Advances in Mechanics
Volume 9, Issue 3, 2021
Page 1014-1024

Design of a Holter Monitor for the Diagnosis of Neonatal Cardiac Dynamics

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Received: *2 March 2021*; accepted: *01 June 2021*; Published: *10 August 2021*

Abstract: Every year, approximately 4 million neonatal deaths are reported, and approximately 98% of which occur in developing countries, where the risk is 6-fold higher than that in developed countries. For this reason, methods for the early detection and diagnosis of potentially life-threatening alterations are needed to avoid these outcomes. Recently, a methodology for the assessment of neonatal cardiac dynamics has been developed, which helps differentiate normal from abnormal cardiac dynamics by counting the spaces occupied by the chaotic cardiac attractors. In order to automate this method, a Holter monitor for newborn infants was designed and built, along with a software tool that performs cardiac function tests. Finally, tests were performed using the Holter monitor and software developed to assess the cardiac dynamics of 100 patients, which validated the proper functioning of the devices designed. In this way, the potential usefulness of this technological development is associated with a decrease in neonatal mortality as it allows for the detection of alterations in cardiac dynamics through an ECG (electrocardiogram) device and a mathematical method that is independent of the clinical assessment.

Keywords: Holter monitor; cardiac dynamics; neonatal

1. Introduction

Over the last decade, public health programs have been developed to reduce early childhood mortality [1]. Neonatal mortality rate is rather disturbing and is still high in different countries [1]. Approximately 60% of neonatal deaths occur during the first week of life, particularly, within the first 24 hours [1]. Some of the primary causes associated with this outcome are premature births, congenital malformations, infections and perinatal complications, low birth weight, and labor complications [1, 2]. Perinatal asphyxia causes approximately 7 deaths per 1,000 live births in developing countries, whereas this ratio falls to approximately 1 death per 1,000 live births in developed countries [2].

In Colombia, the neonatal mortality rate is 9.8 per 1,000 live births; however, this rate is actually 8.6 in urban and 12.8 in rural areas [3]. This rate was observed to be 3.6-fold higher among infants born to women aged 40–49 years than among those born to women aged <20 years [4]. By 2000, 23 perinatal and 14 neonatal deaths per 1,000 inhabitants were reported [2]. According to Colombian

surveys on demographics and health, 14,767 perinatal deaths occurred in Colombia in 2000. By 2005, perinatal mortality rates decreased mainly in the Eastern Colombia and Bogotá. However, these figures are still alarming [5].

The places with the highest perinatal mortality rates are as follows: Chocó (39 per 1,000), San Andrés y Providencia (25 per 1,000), Caldas (25 per 1,000), Huila (22 per 1,000), Vaupés (21 per 1,000), Cesar (20 per 1,000), Santander (20 per 1,000), and Córdoba (20 per 1,000) [6]. Given the heavy medical, social, and economic burden associated with neonatal mortality, tools are necessary for the early detection of potentially life-threatening alterations in newborn babies and for the subsequent assessment of the efficacy of medical interventions aimed at decreasing neonatal mortality.

In order to address this problem, different studies suggesting devices for the prevention and monitoring of various alterations that potentially affect newborns have been developed based on assessment methods of potentially life-threatening diseases or complications in newborns. An example of this is the analysis of heart rate variability (HRV), as this approach has been suggested as a tool for predicting undesired events in adults.

HRV studies the variation of R-R intervals occurring between consecutive heartbeats over time [7-9]. In adults, for example, different studies have proved the usefulness of this measure as a predictor of sudden arrhythmic death syndrome [10], heart failure mortality [11], acute myocardial infarction [12], arrhythmia, and post-infarction death [13, 14]. This measure has also been used for the prediction of certain adverse outcomes in sepsis [15-17]; however, its predicting capacity does not reach satisfactory levels as an abnormal value does not always imply an adverse event.

On the other hand, its use in neonatology has allowed for the prediction of adverse outcomes such as sepsis-related deaths [7-9, 18]. Other studies have also proven that this approach may allow for the differentiation between the cardiac dynamics of pre- and full-term newborns in terms of their time, frequency, normalization, and chaos domains as statistically significant differences have been observed for all the variables studied in these two populations. These studies concluded that cardiac behavior is less complex in preterm populations than in full-term populations [19].

HRV study was performed with the aid of devices that analyze the electrical signals of the heart, such as Holter monitors; based on this, transient rhythm changes and cardiac alterations that could not be identified in a short record can be identified [20, 21]. However, one of the challenges associated with the interpretation of these records is that it greatly depends on the experience of the professional reading said records.

For this reason, and in line with the abovementioned information, one of the limitations of the methods used to study HRV is that normal cardiac dynamics exhibit a variable and irregular behavior, as described by Goldberger [22], instead of a regular pattern, as the traditional homeostasis concept suggested. Moreover, studies based on HRV analysis aim at establishing normal values, among which, a variable is self-regulated. However, this procedure requires the validation of extensive populations to simplify the comparison of parameters in different clinical contexts [23, 24]. On the basis of this statement, the design of new research strategies for cardiac dynamics supported by the theory of dynamic systems has been put forward [22, 25], which would allow for the prediction and quantification of changes in system variables over time [26]. One of them is the method developed by Rodríguez et al. [27], who succeeded in diagnosing normal neonatal cardiac dynamics and dynamics with different pathologies based on the spaces occupied by neonatal chaotic cardiac attractors in the Box-Counting space [28]. A study also evidenced the capacity of this method to assess alterations in neonatal cardiac dynamics before the occurrence of clinical manifestations of neonatal sepsis, establishing differences in cardiac dynamics 3 and 6 hours before sepsis development. Thus, this method has become a preventive measure of clinical application [29].

From this theoretical physics approach, other diagnostic methods of clinical application have been developed to characterize fetal cardiac dynamics through the application of the Zipf-Mandelbrot law [30] and the S/k equation of Boltzmann-Gibbs entropy [31], using fetal monitoring data for such purposes. There are other diagnostic methods that assess cardiac dynamics in adults,

supported by an exponential mathematic law [32], the Zipf-Mandelbrot law [33], the probability theory, and entropy ratios [34, 35].

The use of these new tools may be particularly useful in predicting undesirable outcomes associated with pathologies with a high mortality among neonatal populations, such as neonatal sepsis. Therefore, the use of a Holter monitor that brings together new predictive methods along with the capacity to obtain a diagnosis, both reproducible and independent of the reader, should be implemented. Thus, patients could be treated immediately if needed.

Hence, this paper describes the design of a functional prototype of a Holter-type electrocardiograph applicable to neonatal telemedicine that can store, process, and display signals; incorporates a new diagnostic mathematical method based on the dynamic systems theory for the assessment of devices; and allows for the remote monitoring of patients.

These technological developments provide the scientific community and health professionals with tools for the diagnosis of neonatal cardiac dynamics and the performance of objective follow-ups that enable physicians to objectively assess newborns and conduct interventions aimed at reducing neonatal mortality. This will result in healthcare improvements in the most-affected regions of Colombia.

Likewise, we expect to provide opportunities for the creation of solutions that promote the development of new technologies that improve the quality of life of people without continued access to healthcare who cannot travel to other cities through the remote monitoring of patients' health while considerably reducing the medical costs.

2. Materials and Methods

The study comprised three stages: in the first stage, the clinical application of a physicomathematical method was validated through its manual application in a study of diagnostic concordance between the physicomathematical method and the Gold Standard, defined as the diagnosis made by a neonatologist based on the Holter monitor records. In the second stage, the functional prototype of the Holter monitor was developed, along with the monitoring software that automates the method based on the dynamic systems theory and fractal geometry. These stages were developed simultaneously. In the third stage, the accuracy of the Holter monitor and software was tested by assessing different cardiac dynamics with a simulator and comparing them with the results obtained for the same dynamics manually.

2.1 Stage 1

This is a physicomathematical and descriptive study, which aimed at determining quantitative differences between continuous ECG and/or Holter monitor records of healthy newborns and newborns with different pathologies, regardless of causal considerations. Records were obtained from previous databases of the Insight group.

In total, 100 continuous ECG and/or Holter monitor records from 20 newborns with normal clinical diagnosis and 80 newborns diagnosed with different pathologies were analyzed.

Analysis plan

Key definitions for the study

Phase space: It is the space of two or more dimensions, in which the geometrical attractor representing the behavior of the dynamic variables of a system is laid out, representing the ordered pairs for the values of a dynamic system variable occurring over time.

Fractal: Irregular object or irregularity of said object.

Fractal dimension: Dimensionless measure that quantifies the degree of irregularity of a given object. For this study, the fractal dimension was used according to the Box-Counting method.

Box-Counting fractal dimension (1):

$$D = \frac{LogN\left(2^{-(K+1)}\right) - LogN(2^{-K})}{Log2^{K+1} - Log2^{K}} = Log_2 \frac{N\left(2^{-(K+1)}\right)}{N(2^{-K})} \quad (1)$$

Where D corresponds to the fractal dimension, N is the number of boxes occupied by the object, and K represents the partition degree of the grid.

Procedure

First, clinical diagnoses were masked in order to establish a blind study. Then, the maximal and minimal heart rates were recorded every hour as well as the total number of heartbeats/hour for at least 21 hours. A registration format was designed to record this data, and each input was assigned an identification number.

Data were imported into previously developed software, which generates a pseudorandom algorithm with the aim of simulating the beat-to-beat heart rate dynamics within the ranges provided by the continuous recording. Based on these data, the ordered pairs of a heart rate were plotted against the next heart rate in time, in the phase space, thus creating a chaotic attractor for each of the dynamics. Subsequently, the fractal dimension of the attractor was estimated using the Box-Counting method by overlapping two grids of different sizes and counting the spaces occupied by the attractor on each grid.

In this way, neonatal cardiac dynamics were analyzed for at least 21 hours in each case, identifying the spaces occupied by the attractor and estimating the fractal dimension. Then, the values estimated for the healthy group were compared with the ones estimated for newborns with acute diseases (including neonatal sepsis) to determine mathematical differences between both dynamics using the Box-Counting method. Reference values were identified to differentiate normal dynamics from dynamics associated with acute diseases in a mathematical, objective, reproducible, and clinically applicable way.

Statistical analysis

For the statistical analysis, diagnoses performed by a specialized expert physician based on conventional clinical parameters were considered the Gold Standard. In this phase, diagnoses were unmasked, and the results obtained with the mathematical method were compared with those obtained by conventional clinical diagnosis, calculating both specificity and sensitivity. These measures were performed using a binary classification, in which true positives were the number of newborn infants clinically diagnosed within abnormality limits and whose results lay within the mathematical values for the same diagnosis; false positives were the number of neonatal cardiac dynamics that behaved as abnormal results from a mathematical perspective but whose clinical diagnosis yielded normal results; false negatives were the number of neonatal cardiac dynamics clinically diagnosed as pathological but whose mathematical values matched those of normal dynamics; and finally, true negatives were defined as the number of neonatal cardiac dynamics that were clinically diagnosed as normal and whose mathematical values also suggested normality.

To assess the concordance between the physicomathematical assessment and conventional clinical diagnosis, a kappa coefficient was estimated based on the following equation:

$$K = \frac{Co - Ca}{To - Ca} \quad (2)$$

Co: the number of concordances observed, that is, the number of newborn infants with the same diagnosis according to the new proposed method and Gold Standard.

To: the total amount of observations, that is, the total number of normal and acute cases.

Ca: concordances attributed to chance, which were estimated based on equation 3.

$$Ca = \left[\left(f_1 x C_{1/To}\right)\right] + \left[\left(f_2 x C_2\right)/To\right] \quad (3)$$

Where: f1 is the number of newborns whose mathematical values were within normal limits; C1 is the number of newborns clinically diagnosed within normal limits; f2 is the number of newborns presenting mathematical values associated with acute heart dynamics; C2 is the number of newborns clinically diagnosed with acute heart dynamics, and T0 is the total number of normal cases and acute heart dynamic cases.

2.2 Stage 2

The Holter monitor and platform-software allowing for the automation of the method were developed in this stage. This stage occurred simultaneously with stage 1 and comprised 3 phases:

Phase 1: Revision and documentary analysis

In this phase, publications about neonatal cardiac dynamics were reviewed, along with the documents regarding monitoring platforms using Holter devices and predictive systems for diagnosis based on neonatal heart rates. Subsequently, a comparative analysis of the data collected was performed, followed by a selection of variables and relevant aspects for the design of the software and the Holter device.

Phase 2: Design of the software to monitor ECG signals in newborns

During this phase, the platform was designed and different types of profiles were defined. The patient, clinic, monitoring and diagnosis user profiles were defined, as well as the services to be provided through the platform. Computing architecture and processes were then selected. Finally, the platform was implemented and functional tests were performed.

Phase 3: Design, development, and implementation of the Holter monitor

First, the Holter device was designed and built; the device works with ECG technology to monitor electrical heart activity accurately. This phase also included the identification of the hardware requirements needed to implement the previously designed software. Following selection of the hardware components necessary to activate the functions of the neonatal Holter monitor and the platform, the device was assembled. Finally, tests were run to verify that the device and software worked correctly.

2.3 Stage 3

During the final stage, the values obtained from the assessment of the neonatal cardiac dynamics using the Holter device and software were compared with those obtained through the manual application of the method. Moreover, tests were performed with the Holter device and software by means of a simulator. This stage is essential to confirm the proper functioning of all the integrated technological components and to ensure maximal accuracy of algorithms.

2.4 Ethical aspects

This study was performed pursuant to the ethical, scientific, technical, and administrative rules for health investigation set forth in resolution no. 008430 of 1993, specifically under section 11, regarding human research. This research is included within the minimal risk category as mathematical estimations are performed based on the results of noninvasive tests occurring within

the clinical practice, and the integrity and anonymity of subjects are protected. In addition, this study follows the ethical principles for human medical research set forth in the declaration of Helsinki of the World Medical Association, Nuremberg code, and Belmont report.

3. Results

Table 1 shows the clinical assessment of each continuous and/or outpatient ECG record performed in newborns with normal and pathological results. The spaces occupied by normal neonatal cardiac attractors when overlapping the Kg grid ranged between 317 and 405, and the spaces occupied when overlapping the Kp grid ranged between 1,098 and 1,536. The fractal dimension ranged between 1.658 and 1.928. The spaces occupied by pathological neonatal cardiac attractors when overlapping the Kg grid ranged between 25 and 234, and the spaces occupied when overlapping the Kp grid ranged between 90 and 910. The fractal dimension ranged between 1.655 and 1.966.

These results were compared with the ones previously reported by Rodríguez et al [27], according to whom, neonatal attractors occupying a space >98 when overlapping the Kp grid are associated with normality mathematical values, whereas lower values are associated with acute disease. Based on this, it is possible to observe that the neonatal continuous and/or outpatient ECG within normality limits assessed conventionally lay within the characteristic mathematical values of normality. On the other hand, in the case of ECG record no. 11, when counting the spaces occupied by the cardiac attractor after overlapping the Kp grid, an occupation value <98 was obtained, suggesting acute neonatal heart dynamics.

These results evidence the diagnostic ability of the method as the spaces occupied by the attractors determine the dynamics state of the newborn infant over time. In addition, the blind study performed herein evidences the reproducibility and clinical applicability of the method in the clinical context as it yields sensitivity and specificity values of 100% as well as a kappa coefficient of 1.

Table 1. Mathematical results from 18 of the 100 ECG records assessed, along with their conventional assessment and the values corresponding to the spaces occupied by attractors with the Kg grids: big squares, Kp grids: small squares, and fD: fractal dimension.

No.	Conventional assessment	Age:	Kg	Kp	fD
1	Study shows values within normal limits.	10 days	405	1,536	1.923
2	Study shows values within normal limits.	2 days	371	1,412	1.928
3	Study shows values within normal limits.	1 day	348	1,098	1.658
4	Study shows values within normal limits.	1 day	317	1,145	1.853
5	Isolated episodes of ventricular tachyarrhythmia. Study shows values within normal limits.	1 day	234	910	1.959
6	Study shows values within normal limits.	1 day	143	512	1.840
7	Occasional atrial ectopy. Study shows values within normal limits.	1 day	127	400	1.655
8	Isolated sinus arrhythmia. Study shows values within normal limits.	0 days	110	347	1.657
9	Heart failure. Frequent atrial ectopy.	1 day	97	321	1.727
10	Sustained monomorphic ventricular tachycardia.	2 days	87	340	1.966
11	Cardiac murmur. Sinus rhythm with frequent ventricular ectopy.	7 days	73	271	1.892
12	Atrioventricular re-entrant tachycardia.	2 days	65	237	1.866
13	Mobitz II atrioventricular block.	1 day	41	159	1.955
14	Heart failure. Frequent atrial ectopy.	0 days	33	113	1.776

15	Long QT syndrome.	1 day	29	106	1.870
16	Congenital complete atrioventricular block.	0 days	25	90	1.848

4. Discussion

This is the first study that develops a Holter device and software that allows for the automation of the diagnostic method developed by Rodríguez et al [28, 36] aimed at assessing neonatal cardiac dynamics within the context of the dynamic systems theory and fractal geometry. The accuracy of the automated method was validated with a blind study that included 100 continuous and outpatient ECG records, which confirmed the reproducibility and clinical applicability of the assessment method. The study results evidence that regardless the ECG records selected (outpatient or continuous), the spaces occupied by normal and abnormal neonatal cardiac attractors can be fully differentiated, and it is possible to identify states evolving toward normality or abnormality.

In this research, neonatal continuous and outpatient ECG records have been interpreted mathematically and geometrically by estimating the number of spaces occupied by cardiac attractors when overlapping the Kp grid. In addition, the observation of the changes in the spaces occupied by the attractor in the delay map over different time points would allow evidencing the evolution of the cardiac system based on the distance between this measure and the established normality limit. This characterization of the behavior of neonatal cardiac dynamics will provide relevant information for specialists, allowing for the prevention of adverse situations.

It is worth highlighting that the morphologies and patterns of ECG waves are used as reference to compare normality and abnormality between different populations and even sexes. However, although some signals can be associated with normal heart dynamics, they can actually represent an electrical or morphological heart alteration. This is because there are no standard well-defined comparison prototypes for the analysis of ECG signals [37], similar to the association between HRV and the autonomic nervous system [38]. Although HRV parameterization has elucidated some aspects on heart alterations, it is not extensive enough to be considered a conclusive diagnostic measure. Therefore, this problem has been analyzed based on nonlinear systems and the chaos theory [38], resulting in the development of the method applied in this study, which allows for mathematical and geometrical distinctions. In this sense, ECG signal processing and interpretation can be further optimized when interpreted according to the method applied in this study.

With the Box-Counting method applied in this study, the spaces occupied by each neonatal cardiac attractor could be quantified, as well as their fractal dimension. It was found that dimension fractal values cannot be used to differentiate normal from abnormal heart dynamics. This was also demonstrated in other studies following this line of research, as is the case of a mathematical law that allows for the quantification of all cardiac attractors recorded within 21 hours, both for adults and newborns [36]. The reproducibility and clinical applicability of this mathematical law has been confirmed in a study with cardiac dynamics clinically assessed as heart arrhythmia based on 450 Holter records. This study has also evidenced its capacity to characterize normal and abnormal cardiac dynamics in adults after recording electrical heart signals for 18 hours [39].

Other areas of medicine in which it is possible to observe the potential of studies supported by physical and mathematical theories, such as the one applied in this study, include studies on arterial and cell structures [40, 42]. Moreover, methods contributing to immunology [43], epidemic prediction [44], and CD4+ have been developed based on the leukocyte count of patients with HIV/AIDS [45]. These results show that this type of research can bring solutions in all fields of medicine and that this discipline can have the same predictive level as physics.

Acknowledgments

This study is the result of project ID 2164 and was funded by Universidad Cooperativa de Colombia. We would like to thank the authorities of Universidad Cooperativa de Colombia.

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