presented acute disease, and compared them with the normal cases by means of the binary classification table, achieving a sensitivity and a specificity of 100%, as well as a Kappa coefficient of 1.

DISCUSSION

This is the first work in which a diagnostic and predictive mathematical methodology of neonatal cardiac dynamics is applied, corroborating its clinical usefulness and its ability to obtain objective and reproducible diagnoses in a timely manner, differentiating normal and pathological states from clear mathematical parameters of neonatal cardiac systems, through the spatial occupation of chaotic attractors, which decreases with the aggravation or deterioration of cardiac systems. The highest values of sensitivity and specificity were reached, as well as the highest level of diagnostic agreement, regardless of causal or other considerations.

It was observed that the limits of normality and abnormality established allowed to differentiate quantitatively both types of dynamics. The above suggests that the presented method would be a diagnostic aid tool in the clinic, capable of providing objectivity and diagnostic precision, which could even establish the level of severity of diseases categorized with the same level of severity according to conventional clinical parameters, both in the outpatient and inpatient context. The results exhibit behaviors like those obtained in adults; in both cases, the attractors of normal dynamics exhibit greater occupation in the fractal space of Box-Counting (Rodríguez et al., 2013a); (Rodríguez et al., 2013b); (Rodríguez et al., 2015a).

Heart rate variability and RR interval are evaluated in electrocardiographic tracings and their decrease is related to alterations in the cardiac system (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996); (Bauer et al., 2006). Investigations based on this variability have associated their alterations to several pathologies (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996); (Bauer et al., 2006); (Harris, Stein, Fung & Drew, 2014); (Kazmi et al., 2016); (Maestri et al., 2007); (Ahmad, Tejuja, Newman, Zarychanski & Seely, 2009); (Buchan, Bravi, Seely, 2012). The analysis of the heart rate has been carried out in the adult (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996); (Bauer et al., 2006); (Harris, Stein, Fung & Drew, 2014); (Kazmi et al., 2016); (Maestri et al., 2007), fetal (Gonçalves, Pinto, Silva, Ayres-de-Campos & Bernardes, 2016) and neonatal (Leeuwen et al., 2012) populations. In newborns, associations have been found between abnormal HRV and unfavorable clinical conditions such as sepsis (Fairchild & O'Shea, 2010); (Griffing, Lake & Moorman, 2005) however, more studies are required to corroborate its clinical applicability. In contrast, the present study establishes a quantitative method, with demonstrated clinical applicability (Rodríguez et al., 2015a); (Rodríguez et al., 2016) and predictive character.

In the context of the dynamical systems theory, a prediction has been made (Rodríguez et al., 2014) regarding the development of sepsis based on the spatial occupation of cardiac chaotic attractors 3 and 6 hours prior to this outcome. Besides, the totality of normal cardiac dynamics, as well as those representative of sepsis and sepsis-like states were established (Rodríguez et al., 2014a). In another study, the neonatal behavioral states were differentiated by the spatial occupation of the attractors in the Box-Counting space (Rodríguez et al., 2014b).

The acausal physical-mathematical perspective that underlies the present work is based on the inductive method of modern theoretical physics (Einstein, 1983) where, with few cases, it is possible to generalize phenomena, regardless of population or statistical considerations. From this perspective, diagnoses of cellular morphometry have been developed (Rodríguez et al., 2010b) as well as predictions in immunology (Rodríguez et al., 2013c), public health (Rodríguez et al., 2010c) infectiology (Rodríguez et al., 2013d) and mortality in the Intensive Care Unit (Rodríguez et al., 2015b).

Conflicts of interest: the authors declare no conflicts of interest.

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Table 1. Mathematical results of 15 of the 70 Holter studies evaluated, with their conventional diagnosis and the values of the occupation spaces of the attractors with the Kg grid.

Case	Holter	Attractor		
	Conventional diagnosis	Kg[a]	Kp[b]	Fd[c]
1	Normal	302	1047	1,794
2	Normal	274	986	1,847
3	Normal	267	870	1,704
4	Normal	215	830	1,949
5	Normal	214	827	1,95
6	Normal	168	653	1,959
7	Pathological	95	314	1,725
8	Pathological	89	291	1,709
9	Pathological	71	245	1,787
10	Pathological	64	204	1,672
11	Pathological	62	229	1,885
12	Pathological	62	224	1,853

13	Pathological	59	222	1,912
14	Pathological	56	182	1,7
15	Pathological	55	168	1,611

aKg grid: large squares; bKp: small squares and Fd: fractal dimension.