Research Article

Physical and mathematical evaluation of fetal cardiotocography using a methodology based on probability and entropy

Sandra Catalina Correa Herrera, Javier Oswaldo Rodríguez Velásquez, Magda Liliana Villamizar Osorio, Jaime Alberto Páez Páez, Signed Esperanza Prieto Bohórquez, Fredys Alberto Simanca Herrera, Jairo Augusto Cortés Méndez

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Abstract—the behavior of fetal heart rate in antepartum cardiotocography traces has been evaluated using a methodology based on the theory of probability and entropy, with which it is possible to quantify how much far away is the abnormal fetal heart rate from normal. Objective: to confirm through a blind study the clinical applicability of a mathematical diagnosis based on probability and the entropy S/k proportion designed to evaluate the cardiotocographic tracing. Methodology: 90 cardiotocographic tracings were taken with a duration of 20 minutes. Then, the frequency of occurrence of the maximum and minimum values of the fetal heart rate was calculated in 10-second intervals. Subsequently, the probability and the S/k proportion of each trace were evaluated. Finally, a mathematical diagnosis was obtained to distinguish normal from abnormal fetal cardiac dynamics. Results: the values of the S/k proportion for the reactive traces varied between -1.9415 to -1.7170 and between -2.3152 and -1.2789 for the non-reactive ones, respectively. Sensitivity and specificity values were both 100% for diagnosing normality and disease with a Kappa coefficient of one. Conclusion: the clinical applicability of the diagnostic parameters of the physical-mathematical methodology was confirmed, by differentiating normal from abnormal states in groups of cardiotocography traces in 20 minutes.

Index Terms— probability, fetal heart rate, cardiotocography.

I. INTRODUCTION

THE quantification of the possibility of future occurrence of a given event within a variety of possible events is calculated using probability. Axiomatically, the probability values always take positive values between zero and one, in such a way that the sum of the probability of all possible events will be equal to one [1]. On the other hand, the concept of entropy was formalized in the study of ideal gases, statistical mechanics, and thermodynamics [2,3] and its generalization was achieved by Boltzmann and Gibbs, in which it was defined as a function of the number of states when they are equiprobable, that is, that all the states are equally probable and when the systems present a non-equiprobable distribution [4].

Globally, significant progress has been made in child survival since 1990. However, between 1900 and 2018, neonatal mortality cases have decreased more slowly than expected [5]. In 2018 it was estimated that, worldwide, 2.5 million children died in the first month of life and that approximately 7,000 newborns die every day [5]. For this reason, it is considered vitally important to monitor fetal well-being during pregnancy and labor to improve maternal-neonatal outcomes [6].

Cardiotocography is part of the continuous surveillance tests of the fetal heart rate (FHR) and is performed with the aim of detecting adverse perinatal alterations [6-11]. Antepartum cardiotocography records the FHR obtained through an ultrasound transducer placed on the mother's abdomen, usually for 20 minutes [6,7]. There are different criteria and guidelines established by international scientific societies such as the International Federation of Gynecology and Obstetrics (FIGO) and the American College of Obstetricians and Gynecologists (ACOG), for monitoring FCF [12-15]. Antepartum tracings are classified according to criteria established by these associations and societies based on the values of accelerations and decelerations measured in heartbeats per minute as well as morphological patterns of the waves, among other criteria [14]. However, the lack of uniform parameters to diagnose normality and abnormality of FHR is still a matter of discussion [13-16].

In light of these considerations, studies have been developed which have led to the design of diagnostic methodologies for clinical application based on the framework of mathematics and theoretical physics [17-20]. Among them, there is a methodology that evaluates the behavior of the FCF of cardiotocographic tracings using the theory of probability, entropy, and the S/k proportions [17] to differentiate fetal cardiac normality from abnormality when establishing values of the S/k proportions and diagnostic parameters with which this purpose is achieved [17]. The clinical reproducibility of this diagnostic methodology has been confirmed in the framework of two blinded studies, with 25 and 40 tracings, respectively [14,15], however, these findings should be confirmed with larger patient populations.

The purpose of this study is to apply a methodology based on probability, entropy and the S/k proportion to confirm its reproducibility and clinical applicability with respect to conventional clinical evaluation, within the

framework of a blind study with 90 cardiotocography traces [17].

II. METHODS

A. Population

90 CTG tracings were taken from healthy pregnant patients or with some obstetric pathology that influenced fetal well-being who were older than 21 years and with a gestational age greater than 28 weeks. The data was anonymized databases of San Luis de Bucaramanga Clinic in Colombia and Insight group. Based on the clinical examination and the assessment of the cardiotocography traces, reactivity and non-reactivity were established as a clinical interpretation as a parameter of normality and disease, respectively. Those cases that were considered non-reactive and after the clinical and paraclinical examination chosen by a clinical specialist, were discarded

B. Procedure

Initially, the clinical conclusions of the cardiotocographic tracings were blinded. Subsequently, the maximum and minimum FCF values were taken every 10 seconds for 20 minutes. Then, it was calculated how many times each maximum and minimum value of the FCF was repeated and all the occurrences of these frequencies were added for each trace, to calculate their probability with equation 1, as follows:

$$P_n = \frac{Frequency\ of\ cardiac\ appearance}{Total\ heart\ ratest\ in\ entire\ trace} \quad (1)$$

With this step, it is evaluated whether the probability distributions found are not equiprobable, that is, that the probability values are not equally probable for each of the tracings. Subsequently, the entropy and the S/k proportion were evaluated with equations 2 and 3, as:

$$S = -k \sum_{n=0}^{N} P_n\, Ln(P_n)\ (2) \qquad (2)$$

Where S is entropy, *k* is the Boltzmann constant, $1.38x10^{-23}$Joules/Kelvin.

$$\frac{S}{k} = -\sum_{n=0}^{N} P_n\, ln\,(P_n)\ (3) \qquad (3)$$

Where S is the entropy of the tracing, k equals the Boltzmann constant (1.38x10-23 Joules/kelvin), and Pn is the probability of the n- probability value that was evaluated with equation 1. From the previously obtained values, three possible mathematical diagnostic scenarios are generated, namely: normality, disease and evolution between states. Finally, a blind study was carried out in which the ability of the method to diagnose normality and disease was compared with respect to reactivity and non-reactivity.

C. Statistical analysis

The clinical evaluations of each cardiotocography tracing were unblinded and the interpretation of reactivity and non-reactivity were considered as a gold standard for comparison with the mathematical diagnosis of normality and abnormality, respectively. From this, the sensitivity, specificity, and agreement of the mathematical method in relation to the clinical diagnosis were calculated. The cases considered mathematically as evolution were discarded.

D. Ethical aspects

This research complies with the ethical principles for medical research in human beings of the Declaration of Helsinki of the World Medical Association and in general terms with the ethical, scientific, technical and administrative standards for health research in Colombia based on the Resolution 008430 of 1993, and specifically with title 11 regarding research in human beings, as it is classified in the category of research without risk, since physical calculations are made on the results of non-invasive examinations of clinical practice, protecting the integrity and anonymity of the participants.

III. RESULTS

The probability distributions of the frequency of occurrence of the maximum and minimum values of the FCF of all cardiotocography traces ranged between 0 and 0.525. The probability distributions of the CTG traces evaluated as reactive ranged between 0 and 0.375 while the non-reactive traces ranged between 0 and 0.525 (see

table 1). The values of the entropy S/k proportion for each of the probability distributions of the FCF ranged between -2.315 and -1.278. The values of the S/k proportion varied between -1.941 and -1.717, for the reactive CTG traces, between -2.315 and -1.278 for the non-reactive CTG traces (see table 2).

Based on the above, it was observed that the tracings interpreted as reactive were mathematically diagnosed within a specific range of values, while the non-reactive records were found outside this range. Considering this, in the context of a blinded study, the sensitivity and specificity values calculated were 100% to diagnose normality with the mathematical method. With respect to the cases diagnosed mathematically as in evolution and clinically as reactive or non-reactive, the results suggest that the method detects underdiagnosed alterations that require attention and that there has been an improvement in the fetal state, respectively. However, these cases were not taken into account for the statistical analysis because it was wanted to establish the ability of the method to diagnose normality and abnormality, not intermediate states.

The previous results indicate that mathematically (see table 2), there was a correspondence of the mathematical diagnosis of normality with respect to the clinical one and that the values; such observation is also compatible with the mathematical diagnosis of abnormality with respect to clinical non-reactivity.

Table 1. Probability values of heart rates in ranges of 5 heartbeats

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
70	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
75	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
80	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
85	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
90	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
95	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
100	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
105	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
110	0,02	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
115	0,12	0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,00	0,00	0,01	0,00	0,00	0,01	0,00	0,00
120	0,19	0,03	0,02	0,02	0,01	0,08	0,04	0,00	0,07	0,00	0,00	0,00	0,02	0,01	0,08	0,00	0,01	0,02	0,02	0,00
125	0,38	0,08	0,02	0,04	0,06	0,46	0,64	0,00	0,29	0,02	0,03	0,16	0,03	0,02	0,17	0,04	0,07	0,20	0,19	0,02
130	0,05	0,10	0,04	0,10	0,23	0,04	0,07	0,07	0,09	0,00	0,07	0,00	0,04	0,12	0,03	0,07	0,10	0,01	0,05	0,10
135	0,05	0,33	0,05	0,28	0,33	0,13	0,03	0,37	0,24	0,13	0,38	0,07	0,12	0,47	0,13	0,19	0,31	0,07	0,16	0,02
140	0,08	0,13	0,05	0,19	0,13	0,09	0,13	0,28	0,15	0,43	0,22	0,04	0,11	0,13	0,05	0,18	0,12	0,11	0,11	0,07
145	0,11	0,16	0,21	0,22	0,13	0,08	0,09	0,26	0,07	0,30	0,11	0,10	0,31	0,15	0,48	0,24	0,13	0,20	0,22	0,22
150	0,02	0,06	0,13	0,05	0,04	0,05	0,00	0,01	0,01	0,04	0,08	0,06	0,13	0,06	0,03	0,13	0,06	0,03	0,11	0,07

Table 2. Association of mathematical and clinical diagnoses with respect to the calculated S/k values.

No.	S/K	Max P	Mathematical diagnosis	Clinical diagnosis	Interpretation
1	-1.5963	0.283	Disease	Genitourinary infection	NR
2	-1.7709	0.233	Normal	Normal	R
3	-1.2789	0.525	Disease	Hypertension	NR
4	-1.4974	0.433	Disease	Threatened preterm delivery, gestational diabetes	NR
5	-1, 7170	0.35	Normal	Normal	R
6	-1.7254	0.375	Normal	Normal	R
7	-1.9415	0.275	Normal	Normal	R
8	-2.3152	0.233	Disease	Threatened preterm birth	NR
9	-1.8480	0.341	Normal	Normal	R
10	-1, 8014	0.275	Normal	Normal	R
11	-1.5246	0.258	Disease	Attempted abortion	NR
12	-1.6693	0.275	Evolution	Normal	R
13	-1.3137	0.383	Disease	Severe preeclampsia	NR
14	-1.5248	0.267	Disease	Threatened preterm delivery	NR
15	-1 .6392	0.367	Disease	Risk of loss of fetal well-being	NR

Vertical lines are optional in tables. Statements that serve as captions for the entire table do not need footnote letters.

[a]Gaussian units are the same as cgs emu for magnetostatics; Mx = maxwell, G = gauss, Oe = oersted; Wb = weber, V = volt, s = second, T = tesla, m = meter, A = ampere, J = joule, kg = kilogram, H = henry.

Complementarily, the cases mathematically diagnosed as evolving comprised reactivity and non-reactivity, which suggests that the method detects well for the first case, underdiagnosed alterations and for the second, the improvement of the clinical state from the disease, respectively. The kappa coefficient obtained was 1.

IV. DISCUSSION

This is the first study that confirms the clinical applicability of the methodology designed to evaluate cardiotocography traces in 20 minutes with 90 subjects, from the discrete values of the FHR, calculating the probability and the S/k proportion of entropy. The values of the S/k proportion show the ability of entropy to quantify possible fetal cardiac dynamics and thus differentiate normality of the disease, as well as the evolution between these states. In this context, the application of this methodology in the clinical context may lead to the optimization of surveillance protocols for fetal well-being to improve perinatal outcomes.

The S/k proportion establishes mathematical differences that specify the behavior of normal and abnormal FHR for 20 minutes. Additionally, the probability distributions of the minimum and maximum fetal heart rates are different between normal tracings from those abnormal ones that do not present accelerations or decelerations according to conventional medical observation. Finally, the Boltzmann-Gibbs entropy makes it possible to quantify the different forms of self-organization of probability distributions that make it possible to differentiate normality of disease in fetal cardiac dynamics [17].

In the literature, the FIGO, ACOG and the National Institute of Excellence in Health and Care (NICE) guidelines have been compared, finding strong agreements in the identification of the normal baseline, tachycardia, normal variability, the presence of accelerations and decelerations. However, the study found that it was not possible to classify the decelerations, as established by the guidelines, since these events are defined differently in each one [12]. On the other hand, the applied methodology reveals the importance of having mathematical parameters that evaluate the fetal cardiac dynamics, to objectively establish the level of severity of the disease based on the increase or decreases of the values of the S/k proportion of the probability.

It is worth noting that these ambiguities in the interpretation of the traces do not occur when applying the physical-mathematical diagnosis, because it is a methodology that was developed independently of the guidelines established by international associations, finding, instead, mathematical parameters that evaluate normal and abnormal fetal cardiac dynamics and the evolution towards either of these two states regardless of cause and effect considerations, qualitative criteria and the experience of the evaluator, such as those discussed daily in clinical studies [12, 22].

It is important to highlight that the cases of evolution towards the disease were excluded from the statistical analysis, because this study seeks to verify the capacity of the method to diagnose normality and abnormality, not intermediate states. However, it is important to emphasize that obtaining a compatible mathematical diagnosis as in evolution but with a clinical interpretation of reactivity, suggests an underdiagnosed alteration that requires more attention. On the contrary, the cases clinically diagnosed as abnormal but mathematically evolving, suggests that there may be an improvement in the clinical state. These considerations will be analyzed in future studies to confirm these observations.

The range of possibilities to reduce subjectivity in conventional clinical studies can be observed in other medical settings, such as cardiology, immunology, molecular biology, and public health, among others [23-25]. These investigations obey an acausal understanding of the phenomena of medicine, which are focused on revealing mathematical orders underlying these phenomena, to create objective and reproducible diagnostic methodologies for clinical application.

V. CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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