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FMUP FACULDADE DE MEDICINA
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SIMULTANEOUS COMPUTERIZED ANALYSIS OF MATERNAL AND FETAL HEART RATE RECORDINGS DURING LABOR

ANÁLISE COMPUTORIZADA SIMULTÂNEA DAS FREQUÊNCIAS CARDÍACAS MATERNA E FETAL DURANTE O PARTO

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Dissertação de candidatura
ao grau de Doutor em Investigação Clínica e em Serviços de Saúde
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Electronic fetal monitoring technology is capable of monitoring and recording **maternal heart** rate patterns that **mimic fetal heart** rate patterns.

Murray 2014

Artigo 48º, parágrafo 3º - “A Faculdade não responde pelas doutrinas expendidas na dissertação”
(Regulamento da Faculdade de Medicina do Porto – Decreto-Lei nº 19337, 29 de janeiro de 1931)

To my parents Luís and Teresa

CONTENTS

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ABBREVIATIONS

ApEn	Approximate entropy
auROC	Areas under ROC curves
bpm	Beats per minute
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiography
FIGO	International Federation of Gynaecology and Obstetrics
FHR	Fetal heart rate
HF	High frequency
II	Interval index
K	Kappa coefficient
LDA	Linear discriminant analysis
LF	Low frequency
LOO	Leave-one-out
LTI	Long term irregularity
LTV	Long term variability
min	Minutes
mHR	Mean heart rate
MHR	Maternal heart rate
N	Number of cases
NE	Not estimated
NR	Not reported in the sudies
Pa	Proportions of agreement
PPG	Photoplethysmography
r	Kendall´s tau correlation coefficient
s	Seconds
SamEn	Sample entropy
sd	Standard deviation
sdHR	Standard deviation of heart rate
Sen	Sensitivity
SQ	Signal quality
SL	Signal loss
Spe	Specificity
STV	Short term variability
UAB	Umbilical artery blood
UC	Uterine contractions
VLF	Very low frequency

ABSTRACT

Although the use of cardiotocography monitoring in industrialized countries is widespread, and there is obviously an intimate relationship between the mother and the fetus during pregnancy, few studies have been published about the relationship between maternal heart rate (MHR) and fetal heart rate (FHR) during labor.

The main objective of this thesis was to explore whether combined analysis of MHR and FHR could improve maternal and fetal monitoring during labor.

To overcome the limitations and subjectivity of common visual analysis, we developed and validated a new computerized program for simultaneous MHR and FHR analysis based on a previously developed program for FHR analysis alone, supported in the International Federation of Gynaecology and Obstetrics (FIGO) guidelines for fetal monitoring *(Chapter 2)*. Good to excellent computer-observer agreement and reliability were obtained, and the detection of MHR changes associated with labor progression were studied.

In fact, the morphologic similarity and sometimes coincidence between MHR and FHR, and the well-known possibility of misinterpreting the MHR as FHR, lead us to the assessment of an algorithm to detect and delete MHR-FHR ambiguities *(Chapter 3)*. Improvements in FHR tracing analysis were obtained, with a significant increase of FHR signal loss of 1% and 6%, in cases with minor and major ambiguities, respectively, as well as a significant decrease in FHR decelerations.

Then, to accomplish our main objective, we explored the application of combined conventional *(Chapter 4)* and non-conventional *(Chapter 5)* computerized analysis of MHR and FHR recordings in the assessment of labor progression, fetal acidemia, and maternal-fetal attachment. With conventional analyses, the progression of labor was associated with a significant increase in MHR accelerations and FHR decelerations both in non-acidemic and acidemic fetuses ($p<0.01$). In acidemic fetuses, there was an increase in MHR-FHR correlations and differences in accelerations and decelerations with modest area under the ROC curve (auROC) results. With non-conventional analyses, the progression of labor was also associated with a significant increase in most MHR and FHR linear indices, whereas entropy indices decreased. The inclusion of MHR on bivariate analysis achieved sensitivity and specificity values of nearly 100% and 89.1%, respectively. These two studies represent the first combined MHR and FHR analysis in relation to labor progress and prediction of newborn acidemia.

Finally, to study an easier and alternative method of acquiring MHR signals, we explored the use of pulse oximetry using photoplethysmography (PPG) as an alternative method to electrocardiography (ECG) *(Chapter 6)*. The study has evidenced PPG as an alternative for MHR acquiring signal and monitoring during labor, when appropriate MHR variability indices and reference ranges are used.

In conclusion, our exploratory studies suggest that combined MHR-FHR analysis may improve maternal-fetal monitoring during labor in several ways. More extensive studies are warranted.

RESUMO

Apesar da utilização frequente da monitorização cardiotocográfica nos países industrializados e da evidente relação entre a mãe e o feto durante a gravidez, são poucos os estudos publicados sobre a relação entre a frequência cardíaca materna (FCM) e a frequência cardíaca fetal (FCF), nomeadamente durante o trabalho de parto.

O principal objetivo desta tese foi o de explorar a análise combinada da FCM e a FCF e analisar se esta poderia contribuir para uma melhor monitorização materna e fetal durante o parto.

Para ultrapassar as limitações e subjectividade da análise visual, começamos por desenvolver e validar um novo programa computorizado para a análise combinada da FCM e FCF, com base num programa previamente desenvolvido para a análise da FCF isolada, segundo as orientações da FIGO para a monitorização fetal (*Capítulo 2*). Os resultados demonstraram uma boa a excelente concordância e fiabilidade computador observador e foram estudadas as alterações na FCM associadas à progressão do trabalho de parto.

A semelhança morfológica e por vezes coincidência entre a FCM e FCF e a tão bem conhecida possibilidade de interpretar FCM como FCF, conduziu ao desenvolvimento de um algoritmo para detectar e excluir ambiguidades entre a FCM e a FCF (*Capítulo 3*). Obtivemos uma melhor classificação dos traçados de FCF, com um significativo aumento da perda de sinal da FCF, de 1% e 6%, em casos com menores e maiores ambiguidades, respectivamente, bem como uma diminuição significativa das desacelerações da FCF.

Posteriormente e de forma a atingir o nosso principal objectivo, exploramos a aplicabilidade da análise combinada computadorizada convencional *(Capítulo 4)* e não-convencional *(Capítulo 5)* da FCM e FCF, na avaliação da progressão do trabalho de parto, acidemia fetal e vinculação materno fetal. A progressão do trabalho de parto foi associada a um aumento significativo de acelerações da FCM e desacelerações da FCF, tanto em fetos não-acidemic e acidemic ($p < 0,01$). Nos fetos acidémicos, houve um aumento de correlações da FCM-FCF e diferenças nas acelerações e desacelerações com resultados modestos abaixo da curva de ROC (auROC). Com a análise não-convencional, a progressão do trabalho de parto foi também associada a um aumento significativo da maioria dos índices lineares da FCM e FCF, e a uma redução dos índices de entropia. A inclusão da FCM na análise bivariada alcançou valores de sensibilidade e especificidade de quase 100 % e 89,1%, respectivamente. Estes dois estudos representam a primeira análise combinada da FCM e FCF na progressão do trabalho parto e predição da acidemia neonatal.

Por último, com o intuito de estudar um método mais fácil e alternativo para aquisição do sinal materno, explorámos o uso da oximetria de pulso utilizando a fotopletismografia (PPG) como método alternativo da eletrocardiografia (ECG) *(Capitulo 6)*. Os resultados mostram que a PPG pode ser considerada uma alternativa para a monitorização da FCM durante o trabalho de parto, quando são utilizados os índices apropriados de variabilidade da FCM, com uma adaptação adequada dos intervalos de corte.

Em conclusão, os estudos exploratórios realizados sugerem que a análise combinada da FCM e FCF pode permitir, de várias formas, uma melhor monitorização materno-fetal durante o trabalho de parto. Contudo, estudos mais alargados são necessários.

LIST OF PUBLICATIONS

This PhD thesis is based on the following scientific publications (listed by the same order as they appear in the thesis):

- **Paula Pinto**, João Bernardes, Cristina Costa-Santos, Celia Amorim-Costa, Maria Silva, Diogo Ayres-de-Campos. *Development and evaluation of an algorithm for computer analysis of maternal heart rate during labor*. Computers in Biology and Medicine 2014; 49:30-35.

- **Paula Pinto,** Cristina Costa-Santos, Hernâni Gonçalves, Diogo Ayres-de-Campos, João Bernardes. *Improvement in fetal heart rate analysis by the removal of maternal-fetal heart rate ambiguities*. BMC Pregnancy and Childbirth 2015;15:301

- **Paula Pinto**, Cristina Costa-Santos, Hernâni Gonçalves, Diogo Ayres-de-Campos, João Bernardes. *Computer analysis of maternal-fetal heart rate recordings during labor in relation with maternal-fetal attachment and prediction of newborn acidemia*. J Maternal-Fetal and Neonatal Medicine 2016; 29:440-4.

- Hernâni Gonçalves, **Paula Pinto**, Manuela Silva, Diogo Ayres-de-Campos, João Bernardes. *Toward the improvement in fetal monitoring during labor with the inclusion of maternal heart rate analysis*. Med Biol Eng Comput 2016; 54:691-9.

- Hernâni Gonçalves, **Paula Pinto**, Manuela Silva, Diogo Ayres-de-Campos, João Bernardes. *Electrocardiography versus pulse oximetry in the assessment of maternal heart rate variability during labor*. SpringerPlus (2016) 5:1079

CHAPTER 1

INTRODUCTION

OBJECTIVES

OUTLINE

INTRODUCTION

Although there is an intimate biophysical and biochemical relationship between a mother and a fetus, few studies have evaluated the relationship between maternal heat rate (MHR) and fetal heart rate (FHR). In a PubMed search using the query ((maternal[Title]) AND fetal[Title]) OR maternal-fetal[Title]) AND heart rate[Title], completed with a manual search, updated at the time of the first paper of this thesis, only 16 articles evaluating this subject were identified [1-16].

Most publications pertained to the misinterpretation of the MHR as that of the fetus, namely during labor [1-13], either with external FHR monitoring with Doppler ultrasound [13] or with electrocardiography (ECG) [1-5]. The temporary acquisition of the MHR as that of the fetus may occur in up to 90% of intrapartum recordings when external monitoring is used [12], and this may also occur with internal monitoring, due to the acquisition of the maternal signal through the fetal electrode in cases of fetal death [1,4]. Errors in FHR interpretation due to MHR contamination include missing diagnoses of newborn acidemia [12] and fetal death [1-5]. In a series of 41 twin deliveries where the second twin was born acidemic, this information was reported in only 10% of the cases [12]. Indeed, according to *Nageotte*, confusing the MHR and FHR is one of the five most common FHR monitoring errors [9], and it is not always clinically apparent [6,9], leading to serious misinterpretations of fetal status, with either unnecessary interventions or failure to intervene in a timely way.

To avoid MHR-FHR ambiguities, the use of FHR signal acquisition with internal or transabdominal ECG, rather than with Doppler ultrasound, has been recommended [13]. The detection of P waves in the fetal ECG as a marker of fetal signals may also help [17], and in doubtful cases, a fetal ultrasound or the simultaneous registration of the MHR with ECG or pulse oximetry is advised [6,11]. Nevertheless, misinterpretation of the MHR as that of the fetus remains a frequent problem, even when the most recent technologies are used, as recently reported in a Canadian survey [18].

Only three articles were provided from our literature search on the relation between MHR-FHR [14-16] that did not pertain to the misinterpretation of the MHR as that of the fetus. These publications suggest that the combined analysis of MHR and FHR recording can provide useful physiologic information, specifically on the interaction between MHR-FHR during maternal respiration and episodes of stress.

Another issue raised in our literature search was that visual analysis of MHR tracings can suffer from the same poor observer agreement and reliability problems [19] that are reported for FHR analysis [20-21]. Indeed, some authors report MHR decelerations during labor [22], whereas others report accelerations [7]. Moreover, visual analysis is unlikely to be precise enough to analyze the complexity of maternal-fetal pathophysiologic interactions [14-16].

With the issues presented in mind, in this thesis our objective was to explore the clinical usefulness of simultaneously analyzing MHR and FHR recordings during labor.

OBJECTIVES

1. Development and validation of a new algorithm for computer analysis of MHR during labor, for combined analysis of simultaneous MHR and FHR recordings, based on previous knowledge of computer analysis of FHR recordings.

2. Development and validation of an algorithm to detect and delete MHR-FHR ambiguities during labor.

3. Exploration of the clinical application of the developed algorithms for combined conventional computerized analysis of MHR and FHR recordings in the assessment of labor progression, acidemia, and maternal-fetal attachment.

4. Exploration of the clinical application of combined non-conventional spectral and entropy analysis of MHR and FHR recordings in the assessment of labor progression and acidemia.

5. Exploration of the use of pulse oximetry as an alternative to electrocardiography for the acquisition of MHR signals.

OUTLINE

The core of this thesis is organized in 6 chapters, as follows.

A novel algorithm for on-line computer analysis of MHR is described in **Chapter 2.** The algorithm is designed to overcome the limitations and subjectivity of visual analysis and allow a more precise understanding of the complexity of maternal-fetal pathophysiologic interactions. Using a Microsoft Windows environment, this algorithm is based on a previously existing version for FHR analysis, inspired in the International Federation of Gynaecology and Obstetrics (FIGO) guidelines for fetal monitoring. To evaluate the algorithm´s performance, inter-observer and computer-observer agreement, reliability, and correlation were assessed.

MHR recordings are morphologically similar and sometimes coincident with FHR recordings, particularly during the final hours of labor, and this may produce well-known clinical errors arising from misinterpretation of the MHR as a FHR recording. In **Chapter 3**, we report an exploratory study to evaluate if the computerized removal of MHR-FHR ambiguities improves the interpretation of the FHR pattern and overall tracing classification. An algorithm to detect and delete MHR-FHR ambiguities was developed, and FHR analysis was assessed during the final hour of labor, before and after the algorithm was applied.

Maternal and fetal physiologies are intimately related, and profound changes in hemodynamic and autonomic nervous system activity occur during labor. MHR and FHR analysis provides a non-invasive quantitative evaluation of human autonomic function. **Chapters 4** and **5** explore the simultaneous analysis of MHR and FHR using conventional and non-conventional methods, and discuss their possible clinical application in relation to maternal-fetal attachment, labor progress, and prediction of newborn acidemia.

ECG is the most accurate method to monitor MHR, but it may not always be available or acceptable to the pregnant woman during labor. Pulse oximetry (photoplethysmography-PPG) is an alternative to ECG, but its use has not been previously evaluated for the detailed analysis of MHR complexity. In **Chapter 6**, the evolution of MHR variability during labor is assessed, comparing maternal ECG and PPG signals for the assessment of labor progression, prediction of fetal acidemia, and operative vaginal delivery.

In **Chapter 7,** the **General Discussion**, **Main Conclusions,** and **Future Prospects** are presented.

All presented studies have been published in ISI-indexed international scientific journals, with impact factor, in the area of Obstetrics and Gynecology. They are presented with the same content as that with which they were published.

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CHAPTER 2

DEVELOPMENT AND EVALUATION OF AN ALGORITHM FOR COMPUTER ANALYSIS OF MATERNAL HEART RATE DURING LABOR

Computers in Biology and Medicine 2014; 49:30-35

DEVELOPMENT AND EVALUATION OF AN ALGORITHM FOR COMPUTER ANALYSIS OF MATERNAL HEART RATE DURING LABOR

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ABSTRACT

Background

Maternal heart rate (MHR) recordings are morphologically similar and sometimes coincident with fetal heart rate (FHR) recordings and may be useful for maternal–fetal monitoring if appropriately interpreted. However, similarly to FHR, visual interpretation of MHR features may be poorly reproducible.

Methods

A computer algorithm for on-line MHR analysis was developed based on a previously existing version for FHR analysis. Inter-observer and computer-observer agreement and reliability were assessed in 40 one-hour recordings obtained from 20 women during the last 2 h of labor. Agreement and reliability were evaluated for the detection of basal MHR, long-term variability (LTV), accelerations and decelerations, using proportions of agreement (PA) and Kappa statistic (K), with 95% confidence intervals (95% CI). Changes in MHR characteristics between the first and the second hour of the tracings were also evaluated.

Results

There was a statistically significant inter-observer and computer-observer agreement and reliability in estimation of basal MHR, accelerations, decelerations and LTV, with PA values ranging from 0.72 (95% CI: 0.62–0.79) to 1.00 (95% CI: 0.99–1.00), and K values ranging from 0.44 (95% CI: 0.28–0.60) to 0.89 (95% CI: 0.82–0.96). Moreover, basal MHR, number of accelerations and LTV were significantly higher in the last hour of labor, when compared to the initial hour.

Discussion

The developed algorithm for on-line computer analysis of MHR recordings provided good to excellent computer-observer agreement and reliability. Moreover, it allowed an objective detection of MHR changes associated with labor progression, providing more information about the interpretation of maternal–fetal monitoring during labor.

INTRODUCTION

Maternal heart rate (MHR) can be misinterpreted as that of the fetus, a problem that is still common and important during labor [1–6], both when external (ultrasound) or internal (electrocardiographic) fetal heart rate (FHR) recording methods are used [7]. This may have an important clinical impact as in a recent case series of 41 twin deliveries, where the second twin was born acidemic, 10% of the cases of MHR monitoring were missed by visual analysis [6].

There is also recent evidence that MHR evaluation during pregnancy and in labor may provide useful pathophysiological information on the maternal–fetal clinical state, namely in assessment of hypertensive pregnancy conditions [8,9], gestational diabetes [10], pre-term and term labor diagnosis [11] or labor analgesia [12]. However, it seems that visual analysis of MHR recordings is subject to poor observer agreement and reliability [13], as with FHR analysis [14,15], explaining why some authors report MHR decelerations during labor [16] while others report accelerations [17]. Moreover, visual analysis may not be sufficiently precise to allow an understanding of the complexity of maternal–fetal pathophysiological interactions [18–20]. Computer analysis could help to overcome the limitations and subjectivity of visual analysis [13], to identify MHR recordings misinterpreted as that of the fetus [1–6] and to improve monitoring of the overall maternal–fetal condition.

In this paper, we describe the development of a new algorithm for computer analysis of MHR during labor, based on an existing and tested model for FHR analysis [21–25], following the evidence that MHR recordings are morphologically similar and sometimes coincident with FHR recordings [17]. To our knowledge, no other computer algorithms have been developed for combined on-line analysis of MHR and FHR during labor.

MATERIAL AND METHODS

The study followed the Helsinki Declaration, was approved by the local Ethics Committee, and all women gave their informed consent to participate. Forty simultaneous recordings of MHR and FHR were obtained from 20 women in the last two hours of labor. The average maternal age was 28.7 (SD: 4.9) years and the average gestational age 39.2 (SD:0.9) weeks. Thirteen women were nulliparous, two underwent a cesarean section and all but one was under epidural analgesia. The average one and five minute Apgar scores were, respectively, 9.4 (SD:0.5) and 9.9 (SD:0.3), and the average umbilical artery blood pH was 7.23 (SD:0.8).

For acquisition of the MHR and FHR signals a conventional STAN® 31 fetal monitor (Neoventa Medical, Gothemburg, Sweden) was used. The STAN® 31 fetal monitor has two sockets for heart rate acquisition, one for an electrocardiography sensor and another for an ultrasound sensor. MHR was acquired with an electrocardiography sensor connected to three electrodes on the maternal thorax, while FHR was acquired with an ultrasound sensor placed in the abdomen (as usually performed in clinical practice), both connected to the STAN® 31 fetal monitor (Neoventa Medical, Gothemburg, Sweden). This monitor was connected, via a standard computer cable to the Omniview-SisPorto® system for computer analysis of FHR tracings (Speculum, Lisbon, Portugal), using a RS232 or RS485 protocol and a computer program developed in Visual Basic, running under a Microsoft Windows environment [22,23].

Computer analysis of MHR recordings was performed using a specifically developed algorithm (Fig. 1), based on the Omniview-SisPorto® algorithms for FHR analysis, also following the FIGO guidelines for fetal monitoring [23,26]. In short, MHR signals conveyed from the fetal monitor at 4 Hz underwent a scale conversion obtained by adding 50 beats/min (bpm) to the original MHR values, except when these values were equal to zero. After that, they were

subjected to a pre-processing algorithm, for removal of noise and calculation of signal loss and signal quality. Short-term variability (STV) was determined as the difference between two adjacent MHR beats and considered abnormal when lower than 1 bpm. After that, basal MHR was estimated, using a complex algorithm based on histogram and STV analysis [21,22,27]. Accelerations and decelerations were subsequently detected as MHR deviations, above or below baseline, with at least 15 bpm amplitude and 15 s duration. Finally, LTV was estimated, in segments not displaying accelerations or decelerations, as the difference between the highest and lowest values in a sliding window of one minute and was classified as abnormal when < 5 bpm [21,22,27] (Figs. 1 and 2).

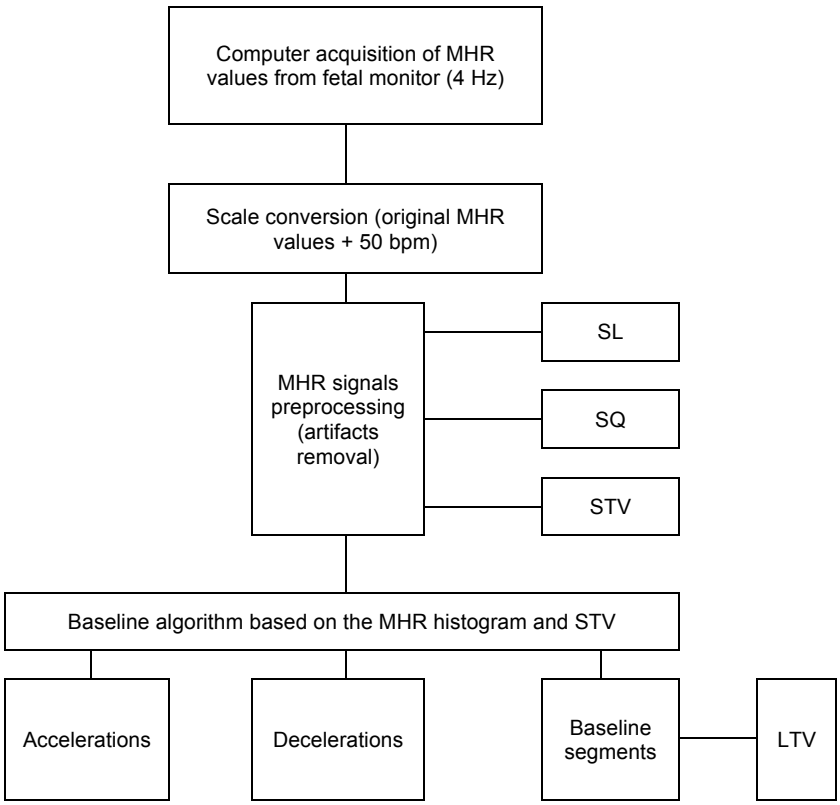

Figure 1. Schematic representation of the novel maternal heart rate (MHR) processing algorithm. SL: signal loss; SQ: signal quality; STV: short-term variability; LTV: long-term variability.

Visual analysis of basal MHR, long-term variability (LTV), accelerations and decelerations was also performed by three expert clinicians with a special interest in the field. Experts analyzed tracings independently and with no knowledge of each other's or the computer's evaluation. For visual analysis, the FIGO guidelines were closely followed [26] with the needed scale adaptations (Figs. 2 and 3). In short, basal MHR was defined as the mean of the lowest stable segment(s) lasting at least 2 min, preferably with a LTV less than 15 bpm and a mean value within 60–100 bpm. LTV was defined as the difference, in bpm, between the highest peak and lowest trough, in a 1-min segment of baseline oscillations. Accelerations and decelerations were defined as transient increases or decreases in MHR, in relation to the baseline, of at least 15 bpm of amplitude and lasting 15 s or more [26].

Agreement, reliability and correlation among experts and between the majority of experts and the computer were assessed in one hour segments for basal MHR and LTV, and in 10 min

segments for accelerations and decelerations, with the proportions of agreement (PA), Light's Kappa statistic (K), calculated with 95% bootstrap confidence intervals (95% CI) [28,29], and the Kendall's tau correlation coefficient, respectively (Tables 1 and 2, and Fig. 3).

For each MHR segment, three trials of agreement, reliability and correlation among experts (1 versus 2, 1 versus 3 and 2 versus 3) and one trial between the majority of experts and the computer were considered. For assessment of agreement and reliability in basal MHR estimation, concordant evaluations were considered when the difference in estimations was equal to or less than 5 bpm [30]. LTV was categorized as normal (1), when ≥5 bpm, and abnormal (0) when inferior to this. Accelerations and decelerations were categorized as sporadic (0–1/10min) or repetitive (>1/10 min). For a better explanation of the procedure a case-example is provided in Table 1 and Fig. 3. Experts 1, 2 and 3 assigned basal MHR as 90, 90 and 100 beats/min (bpm), respectively; there was agreement between experts 1 versus 2 (in the 90–94 bpm category) and disagreement between observers 1 versus 3 and 2 versus 3 (in the 90–94 and 100–104 bpm categories). On the other hand, the majority of experts and the computer assigned basal MHR as 90 and 92 bpm, respectively; there was agreement between them (both in the 90–94 bpm category). Experts 1, 2, 3 and their majority, as well as the computer, assigned LTV as normal (category 1); there was agreement between experts 1 versus 2, 1 versus 3 and 2 versus 3, as well as between the experts majority versus the computer. Experts 1, 2, 3 and their majority, as well as the computer, assigned all accelerations as repetitive and all decelerations as sporadic (except in the 10 min segment number 3, where expert 2 assigned repetitive decelerations); there was agreement between experts 1 versus 2, 1 versus 3 and 2 versus 3, as well as between the experts majority versus the computer (except in the detection of decelerations in the 10 min segment number 3, where expert 2 disagreed with experts 1 and 3).

PA with inferior limits of 95% CI higher than 0.50 were considered indicators of significant agreement, whereas K values larger than 0.75 were considered indicators of excellent reliability, those between 0.40 and 0.75 indicators of fair to good reliability, and those below 0.40 indicators of poor reliability [29]. Changes in MHR between the initial and final hours of labor were evaluated using the t-test and the Wilcoxon rank test, with a significance level set at p value <0.05.

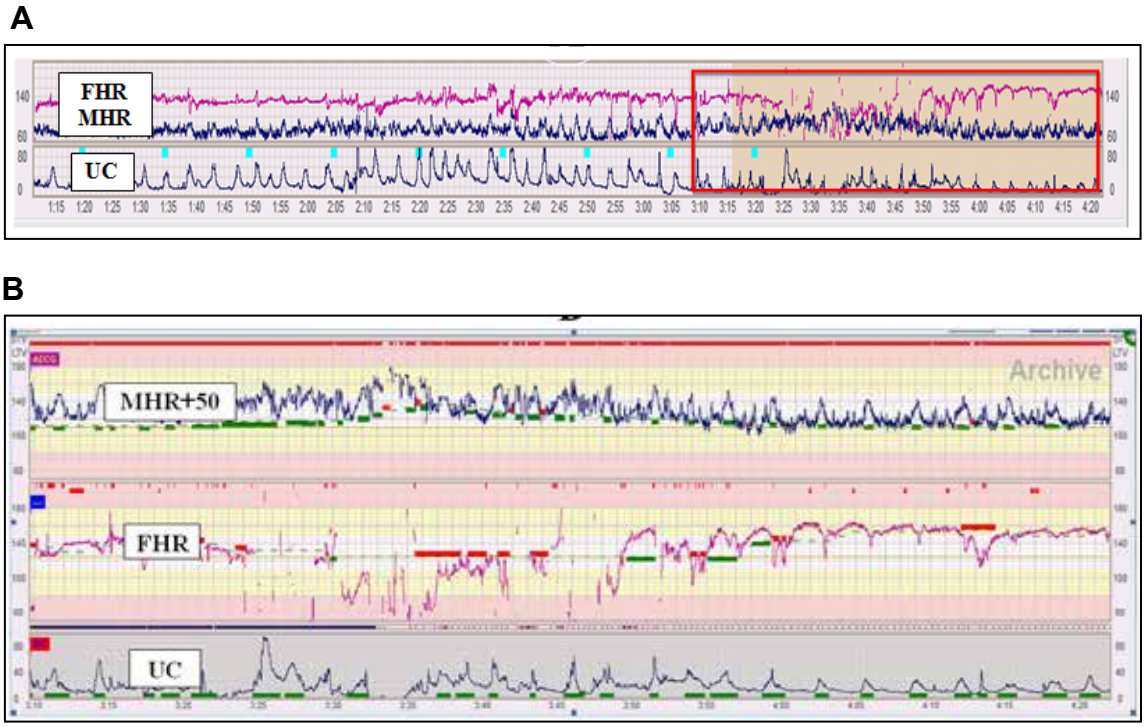

Figure 2. (A and B) Simultaneous recording of maternal heart rate (MHR), fetal heart rate (FHR) and uterine contractions (UC). **A:** the 4 hours before delivery showing, inside the red rectangle, how similar can be MHR and FHR, during episodes of MHR accelerations (green bars) and FHR decelerations (red bars). **B:** the segment depicted inside the rectangle shown in A, with a scale change of MHR (MHR + 50 beats per minute), showing how computer analysis may help to better characterize each tracings.

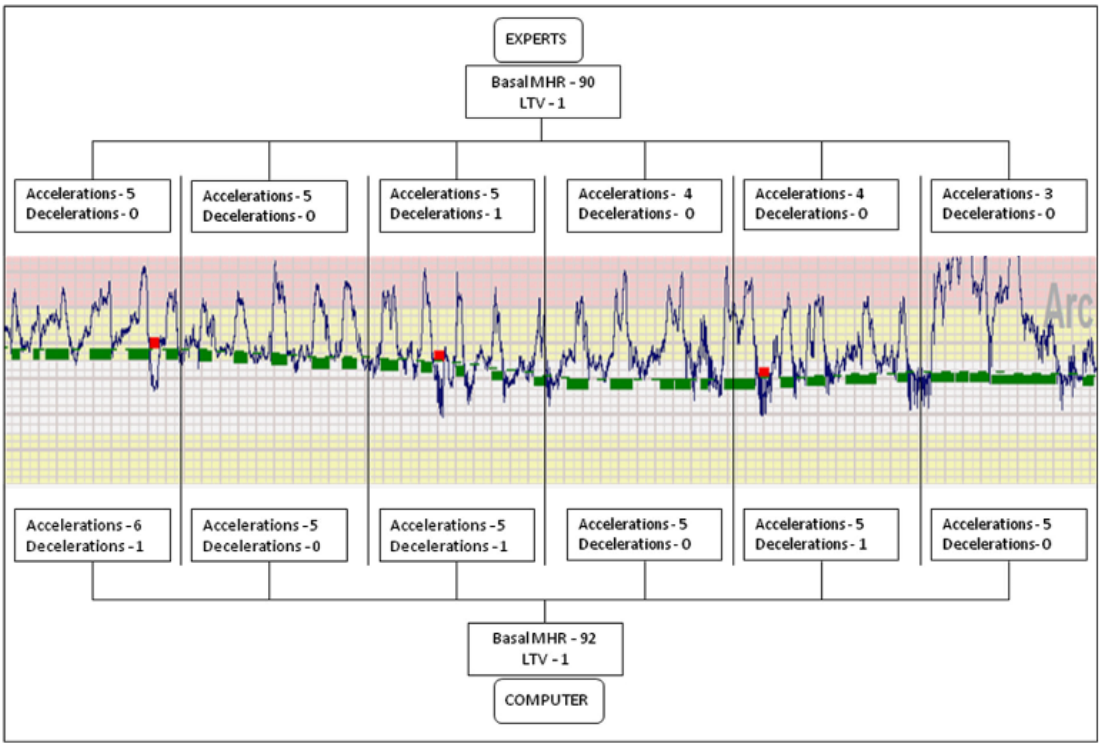

Figure 3. Exemplification of how maternal heart rate (MHR) was analyzed bu the majority-of-experts and by the computer in the second hour of one of the cases included in the study as presented in Table 1 (raw data). Basal MHR and LTV were estimated in a 1h segment and accelerations and decelerations in 10 min segments. For further explanations please see text.

Table 1

Basal maternal heart rate (MHR), long-term variability (LTV), accelerations and decelerations, provided by experts 1-3, by their majority (Maj) and by the computer (Comp), in the second hour of one of the study cases (Fig 3). Basal MHR and LTV were estimated in a 1 h segment and accelerations and decelerations in 10 min segments (raw data). For further explanations please see text.

Hour	10 min segments	Basal MHR					LTV					Accelerations					Decelerations				
		Experts				Comp	Experts				Comp	Experts				Comp	Experts				Comp
		1	2	3	Maj		1	2	3	Maj		1	2	3	Maj		1	2	3	Maj	
2	1	90	90	100	90	92	1	1	1	1	1	5	3	6	5	6	0	0	1	0	1
	2											5	4	5	5	5	0	0	0	0	0
	3											5	5	5	5	5	0	2	1	1	1
	4											4	5	4	4	5	0	0	1	0	0
	5											4	4	5	4	5	0	0	0	0	1
	6											2	3	3	3	5	0	0	0	0	0

Table 2
Inter-observer and computer-observer agreement, reliability and correlation in the estimation of basal maternal heart rate (MHR), accelerations, decelerations and long-term variability (LTV), during an initial and the final hour of labor (hours 1 and 2). PA: Proportion of Agreement; K: Kappa statistic; CI: confidence interval; r: Kendall's tau correlation coefficient; na: not appropriate.

	Agreement, reliability and correlations									
	Inter-observer					Computer-Observer				
	PA	95%CI	K	95%CI	r	PA	95%CI	K	95%CI	r
Hour 1										
Basal MHR	0.97	[0.87,0.99]	0.96	[0.92,1.00]	0,933	0.80	[0.55,0.93]	0.76	[0.57,0.95]	0,907
Accelerations	0.79	[0.74,0.83]	0.57	[0.49,0.66]	0,574	0.72	[0.62,0.79]	0.44	[0.28,0.60]	0,459
Decelerations	0.98	[0.96,0.99]	*Na*	-	*na*	0.99	[0.95,1.00]	*na*	-	*na*
LTV	1.00	[0.99,1.00]	*Na*	-	*na*	1.00	[0.96,1.00]	*na*	-	*na*
Hour 2										
Basal MHR	0.85	[0.80,0.90]	0.83	[0.74,0.92]	0,892	0.90	[0.83,0.97]	0.89	[0.73,1.00]	0,951
Accelerations	0.90	[0.86,0.92]	0.75	[0.67,0.82]	0,748	0.86	[0.78,0.91]	0.67	[0.52,0.81]	0,678
Decelerations	0.99	[0.97,1.00]	*Na*	-	*na*	0.95	[0.90,0.98]	*na*	-	*na*
LTV	1.00	[0.99,1.00]	*Na*	-	*na*	1.00	[0.96,1.00]	*na*	-	*na*
Overall										
Basal MHR	0.91	[0.88,0.94]	0.89	[0.82,0.96]	0,942	0.85	[0.79,0.91]	0.83	[0.71,0.94]	0,935
Accelerations	0.84	[0.81,0.87]	0.66	[0.61,0.72]	0,664	0.79	[0.73,0.84]	0.56	[0.46,0.67]	0,578
Decelerations	0.99	[0.98,0.99]	*Na*	-	*na*	0.98	[0.94,0.99]	*na*	-	*na*
LTV	1.00	[0.99,1.00]	*Na*	-	*na*	1.00	[0.98,1.00]	*na*	-	*na*

RESULTS

There was a statistically significant inter-observer and computer-observer agreement, reliability and correlation in estimation of basal MHR, accelerations, decelerations and LTV, with PA values ranging from 0.72 (95% CI: 0.62–0.79) to 1.00 (95% CI: 0.99–1.00), K values, where appropriate, from 0.44 (IC95%: 0.28–0.60) to 0.89 (95% CI: 0.82–0.96) and coefficients of correlation, where appropriate, from 0.46 to 0.94 (Table 2). K estimation for decelerations and LTV estimation was not performed, as no observer or computer assessments identified repetitive decelerations (except one observer in one 10-min segment), and all assessments identified a normal LTV (≥5 bpm) (Table 2).

MHR exhibited a significantly higher basal MHR, number of accelerations and LTV, in the last hour of labor, when compared to the initial hour (Table 3).

Table 3

Basal maternal heart rate (MHR) and long-term variability (LTV), expressed in beats per minute, as well as number of accelerations and decelerations, in the initial and final hours of labor. Basal MHR and LTV were estimated in a 1 h segment and accelerations and decelerations in 10 min segments. For further explanations please see text.

	Computer analysis of MHR tracings		*p*
	Initial hour	**Final hour**	
Basal MHR *mean (sd)*	76 (11)	81 (12)	0.040
LTV *mean (sd)*	20 (5)	24 (8)	0,002
Accelerations *median (range)*	1 (0-4)	3 (0-6)	< 0.001
Decelerations *median (range)*	0 (0-3)	0 (0-5)	0.028

DISCUSSION

The main motivation for the development of a computer algorithm for on-line MHR analysis was the evidence that an objective method was needed to overcome the limitations and subjectivity of common visual analysis [6,13]. We hope this will improve our approach to MHR recordings misinterpreted as that of the fetus [1–6]. This may also have the potential to improve our capability to monitor the overall maternal–fetal condition, with, or without, other methods for linear and non-linear heart rate analysis, to be explored in future studies [8–12].

A novel algorithm for on-line computer analysis of MHR tracings was developed based on the experience obtained in FHR analysis using the FIGO guidelines for fetal monitoring [21–26] based, essentially, on the evidence that MHR and FHR recordings are morphologically similar (and sometimes coincident) and have similar sympathetic and parasympathetic backgrounds [11,12,17]. An inter-observer and computer-observer agreement and reliability study was performed according to the Guidelines for Reporting Reliability and Agreement Studies [28,29], as well as a correlation study. A relatively higher agreement, expressed by the PA, was obtained, when compared to the reliability, expressed by the K statistic, and to the correlation, expressed by Kendall's tau coefficient of correlation, because of the dispersion of results in the different categories considered for each MHR variable [29,31]. This was particularly evident in the assessment of LTV (Table 2), where spuriously high PA values were obtained because all cases were assigned to category 1 (LTV ≥5 bpm) and none to category 0 (<5 bpm). K statistics and correlation were not assessed for this variable, as inadequately biased K values and correlation coefficients are obtained when only one of the categories is assigned by observers [29,31]. A similar situation occurred with decelerations, where in all, but one, of the 240 considered 10-min MHR segments, experts assigned sporadic decelerations. Rarely will mothers attain health conditions associated with reduced LTV and repetitive decelerations. Therefore, these aspects may warrant further investigation and refinement of MHR analysis.

Inter-observer agreement and reliability in visual assessment of MHR tracings, with high PA and fair to good K statistics and correlation coefficients, (Table 2) compare well to the results obtained by Sherman et al. in a study on visual analysis of simultaneous MHR and FHR recordings [17]. The results also compare favorably with studies on inter-observer agreement and reliability performed in visual assessment of FHR tracings [14,15]. This suggests that

agreement, reliability and correlation may be more of a problem when equivocal guidelines are used, or when too many categories are analyzed. Computer-observer agreement, reliability and correlation, namely in estimation of basal MHR and accelerations, also provided high PA, K and correlation values (Table 2). These results are similar to those obtained by the Omniview-SisPorto® system in FHR analysis [30,32,33], and suggest that the algorithm developed for MHR analysis may be used as a valid tool for on-line intrapartum maternal–fetal monitoring.

We also observed that normal MHR recordings during labor exhibit a well-defined basal MHR and accelerations (Figs. 2 and 3), as reported by Sherman et al. [17], rather than decelerations, as claimed by Van Veen et al. [16]. This may explain why these signals can be so easily confused with FHR signals, namely during episodes of MHR accelerations associated with uterine contractions and FHR decelerations (Fig. 2). Confusion may also occur more frequently when MHR is increased, as with fever or infection, or when FHR is decreased in association with hypoxia or cardiac block. However, it should be taken into account that in our study all but one woman received epidural anesthesia. Epidural use during labor is very prevalent in many countries [34] and this allows the generalization of the study conclusions to centers where the technique is available. However, epidural may have influenced the type of MHR patterns recorded by us. In our study, women under epidural anesthesia remained with stable blood pressures, and mean MHR, and with similar MHR patterns to the ones reported by other authors [17]. Further studies are warranted to evaluate whether epidural anesthesia influences MHR patterns. To our knowledge, this has only been studied by Lao et al., who found differences in MHR variability between women requesting the technique, but only before epidural placement, and not after that [12]. A parallel observation, in alignment with the report of Sherman et al. [17], was of a higher basal MHR and number of accelerations, in the last hour of labor (Table 3). This suggests that developed computer analysis of MHR recordings may also be useful to characterize maternal–fetal pathophysiological changes occurring with the progression of labor. Further studies with the developed algorithm and other alternatives, such as spectral and entropy analysis [8–12], are warranted.

Hopefully, the more objective method for visual analysis of MHR tracings and the novel algorithm for on-line computer analysis described in this paper may improve maternal–fetal monitoring. Furthermore, computer analysis provides better tracing storage and retrieval, as well as MHR analysis using algorithms with improved diagnostic capabilities.

SUMMARY

Maternal heart rate (MHR) recordings are morphologically similar and sometimes coincident with fetal heart rate (FHR) recordings and may be useful for maternal–fetal monitoring during labor if appropriately interpreted. However, similarly to FHR, visual interpretation of MHR features may be poorly reproducible. With this in mind, a computer algorithm for on-line MHR analysis running under a Microsoft Windows environment was developed based on a previously existing version for FHR analysis, inspired in the FIGO guidelines for fetal monitoring.

MHR signals were acquired with electrocardiography and conveyed at 4 Hz to a personal computer, along with FHR and uterine contraction signals. The analysis algorithm was similar to a previously developed version for on-line FHR analysis, with a scale conversion obtained by adding 50 beats/min (bpm) to the original MHR values, except when those values corresponded to periods of signal loss. The signal was subjected to a pre-processing algorithm, for removal of noise and calculation of signal loss and signal quality. Short-term variability (STV) was determined as the difference between two adjacent MHR beats and considered abnormal when lower than 1 bpm. MHR baseline was estimated using a complex algorithm, based on histogram and STV analysis. Accelerations and decelerations were subsequently detected as deviations,

above or below baseline, with at least 15 bpm in amplitude and 15s duration. Finally, LTV was estimated in segments not considered accelerations or decelerations, as the difference between the highest and lowest values in a sliding window of one minute, and was classified as abnormal when < 5 bpm.

To evaluate the algorithm's performance, inter-observer and computer-observer agreement, reliability and correlation were evaluated in 40 one-hour recordings obtained from 20 women in the last 2 h of labor. Agreement was assessed in the detection of basal MHR, LTV, accelerations and decelerations. The proportions of agreement (PA) and Kappa statistic (K), with 95% confidence intervals (95% CI), as well as Kendall's tau correlation coefficient, were used for statistical analysis. Changes in MHR characteristics between the first and second hours of the tracings were evaluated using the Wilcoxon rank test. There was a statistically significant inter-observer and computer-observer agreement, reliability and correlation in estimation of the basal MHR, accelerations, decelerations and LTV, with PA values ranging from 0.72 (95% CI: 0.62–0.79) to 1.00 (95% CI: 0.99–1.00), K values from 0.44 (IC95%: 0.28–0.60) to 0.89 (95% CI: 0.82–0.96) and correlation coefficients from 0.46 to 0.94. Moreover, MHR exhibited a significantly higher basal MHR, number of accelerations and LTV in the last hour of labor, when compared to the initial hour.

The developed algorithm for on-line computer analysis of MHR recordings provided good to excellent computer-observer agreement and reliability, showing that it can be safely used for MHR analysis. Moreover, it allowed the detection of MHR changes associated with labor progression, providing more information about the interpretation of maternal–fetal monitoring during labor.

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CHAPTER 3

IMPROVEMENT IN FETAL HEART RATE ANALYSIS BY THE REMOVAL OF MATERNAL-FETAL HEART RATE AMBIGUITIES

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IMPROVEMENT IN FETAL HEART RATE ANALYSIS BY THE REMOVAL OF MATERNAL-FETAL HEART RATE AMBIGUITIES

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ABSTRACT

Background

Misinterpretation of the maternal heart rate (MHR) as fetal may lead to significant errors in fetal heart rate (FHR) interpretation. In this study we hypothesized that the removal of these MHR-FHR ambiguities would improve FHR analysis during the final hour of labor.

Methods

Sixty-one MHR and FHR recordings were simultaneously acquired in the final hour of labor. Removal of MHR-FHR ambiguities was performed by subtracting MHR signals from their FHR counterparts when the absolute difference between the two was less or equal to 5 beats per minute. Major MHR-FHR ambiguities were defined when they exceeded 1% of the tracing. Maternal, fetal and neonatal characteristics were evaluated in cases where major MHR-FHR ambiguities occurred and computer analysis of FHR recordings was compared, before and after removal of the ambiguities.

Results

Seventy-two percent of tracings (44/61) exhibited episodes of major MHR-FHR ambiguities, which were not significantly associated with any maternal, fetal or neonatal characteristics, but were associated with MHR accelerations, FHR signal loss and decelerations. Removal of MHR-FHR ambiguities resulted in a significant decrease in FHR decelerations, and improvement in FHR tracing classification.

Conclusions

FHR interpretation during the final hour of labor can be significantly improved by the removal of MHR-FHR ambiguities.

BACKGROUND

Fetal heart rate (FHR) monitoring may be affected by the temporary acquisition of the maternal heart rate (MHR), both when using external monitoring with Doppler ultrasound [1], and when using internal monitoring with electrocardiography (ECG) [2-6]. Inadvertent MHR acquisition with external monitoring has been reported in up to 90% of intrapartum recordings, for an average of 6.2% of tracing length [1], while with internal monitoring it is usually due to the detection of maternal signals transmitted via the fetal electrode in cases of fetal death [2,5]. Overall, significant errors in FHR interpretation may occur, including missing the diagnoses of newborn acidemia [7,8] and fetal death [2-6].

Some methods reduce the occurrence of these MHR-FHR ambiguities. FHR signal acquisition with internal [9,10] or transabdominal [1] ECG, rather than with Doppler ultrasound, has been shown to improve signal quality, making it less prone to MHR-FHR ambiguities [1,9,10]. Simultaneous registration of the MHR using ECG or oximetry [7,11] allows a comparison of MHR and FHR recordings and facilitates the detection of overlapping segments. Detection of P waves in the fetal ECG may be also helpful as a marker of fetal signals [12]. Visualization of FHR movements on ultrasound is recommended in doubtful cases, namely when fetal death is suspected [11].

While there is a reasonable amount of evidence to document cases of missed newborn acidemia and fetal death associated with MHR-FHR ambiguities, little research has been published on more subtle signal contaminations [1]. In particular, the effect of systematic cleaning of the FHR signal when MHR is suspected has, to our knowledge, not been previously evaluated.

The objective of this study was to assess the effect of removal of MHR-FHR ambiguities on the analysis of FHR recordings, during the last hour of labor. The hypothesis was that this would alter the identification of some FHR features and thus improve overall tracing classification.

METHODS

The study followed the Helsinki Declaration, was approved by the local Ethics Committee (“Comissão de Ética do SESARAM”) and all women gave their informed written consent to participate. Sixty-two consecutively acquired simultaneous recordings of MHR and external FHR, with good signal quality were selected, from the same number of labouring women, with uneventful singleton pregnancies, with fetuses in cephalic presentations, in the last recorded hour before birth (with a maximum 10-minute interval before vaginal delivery or 30 minutes before caesarean delivery). All but two women were under epidural analgesia on request. Labor protraction or arrest, secondary to poor uterine activity, was treated with oxytocin, according to the local protocol. No other drugs with a potential to effect MHR or FHR were administered, namely salbutamol or parasympathetic agonists.

Gestational ages were confirmed by first trimester ultrasound dating, Apgar scores were estimated by the attending healthcare professional, and umbilical artery blood pH was obtained by paired sampling immediately after birth.

For acquisition of MHR signals, an ECG sensor was connected to three electrodes positioned on the maternal thorax, and for FHR signals a Doppler ultrasound probe was placed on the maternal abdomen. One case was excluded because of poor signal quality that required conversion to internal FHR monitoring. Acquisition of signals at 1600 Hz and heart rate (HR)

extraction was performed using a STAN® 31 fetal monitor (Neoventa Medical, Gothemburg, Sweden).

HR, in beats per minute (bpm), was then conveyed at 4-Hz via the digital port of the fetal monitor to the Omniview-SisPorto® system (Speculum, Lisbon, Portugal) for signal recording and analysis. The system closely follows the International Federation of Gynaecology and Obstetrics (FIGO) guidelines for fetal monitoring [13-16] and has been extensively validated both in the ante [16,17] and intrapartum periods [15,17,18,19]. Analysis is carried out without signal reduction or averaging (Figure 1). The baseline is estimated using a complex algorithm based on histogram and STV analysis, aimed at finding the HR level of stable segments with normal variability, within the physiological limits of 110-150 bpm [14,15,16]. STV is determined as the difference between two adjacent HR beats, and considered abnormal when lower than 1 beat per minute. Accelerations and decelerations are detected as HR deviations, above or below baselines, with at least 15 bpm of amplitude and 15 seconds duration. LTV is estimated in HR segments that do not display accelerations or decelerations, as the difference between the highest and lowest values, in a sliding window of one minute, and is classified as abnormal when < 5 bpm [13,14,15,16]. All of these basic FHR features are then used by the system to elicit an overall tracing classification, as green or blue (normal tracing), yellow (suspicious tracing) or red (pathologic tracing) [13,14]. The system was developed essentially for FHR analysis, but the same principles were applied in this study for analysis of the MRH, after scale conversion [13].

To remove MHR-FHR ambiguities, FHR signals were subtracted of their MHR counterparts when the absolute difference between them was equal or less than 5 bpm. This threshold was based on a report by Reinhard et al [1] and on a pilot test performed in five cases with typical MHR-FHR ambiguities detected by visual analysis. Major MHR-FHR ambiguities were defined when more than 1% of the tracing was affected and minor ambiguities when this value was between 0 and 1% (Table 1).

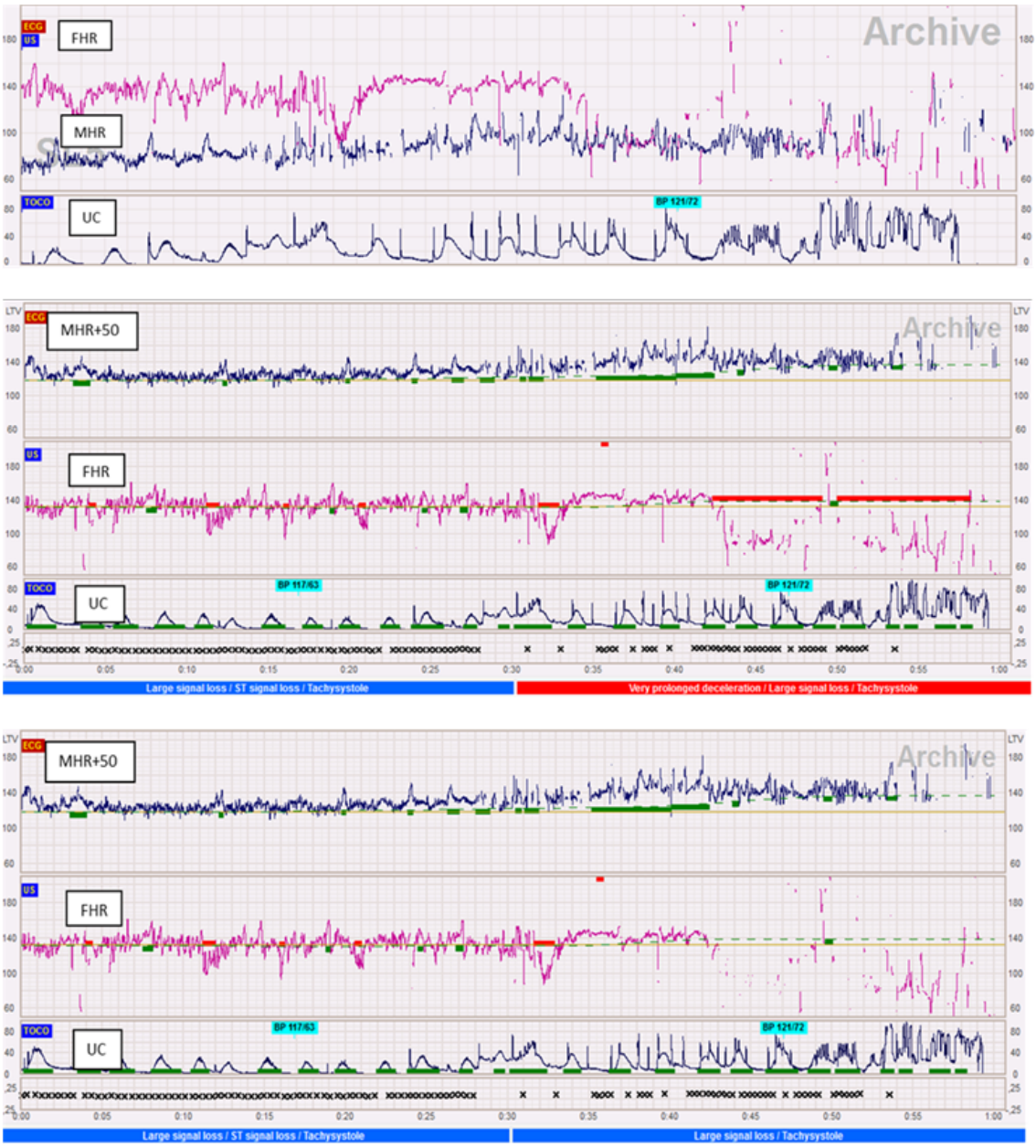

Figure 1 Maternal heart rate (MHR) baseline misinterpreted as a prolonged fetal heart rate (FHR) deceleration. **Detailed legend:** Top: simultaneous recording of the last 45 minutes of the MHR (black), FHR (pink) and uterine contractions (UC) signals; Middle and Bottom: computer analysis before and after removal of MHR-FHR ambiguities. For computerized analysis of MHR tracings, a scale change (MHR + 50 beats per minute) was performed (last hour). After the removal of ambiguities, the FHR alarm changed from red to blue.

Maternal, fetal and neonatal characteristics associated with major and minor MHR-FHR ambiguities were evaluated (Table 2). In tracings with and without major ambiguities, computer analysis of FHR recordings before and after the deletion of ambiguities was compared, (Table 3), and the association between FHR classification and newborn umbilical artery blood pH < or ≥ 7.15 was assessed (Table 4).

For statistical analysis, the results were expressed as medians (with inter-quartile ranges), for skewed continuous variables. The Mann-Whitney test was used to compare the groups with minor or major ambiguities (Table 1) and the Wilcoxon sign rank was used to compare the classification results before and after removal of ambiguities (Table 2). For other continuous

variables, results were expressed as means and standard deviations. The independent sample t test was used to compare the groups with minor or major ambiguities (Table 1) and the paired t test was used to evaluate results before and after removal of ambiguities (Table 2). To compare categorical variables between minor or major ambiguity groups (Table 1) and before and after ambiguity removal (Tables 2 and 3), the Chi-square (or Fisher exact test) and McNemar tests were used, respectively. Ninety-five percent confidence intervals were calculated as appropriate and p-values considered significant at less than 0.05.

RESULTS

The general maternal, fetal, delivery and newborn characteristics, in relation with the presence of minor and major MHR-FHR ambiguities, are presented in Table 1. Overall, average maternal body mass index and age were, respectively, 27 Kg/m^2 (SD:3) and 28 years (SD:5). Average gestational age was 39 weeks (SD:1). Twenty-six percent of women were multiparous and all fetuses were in cephalic presentation. The average systolic and diastolic blood pressures were, respectively, 122 (SD:11) and 74 mm Hg (SD:8) and the average axillary temperature was 36.2 ºC (SD:0).

C-section was performed in 10% of the group and instrumental vaginal delivery in 38%. All C-sections were performed during the first stage of labor because of protracted or arrested labour. Forty-four percent of newborns were males, with an average one and five-minute Apgar score of 9 (range: 9-10) and 10 (range:10-10), respectively. The average umbilical artery blood pH was 7.24 (SD:0.07). The average length of the active phase of labour was 297 minutes (SD:170).

Five tracings did not exhibit any MHR-FHR ambiguity, 12 exhibited 1% of ambiguities and 44 (72%) exhibited major MHR-FHR ambiguities (11 tracings with 2%, 7 with 3%, 5 with 4% and 21 with 6-33%).

In the group with minor MHR-FHR ambiguities, maternal, fetal, delivery and newborn characteristics were similar in the five cases that did not exhibit any ambiguity compared with the 12 cases that exhibited 1% of ambiguities. Major ambiguities were significantly associated with MHR accelerations, FHR signal loss, decelerations and yellow or red alarms, when compared with minor ambiguities (Table 1).

Table 1. Maternal, fetal, delivery and newborn characteristics associated with minor and major MHR-FHR ambiguities. SD: standard deviation; IQR: inter-quartile range. BMI: body mass index

	MHR-FHR ambiguity		
	Minor (n=17)	**Major (n=44)**	**p**
Maternal characteristics			
Age (years) *mean (SD)*	26 (6)	28 (5)	0.134
BMI *mean (SD)*	27 (3)	28 (3)	0.186
Multiparity *n (%)*	5 (29)	11 (25)	0.752
Labour			
Epidural *n (%)*	17 (100)	42 (95)	1.000
Mode of delivery			0.105
Cesarean *n (%)*	4 (24)	2 (4)	
Operative vaginal *n (%)*	5 (29)	18 (41)	
Normal vaginal *n (%)*	8 (47)	24 (55)	
MHR			
Signal loss (%) *median (IQR)*	9 (1 to 11)	6 (1 to 16)	0.834
Basal MHR (bpm) *mean (SD)*	80 (12)	77 (12)	0.292
Accelerations (n) *mean (SD)*	12 (6)	18 (10)	**0.013**
Decelerations (n) *median (IQR)*	0 (0 to 0.5)	0 (0 to 0)	0.913
Abnormal LTV (%) *median (IQR)*	0 (0 to 0)	0 (0 to 0)	0.705
FHR			
Signal loss (%) *mean (SD)*	13 (7)	22 (11)	**0.002**
Baseline(bpm) *mean (SD)*	140 (10)	136 (12)	0.180
Accelerations (n) *median (IQR)*	9 (3 to 15)	7 (4 to10)	0.415
Decelerations (n) *median (IQR)*	3 (1 to 7)	8 (6 to 10)	**0.002**
Prolonged decelerations (n) *median (IQR)*	0 (0 to 0)	0 (0 to 1)	0.073
Abnormal LTV (%) *median (IQR)*	3 (1 to 9)	1 (0 to 3)	0.055
Alarm *n (%)*			**0.001**
Green-blue	14 (82)	15 (34)	
Yellow-red	3 (18)	29 (66)	
Newborn			
Gestational age (weeks) *mean (SD)*	39 (1)	39 (1)	0.672
Male *n (%)*	8 (47)	26 (59)	0.396
Birthweight (grams) *mean (SD)*	3171 (366)	3254 (318)	0.384
Apgar 1 *median (IQR)*	9 (9 to 10)	9 (9 to 10)	0.530
Apgar 5 *median (IQR)*	10 (10 to 10)	10 (10 to 10)	0.298
UAB pH *mean (SD)*	7.25 (0.08)	7.24 (0.07)	0.586

Removal of ambiguities resulted in a significant increases in FHR signal loss, both in cases with minor and major ambiguities. When major ambiguities occurred, a decrease in the number of FHR decelerations, and a decrease in the false positive rate of yellow-red alarms for the detection of acidemic fetuses, were also observed, but this was not seen with minor ambiguities (Tables 2 and 3).

Table 2. Computer analysis of FHR tracings in cases with and without major MHR-FHR ambiguities, before and after their removal. SD: standard deviation; IQR: inter-quartile range.

	N	Before	After	p
No major MHR-FHR ambiguity				
Signal loss (%) *mean (SD)*	17	13 (7)	14 (7)	**<0.001**
Basal FHR (bpm) *mean (SD)*	17	140 (10)	140 (10)	1.000
Accelerations (n) *median (IQR)*	17	9 (3 to 15)	9 (3 to 15)	0.157
Sporadic decelerations (n) *median (IQR)*	17	3 (2 to 11)	3 (1 to 8)	0.317
Prolonged decelerations (n) *median (IQR)*	17	0 (0 to 0)	0 (0 to 0)	1.000
Abnormal LTV (%) *median (IQR)*	17	3 (0 to 7)	3 (1 to 11)	0.317
Alarm *n (%)*	17			1.000
Green-Blue		14 (82)	14 (82)	
Yellow-red		3 (18)	3 (18)	
Major MHR-FHR ambiguity				
Signal loss (%) *mean (SD)*	44	22 (11)	28 (13)	**<0.001**
Basal FHR (bpm) *mean (SD)*	44	136 (13)	136 (12)	0.129
Accelerations (n) *median (IQR)*	44	7 (4 to 10)	6 (3 to 10)	0.285
Sporadic decelerations (n) *median (IQR)*	44	8 (6 to 10)	6 (4 to 10)	**0.001**
Prolonged decelerations (n) *median (IQR)*	44	0 (0 to 1)	0 (0 to 0)	**0.046**
Abnormal LTV (%) *median (IQR)*	44	1 (0 to 3)	1 (0 to 3)	0.414
Alarm *n (%)*	44			**0.021**
Green-Blue		15 (34)	23 (52)	
Yellow-red		29 (66)	21 (48)	
Overall				
Signal loss (%) *mean (SD)*	61	20 (11)	24 (13)	**<0.001**
Basal FHR (bpm) *mean (SD)*	61	137 (12)	137 (12)	0.129
Accelerations (n) *median (IQR)*	61	7 (4 to 10)	7 (3 to 10)	0.170
Sporadic decelerations (n) *median (IQR)*	61	7 (4 to 10)	6 (3 to 9)	**0.001**
Prolonged decelerations (n) *median (IQR)*	61	0 (0 to 1)	0 (0 to 0)	**0.046**
Abnormal LTV (%) *median (IQR)*	61	1 (0 to 4)	2 (0 to 5)	0.197
Alarm *n (%)*				**0.021**
Green-Blue		29 (48)	37 (61)	
Yellow-red		32 (52)	24 (39)	

Table 3. Changes in overall FHR classification before and after the removal of MHR-FHR ambiguities, in acidemic and non-acidemic cases (umbilical artery blood pH < 7.15 or ≥ 7.15).

	Before n (%)	After n (%)	P
Acidemic newborns (n=7)			1.000
Green-Blue	3 (57)	3 (57)	
Yellow-red	4 (43)	4 (43)	
Non-acidemic newborns (n=54)			**0.021**
Green-Blue	26 (48)	34 (63)	
Yellow-red	28 (52)	20 (37)	

DISCUSSION

In this study, 72% of tracings acquired in the last recorded hour of labour exhibited episodes of major MHR-FHR ambiguity. This concurs with the report by Reinhard et al. [1] showing that MHR-FHR ambiguities with clinical significance may be much more frequent and subtle than suggested by anecdotal reports published in the literature, most of them confined to extreme cases of fetal acidemia or death [2-8].

Another finding in the present study is that MHR-FHR ambiguities should not only be suspected when accelerations coincide with uterine contractions [2-8,10], but also when FHR decelerations occur in association with signal loss (Table 1 and Figure 1). Most MHR tracings are characterized by repetitive accelerations, which may overlap FHR signals and mimic FHR decelerations or baseline segments during episodes of FHR signal loss [15,20,21] (Figure 1). With the high epidural rate observed in this population, it is possible that there was a lower increase in MHR during active pushing, and therefore only a few cases of suspected FHR accelerations due to inadvertent MHR recording were detected. Only 7% cases had a MHR baseline above 100 bpm, and in no cases it exceeded 110 bpm. MHR accelerations rarely reached the FHR baseline and this resulted in frequent MHR-FHR ambiguities being caused by MHR baseline segments being confused with FHR decelerations (Figure 1). It may be almost impossible to detect subtle misinterpretations without computer analysis of simultaneous MHR and FHR recordings [20], with automated detection of ambiguities.

C-sections were not evaluated separately as risk factor of MHR-FHR ambiguities because of the small number of cases. However, it was observed that C-sections were associated with fewer MHR-FHR ambiguities, although without assessing statistical significance. This probably occurred because C-sections were performed predominantly during the first stage of labour. The second stage is characterized by higher signal loss, more frequent MHR accelerations and FHR decelerations. Further studies to assess if C-section is an independent risk factor for major MHR-FHR ambiguities are warranted.

To our knowledge, the effect of systematic removal of MHR-FHR ambiguities has not been previously assessed. In this study, removal of ambiguities resulted in a significant increase in FHR signal loss, along with a decrease in the number of FHR decelerations and an improvement in tracing classification (Tables 2 and 3). Again, the improvements were more often related with the misinterpretation of FHR decelerations than accelerations. If our results are confirmed in larger studies, it may be possible to decrease the unnecessary intervention associated with false positive yellow-red alarm in non-acidemic fetuses, without compromising sensitivity.

Several limitations need to be considered in this study and should be taken in consideration of future research. Firstly, a higher-risk population needs to be evaluated, as the number of cases with umbilical artery pH under 7.15 was low, and this 10th percentile cut-off value has limited clinical significance [22,23]. Secondly, other methods for simultaneous MHR signal acquisition need to be evaluated, namely those using oximetry. Thirdly, the criterion used for removal of MHR-FHR ambiguities [1] may benefit from refinement after analysis of cases with adverse perinatal outcome, ideally using simultaneous internal FHR monitoring as the gold standard for fetal signals.

In conclusion, removal of MHR-FHR ambiguities resulted in a significant decrease in FHR decelerations and an improvement in tracing classification. Larger studies are needed to confirm the impact of this methodology on the diagnostic accuracy of intrapartum cardiotocography.

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CHAPTER 4

COMPUTER ANALYSIS OF MATERNAL-FETAL HEART RATE RECORDINGS DURING LABOR IN RELATION WITH MATERNAL-FETAL ATTACHMENT AND PREDICTION OF NEWBORN ACIDEMIA

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COMPUTER ANALYSIS OF MATERNAL-FETAL HEART RATE RECORDINGS DURING LABOR IN RELATION WITH MATERNAL-FETAL ATTACHMENT AND PREDICTION OF NEWBORN ACIDEMIA

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ABSTRACT

Objective

To assess combined maternal (MHR) and fetal heart rate (FHR) recordings during labor, in relation with maternal-fetal attachment and prediction of newborn acidemia.

Study design

Fifty-nine simultaneous MHR and FHR recordings were acquired in the final minutes of labor. Computer analysis followed the FIGO guidelines with estimation of MHR and FHR baselines, accelerations, decelerations, short (STV) and long term variabilities. MHR and FHR characteristics, their differences and correlations were assessed in relation to labor progression and to newborn umbilical artery blood pH lower than 7.15 and 7.20. To assess prediction of acidemia, areas under ROC curves (auROC) were calculated.

Results

Progression of labor was associated with a significant increase in MHR accelerations and FHR decelerations both in non-acidemic and acidemic fetuses ($p<0.01$). At the same time there was an increase in MHR-FHR correlations and differences in accelerations and decelerations in acidemic fetuses. The auROC ranged between 0.50 for FHR accelerations to 0.77 for MHR baseline plus FHR STV.

Conclusions

MHR and FHR respond differently during labor with signs of increased maternal-fetal attachment during labor progression in acidemic fetuses. Combined MHR-FHR analysis may help to improve prediction of newborn acidemia compared with FHR analysis alone.

INTRODUCTION

There is scarce information about maternal (MHR) and fetal heart rate (FHR) interaction during labor and research has mainly focused on the misidentification of MHR as FHR [1,2]. Some studies have assessed the relationship between maternal pathological conditions and neonatal mother-infant attachment [3], as well as the underlying physiopathological pathways [4], keeping in mind the importance of this for the future development of the child [5]. There is also evidence of increased heart rate variability correlation between mother and child immediately pre-operation [6]. However, to our knowledge, these aspects have never been assessed in relation to labor progression. Moreover, combined analysis of MHR and FHR recordings [1] in prediction of newborn acidemia has also never been explored.

In this study we explore the evolution of simultaneous MHR and FHR recordings during labor in relation to the maternal-fetal attachment concept [3,4] and the prediction of newborn acidemia.

MATERIAL AND METHODS

The study followed the Helsinki Declaration, was approved by the local Ethics Committee and all women gave their informed consent to participate.

Fifty-nine 100 min simultaneous MHR and FHR recordings, with good signal quality, consecutively acquired by the same researcher, were obtained from uneventful singleton pregnancies, with fetuses in cephalic presentation, until a maximum of 10 minutes before a vaginal delivery or 30 minutes before a caesarean birth. As the study was exploratory from its outset, implying the implementation of a MHR-FHR monitoring protocol not used in clinical practice, and limited resources to do it, a pragmatic population selection was adopted based on a previous study on FHR analysis alone [7].

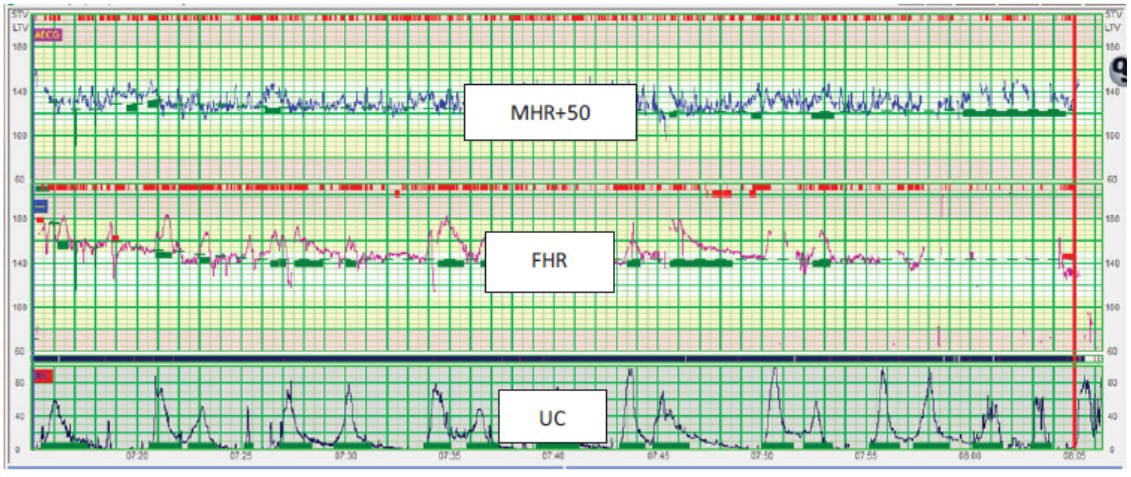

Figure 1. Example of a computer analysis of a simultaneous maternal (MHR), fetal heart rate (FHR) and uterine contraction (UC) recording, as displayed by the Omniview-SisPorto system. MHR is displayed plus 50 beats per minute (MHR+50). Accelerations and UC are depicted with green bars underneath and deceleration with red bars on top, in colour prints, or just gray bars, in black and white prints. For further explanations please see text and reference [1].

For acquisition and analysis of MHR and FHR signals a specially conceived system, following the FIGO guidelines [8] was used, based on the Omniview-SisPorto® system (Speculum, Lisbon, Portugal) described in detail elsewhere [1]. In short, MHR signals were obtained via an

electrocardiography (ECG) sensor connected to the maternal thorax, while for the FHR signals an ultrasound sensor was placed on the maternal abdomen [1]. Both MHR and FHR sensors were connected to a conventional STAN® 31 fetal monitor (Neoventa Medical, Gothemburg, Sweden) coupled to the Omniview-SisPorto® system. Computer analysis (Figure 1) included the estimation of signal loss (SL), abnormal short-term variability (STV), baseline, abnormal long-term variability (LTV), accelerations, decelerations and uterine contractions. STV was determined as the difference between two adjacent MHR beats and considered abnormal when lower than 1 beat per minute (bpm). MHR and FHR baselines were estimated using complex algorithms based on histogram and STV analysis. Accelerations and decelerations were detected as sharp deviations above or below baselines, with at least 15 bpm amplitude and 15 seconds duration. LTV was estimated, in segments not displaying accelerations or decelerations, as the difference between the highest and lowest values in a sliding window of one minute and was classified as abnormal when under 5 bpm [1,8].

FHR baseline has been associated with the intrinsic fetal cardiac chronotropic activity, under basal, central and autonomic, nervous system activities, while STV and LTV reflect the continuous, basal and active, balance between the mentioned nervous activities; accelerations are associated with fetal behavioural states and sympathetic activity and decelerations with parasympathetic activity, generally elicited by chemo or baroreceptor stimulation [8]. MHR baseline, STV, LTV, accelerations and decelerations may be observed in similar situations, as the ones described for FHR, but, to our knowledge, these MHR variables have only been scarcely assessed before [1,9].

Individual MHR and FHR characteristics, their differences and correlations were assessed in relation to labor progression and to the newborn umbilical artery blood (UAB) pH.

The main maternal and fetal characteristics were described using means and standard deviations, medians and ranges or frequencies, as appropriate (Table 1). Mann-Whitney tests, t-tests or chi-square tests were used to compare non-acidemic with acidemic fetuses (Tables 1 and 2) and paired sample t-tests or Wilcoxon rank signed tests to compare the first and the last 50 recording minutes (Table 2). Mean differences between FHR and MHR values were presented with 95% confidence intervals and MHR-FHR correlations were calculated using the Pearson or Spearman correlation coefficients with 95% confidence intervals (Table 3). To assess prediction of acidemia, areas under ROC curves (auROC) with 95% confidence intervals were calculated, using uni and bivariate logistic regression, considering the FHR or/and MHR baselines, accelerations, decelerations, STV<1 and LTV<5, obtained during the last 50 recording minutes (Table 4). Statistical significance was set at p values < 0.05.

Given the small number of cases with low UAB pH values, we considered the relatively high, but still clinically significant, UAB pH thresholds of 7.20 and 7.15 [10].

Table 1

Main maternal and fetal characteristics of the studied population in relation to the newborn umbilical artery blood pH ≥ 7.20 or < 7.20 (non-acidemic and acidemic fetuses, respectively).

	Non-acidemic fetuses n=45	Acidemic fetuses n=14	p
Maternal data			
Age (years) *mean (sd)*	27 (5)	27 (6)	0.680
Multipara *n (%)*	13 (29)	3 (21)	0.738
Gestational age (weeks) *mean (sd)*	39 (1)	39 (1)	0.119
Delivery: *n (%)*			1.000
Vaginal	32 (71)	10 (71)	
Operative vaginal	8 (18)	3 (21)	
Cesarean section	5 (11)	1 (7)	
Epidural analgesia *n (%)*	43 (96)	14 (100)	1.000
Newborn data			
Birthweight (grams) *mean (sd)*	3241 (340)	3200 (292)	0.682
1 minute Apgar score *med (min-Max)*	9 (9-7)	9 (8-10)	0.143
5 minute Apgar score *med (min-Max)*	10 (9-10)	10 (9-10)	0.563
Umbilical artery blood pH *mean (sd)*	7.276 (0.044)	7.146 (0.052)	**<0.001**
Male Gender *n (%)*	27 (60)	7 (50)	0.508

Table 2. Maternal (MHR) and fetal heart rate (FHR) variables, during the last two periods of 50 minutes of labor, in fetuses delivered with umbilical artery bloo pH ≥ 7.20 (non-acidemic) and < 7.20 (acidemic). Means (standard deviations) or medians (minimum-maximum) are presented as appropriate.

	First 50 minutes				Last 50 minutes				p	p
	MHR		FHR		MHR		FHR		First *versus* Last Minutes	Non-acidemic *versus* acidemic
	Non-acidemic	Acidemic	Non-acidemic	acidemic	Non-acidemic	acidemic	Non-acidemic	Acidemic		
Baseline *mean (sd)*	132 (14)	128 (10)	142 (9)	137 (12)	135 (13)	129 (11)	140 (10)	139 (15)		
Accelerations total *med (m-M)*	8 (0-31)	7 (1-22)	5 (0-24)	5 (0-17)	11 (0-34)	14 (2-23)	5 (0-21)	4.5 (1-22)	1,2	
Decelerations total *med (m-M)*	0 (0-2)	0 (0-20)	3 (0-18)	4 (0-10)	0 (0-8)	0 (0-3)	5.5 (0-16)	5.5 (3-20)	3	
STV < 1 *mean (sd)*	32 (12)	26 (10)	48 (10)	40 (8)	31 (10)	26 (10)	44 (11)	37 (8)	3	b,d
LTV < 5 *med (m-M)*	0 (0-78)	0 (0-0)	5 (0-28)	0 (0-29)	0 (0-25)	0 (0-0)	1.5 (0-21)	1.5 (0-9)	3	b
Accelerations *med (m-M)*										
10 min S1 (FCM1 or FCF1)	1 (0-7)	1 (0-5)	1 (0-6)	1 (0-6)	1 (0-8)	1 (0-4)	1 (0-6)	1 (0-6)		
10 min S2 (FCM2 or FCF2)	2 (0-6)	0 (0-3)	0.5 (0-7)	1.5 (0-6)	2 (0-7)	1.5 (0-7)	0.5 (0-6)	1 (0-4)	2	a
10 min S3 (FCM3 or FCF3)	1 (0-6)	2 (0-4)	0 (0-6)	1 (0-5)	2 (0-8)	3.5 (0-6)	1 (0-5)	0.5 (0-4)	1	
10 min S4 (FCM4 or FCF4)	2 (0-9)	1.5 (0-7)	1 (0-6)	0.5 (0-4)	2 (0-8)	3 (0-6)	0 (0-6)	1 (0-4)	1	
10 min S5 (FCM5 or FCF5)	2 (0-7)	1.5 (0-6)	0 (0-4)	0.5 (0-6)	3 (0-7)	3.5 (1-6)	0 (0-5)	0.5 (0-5)	1,2	
Decelerations *med (m-M)*										
10 min S1 (FCM1 or FCF1)	0 (0-2)	0 (0-1)	0 (0-5)	0 (0-4)	0 (0-5)	0 (0-1)	0 (0-3)	1 (0-3)		
10 min S2 (FCM2 or FCF2)	0 (0-1)	0 (0-0)	-	-	0 (0-3)	0 (0-1)	0 (0-4)	1 (0-3)		
10 min S3 (FCM3 or FCF3)	0 (0-1)	0 (0-0)	0 (0-6)	1 (0-3)	0 (0-1)	0 (0-2)	1 (0-6)	1 (0-8)	3	b
10 min S4 (FCM4 or FCF4)	0 (0-1)	0 (0-0)	0 (0-5)	0 (0-2)	0 (0-2)	0 (0-1)	1 (0-5)	1.5 (0-5)	4	
10 min S5 (FCM5 or FCF5)	0 (0-1)	0 (0-0)	1 (0-7)	1 (0-3)	0 (0-1)	0 (0-1)	2 (0-5)	1 (0-3)	3	

[1] $MHR_{first\ 50\ min}$ versus $MHR_{last\ 50\ min}$ (non-acidemic); [2] $MHR_{first\ 50\ min}$ versus $MHR_{last\ 50\ min}$ (acidemic); [3] $FHR_{first\ 50\ min}$ versus $FHR_{last\ 50\ min}$ (non-acidemic);
[4] $FHR_{first\ 50\ min}$ versus $FHR_{last\ 50\ min}$ (acidemic).
[a] $MHR_{acidemic}$ versus $MHR_{non\text{-}acidemic}$ (first 50 minutes); [b] $MHR_{acidemic}$ versus $MHR_{non\text{-}acidemic}$ (last 50 minutes); [c] $FHR_{acidemic}$ versus $FHR_{non\text{-}acidemic}$ (first 50 minutes);
[d] $FHR_{acidemic}$ versus $FHR_{non\text{-}acidemic}$ (last 50 minutes).

Table 3. Mean differences and correlations (with 95% confidence intervals) between maternal (MHR) and fetal heart rate (FHR) variables, during the last two 5(minute periods of labor, in fetuses delivered with umbilical artery blood pH ≥ 7.20 (non-acidemic) and < 7.20 (acidemic). Results different from zero with statistical significance are presented in bold.

	First 50 minutes				Last 50 minutes			
	Mean MHR-FHR		r FHR,MHR		Mean MHR-FHR		r FHR,MHR	
	Non-acidemic	Acidemic	Non-acidemic	Acidemic	Non-acidemic	acidemic	Non-acidemic	Acidemic
Baseline	**-9 [-15,-4]**	**-9 [-16,-1]**	-0.01 [-0.30,0.26]	0.26 [-0.15,0.65]	-5 [-11,0]	-9 [-22,3]	0.01 [-0.27,0.28]	-0.40 [-0.84,0.44]
Accelerations total	**3 [1,5]**	1 [-3,5]	0.13 [-0.16,0.42]	0.12 [-0.50,0.76]	**6 [3,9]**	**6 [3,10]**	0.09 [-0.19,0.39]	**0.58 [0.10,0.89]**
Decelerations total	**-4 [-5,-2]**	-3 [-7,1]	0.13 [-0.13,0.38]	-0.30 [-0.67,0.15]	**-5 [-6,-4]**	**-6 [-9,-4]**	0.38 [-0.12,0.60]	**0.55 [0.14,0.90]**
STV < 1	**-16 [-20,-11]**	**-14 [-21,-7**]	-0.05 [-0.34,0.28]	0.08 [-0.38,0.55]	**-13 [-18,-8]**	**-11 [-18,-4]**	-0.09 [-0.36,0.21]	0.09 [-0.69,0.71]
LTV < 5	-4 [-8,0]	-3 [-8,1]	-0.02 [-0.23,0.19]	-	-2 [-5,0]	**-2 [-4,-1]**	-0.02 [-0.29,0.25]	-
Accelerations								
10 min S1	0.0 [-0.7,0.6]	0.4 [-0.6,1.4]	-0.01 [-0.33,0.29]	0.21 [-0.40,0.71]	-0.1 [-0.8,0.6]	-0.1 [-1.5,1.2]	-0.03 [-0.34,0.30]	-0.10 [-0.63,0.49]
10 min S2	**-0.9 [-1.5,-0.2]**	0.6 [-0.5,1.8]	**0.35 [0.09,0.61]**	0.05 [-0.48,0.61]	**-1.0 [-1.8,-0.2]**	-1.1 [-2.2,0.1]	0.02 [-0.28,0.29]	0.22 [-0.34,0.73]
10 min S3	**-0.7 [-1.4,-0.1]**	-0.6 [-1.8,0.7]	**0.30 [0.01,0.55]**	-0.13 [-0.71,0.51]	**-1.2 [-1.9,-0.5]**	**-1.4 [-2.8,-0.1]**	0.25 [-0.05,0.52]	0.39 [-0.25,0.82]
10 min S4	-0.6 [-1.3,0.1]	-0.8 [-2.5,0.8]	0.11 [-0.18,0.41]	-0.37 [-0.76,0.14]	**-1.6 [-2.3,-1.0]**	**-1.5 [-2.5,-0.4]**	0.13 [-0.14,0.41]	**0.58 [0.18,0.84]**
10 min S5	**-1.0 [-1.7,-0.4]**	-0.6 [-1.9,0.7]	0.09 [-0.21,0.41]	0.27 [-0.28,0.75]	**-2.3 [-3.1,-1.5]**	**-2.4 [-3.6,-1.3]**	-0.21 [-0.50,0.09]	0.13 [-0.47,0.70]

Table 4. Areas under the ROC curves (auROC) for prediction of umbilical artery blood pH < 7.20, considering the last 50 minutes of FHR and MHR recordings. The highest auROC are presented in bold.

	auROC [95%CI]
Univariate Analysis	
FHR	
Baseline	0.51 [0.30,0.71]
Accelerations	0.50 [0.33,0.67]
Decelerations	0.53 [0.36,0.69]
STV < 1	**0.71 [0.55,0.86]**
LTV < 5	0.51 [0.35,0.67]
MHR	
Baseline	0.63 [0.46,0.79]
Accelerations	0.57 [0.40,0.73]
Decelerations	0.51 [0.34,0.68]
STV < 1	0.65 [0.48,0.82]
LTV < 5	0.58 [0.42,0.74]
Bivariate Analysis	
FHR baseline and STV<1	**0.71 [0.56,0.86]**
MHR baseline and STV<1	**0.68 [0.51,0.85]**
MHR and FHR Accelerations	0.53 [0.35,0.70]
MHR and FHR Decelerations	0.54 [0.39,0.69]
FHR and MHR STV<1	**0.77 [0.63,0.92]**
MHR baseline and FHR STV<1	**0.77 [0.63,0.90]**

RESULTS

In Table 1, the main maternal and fetal characteristics of the studied population are presented, comprising fetuses born with UAB pH > or < 7.20, which were statistically similar, except in the mean UAB pH. Similar results were obtained considering UAB pH < 7.15, but only 6 cases presented an UAB pH below that value.

In Tables 2 and 3, the individual MHR and FHR characteristics, their differences and correlations are presented, in relation to labor progression and to newborn UAB pH > or < 7.20.

Progression of labor was associated with a significant increase of MHR accelerations and FHR decelerations, both in non-acidemic and acidemic fetuses, as well as to a decrease in FHR STV (Table 2). At the same time, in non-acidemic fetuses, there was a decrease of statistically significant MHR-FHR correlations, regarding the number of accelerations, as well as an increase in the number of significant differences from zero (Table 3). On the other hand, in acidemic fetuses, there was a modest, but significant, increase in the number of MHR-FHR correlations, regarding the number of accelerations (from r=0,12, p>0.05, to r=0.58, p<0.05) and decelerations (from r=-0.30, p>0.05, to r=0.55, p<0.05) , as well as of increase in the number of significant differences from zero (Table 3). Similar results were obtained considering UAB pH <7.15, but with less situations attaining statistical significance, in relation with the lower number of cases under the UAB pH threshold.

In the last 50 minutes of labor, the auROC for MHF and FHR features in the prediction of newborn acidemia ranged from 0.50 (95% CI: 0.33-0.67) for FHR accelerations to 0.77 (95% CI: 0.63-0.90) for MHR baseline plus FHR STV<1 (Table 4), considering the UAB pH threshold of 7.20, and from 0.51 (95% CI: 0.30-0.73) for FHR LTV<5 to 0.70 (95% CI: 0.45-0.96) for MHR baseline plus FHR STV<1, considering the UAB pH threshold of 7.15.

COMMENT

In this study, the interaction between MHR and FHR recordings during labor was analysed for the first time in relation to labor progress and prediction of newborn acidemia.

Progression of labor was associated to a significant increase of MHR accelerations and FHR decelerations, as well as to a decrease in FHR STV, both in non-acidemic and acidemic fetuses. This is consistent with previous reports pertaining to pregnancies with normal outcomes [1,9], as well as with isolated reports on FHR [7,11]. To our knowledge, there are not similar reports pertaining to acidemic fetuses.

Progression of labor was also associated, in non-acidemic fetuses, to a decrease in the number of significant MHR-FHR correlations regarding the number of accelerations and with an increase in the number of significant differences from zero (Table 3). On the other hand, in acidemic fetuses, there was an increase in the number of significant MHR-FHR correlations, regarding both the number of accelerations and decelerations, as well as of increase in the number of significant differences from zero (Table 3). This suggests that during progression of labor in non-acidemic fetuses, the mother and the fetus react to physiological stimulus with different amplitudes while keeping their autonomy, whereas situations of fetal acidemia the fetus tends to loose its autonomy, evidencing signs of more intense maternal-fetal attachment. To our knowledge, this finding has not been previously reported, but is consistent with the increased mother-infant attachment observed in stressful maternal-fetal and mother-infant situations [3-6]. This is also consistent with an increased secretion of oxitocyn as labor progresses, one of the hormones that has been linked with mother-infant attachment, namely during breastfeeding

[4,5]. This suggests that maternal-fetal attachment may be a way to protect fetuses that are born acidemic and one that may be important to consider for subsequent child survival and future development [5].

The capacity of isolated FHR or MHR analysis to predict newborn acidemia was relatively limited and similar with the ones reported in other studies on this topic using FHR analysis alone [7,11], but combined analysis of MHR and FHR may improve it (Table 4). If these results are confirmed in larger studies, they may signify that combined analysis will be the way forward for intrapartum monitoring. To our knowledge, there are no other studies evaluating combined MHR and FHR analysis in this context.

The results of this study need to be interpreted with caution as they pertain to a small number of fetuses with a mildly low UAB pH [10]. Further studies are necessary to confirm these findings, perhaps using easier ways of simultaneous MHR-FHR recording, namely oximetry for MHR and internal electrocardiography for FHR, or transabdominal ECG for extraction of MHR and FHR signals [12].

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CHAPTER 5

TOWARD THE IMPROVEMENT IN FETAL MONITORING DURING LABOR WITH THE INCLUSION OF MATERNAL HEART RATE ANALYSIS

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TOWARD THE IMPROVEMENT IN FETAL MONITORING DURING LABOR WITH THE INCLUSION OF MATERNAL HEART RATE ANALYSIS

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ABSTRACT

Fetal heart rate (FHR) monitoring is used routinely in labour, but conventional methods have a limited capacity to detect fetal hypoxia/acidosis. We performed a preliminary study on simultaneous assessment of maternal heart rate (MHR) and FHR variability to evaluate their evolution during labour and their capacity to detect newborn acidemia.

MHR and FHR were simultaneously recorded in 51 singleton term pregnancies during the last two hours of labour and compared with newborn umbilical artery blood (UAB) pH. Linear/nonlinear indices were computed separately for MHR and FHR. Interaction between MHR and FHR was quantified through the same indices on FHR-MHR, and through their correlation and cross-entropy. Univariate and bivariate statistical analysis included non-parametric confidence intervals and statistical tests, receiver operating characteristic curves and linear discriminant analysis.

Progression of labour was associated with a significant increase in most MHR and FHR linear indices, whereas entropy indices decreased. FHR alone and in combination with MHR as FHR-MHR, evidenced the highest auROC values for prediction of fetal acidemia, with 0.76 and 0.88 for the UAB pH thresholds 7.20 and 7.15, respectively. The inclusion of MHR on bivariate analysis achieved sensitivity and specificity values of nearly 100% and 89.1%, respectively.

These results suggest that simultaneous analysis of MHR and FHR may improve the identification of fetal acidemia compared with FHR alone, namely during the last hour of labour.

INTRODUCTION

Intrapartum fetal heart rate (FHR) monitoring is used routinely in high-income countries to detect signs of decreased fetal oxygenation, but the technology has a limited capacity to predict newborn hypoxia/acidosis. Linear and nonlinear methods of FHR analysis have achieved promising results in the discrimination between different thresholds of umbilical artery blood (UAB) pH values [9,11,18]. Using the low-frequency index, Kwon et al. [18] reported significant differences in FHR indices between normal fetuses and those with an UAB pH less than 7.20, with areas under the receiver operator characteristic (auROC) curves of 0.794 in preterm and 0.595 in term fetuses. Georgieva et al. [9] found that phase-rectified signal averaging outperformed the short-term variation index, leading to an auROC of 0.665 in prediction of an UAB pH under 7.05.

Both mother and fetus are subject to profound changes in hemodynamic and autonomic nervous system activity during labor [11,16], which can be accessed via maternal heart rate (MHR) and FHR analysis [3,11,33]. It is also known that maternal and fetal pathophysiological conditions are intimately related, namely concerning blood gas and H+ exchange [5,21,28]. The occurrence of strenuous uterine contractions leading to maternal acidemia of myometrial origin and the secretion of neuro-endocrine mediators associated with uterine activity could lead to changes in MHR variability in addition tom the well-known changes in FHR. There is also evidence that during the final minutes of labor there are significant MHR changes in relation to the uterine contractions rate [26,30], which has a well-established relation with fetal acidemia [2,17]. In spite of this, joint MHR and FHR analysis has never been explored or translated into clinical practice. Indeed, the majority of studies have focused more on similarities between MHR and FHR recordings, particularly during the final hours of labor, giving rise to the weel-known possibility of misinterpreting the MHR as a FHR recording [15,22,23], than on the similarities or disparities of MHR and FHR pathophysiological dynamics.

In this exploratory study, we performed simultaneous analysis of MHR and FHR variability, to evaluate their evolution during labor and their capacity to detect newborn acidemia, quantifying variables that have been shown to be associated with autonomous nervous system function, sympatho-vagal balance and activity of more complex heart rate control systems.

METHODS

Data acquisition

Fifty-one simultaneous MHR and FHR recordings were consecutively obtained from an equal number of singleton term pregnancies, during the last two hours of labor, and analyzed in relation to the occurrence of a newborn UAB pH considering the thresholds 7.15 and 7.20. The population size was estimated based on a previous study on isolated FHR analysis, using similar variability measures [11]. Table 1 displays the main perinatal characteristics of the included cases. The study was approved by the local Ethics Committee and all participants gave informed consent to participate.

Table 1: Main perinatal characteristics of the normal and acidemic groups, considering the umbilical artery blood pH (UAB pH) thresholds as 7.20 and 7.15.

	Fetuses born with UAB pH ≥ 7.20 (n=39)	Fetuses born with UAB pH < 7.20 (n=12)	P-value	Fetuses born with UAB pH ≥ 7.15 (n=46)	Fetuses born with UAB pH < 7.15 (n=5)	P-value
Maternal data, mean (SD)						
Age (years)	27.4 (5.2)	27.8 (5.8)	0.672	27.6 (5.2)	26.4 (6.7)	0.656
Parity	0.3 (0.5)	0.3 (0.5)	0.797	0.3 (0.5)	0.4 (0.5)	0.656
Gestational age (weeks)	39.7 (1.1)	39.8 (0.9)	0.938	39.7 (1.0)	39.9 (1.3)	0.548
Delivery, n (%)			0.834			0.767
Vaginal	21 (53.9%)	6 (50.0%)		25 (54.3%)	2 (40.0%)	
Operative vaginal	13 (33.3%)	5 (41.7%)		16 (34.8%)	2 (40.0%)	
Cesarean section	5 (12.8%)	1 (8.3%)		5 (10.9%)	1 (20.0%)	
Epidural analgesia, n (%)	39 (100%)	12 (100%)	-	46 (100%)	5 (100%)	-
Newborn data, mean (SD)						
Birthweight (grams)	3238 (361)	3283 (179)	0.357	3252 (340)	3215 (154)	0.939
1 minute Apgar score	9.3 (0.6)	9.1 (0.5)	0.272	9.2 (0.6)	9.2 (0.4)	0.866
5 minute Apgar score	9.9 (0.3)	9.8 (0.4)	0.551	9.9 (0.3)	9.8 (0.4)	0.747
UAB pH	7.28 (0.05)	7.15 (0.05)	0.000	7.26 (0.05)	7.09 (0.04)	0.000
Gender, n (%)			0.749			0.162
Males	22 (56.4%)	6 (50.0%)		27 (58.7%)	1 (20.0%)	
Females	17 (43.6%)	6 (50.0%)		19 (41.3%)	4 (80.0%)	

Continuous MHR was obtained by ECG, as pulse oximetry provides signals with a lower precision. Two unipolar chest electrodes were placed on three classical locations (2nd right and left intercostal spaces and 5th left intercostal space in the medioclavicular line) linked to a conventional STAN®31 fetal monitor (Neoventa, Gothemburg, Sweden). The monitor amplifies the signals, digitalizes them at a sample rate of 1600 Hz with a 12-bit precision and then they are filtered [31]. A heart period is calculated from the RR interval and converted to the nearest quarter of a beat, in beats per minute [4]. The MHR signal was subsequently exported from the STAN monitor at a sampling rate of 4Hz, via an RS232 port, into the Omniview-SisPorto® 3.5 system (Speculum, Lisbon, Portugal) [1,26]. Due to the occurrence of episodes of signal loss and artifacts, MHR signals were then pre-processed using an algorithm for FHR pre-processing described by Gonçalves et al [8], adapted to the MHR scale. The algorithm preserves the temporal basis, by using either spline interpolation or replication of previous samples in periods of signal loss or artifacts.

FHR was obtained with a conventional external ultrasound sensor placed on the maternal abdomen, conveying signals to the STAN®31 fetal monitor, where an autocorrelation function was used to calculate the heart periods, in beats per minute (bpm) rounded to the nearest quarter of a beat. While acquiring the signal, the STAN® 31 monitor was connected via a digital RS232 port to the Omniview-SisPorto® 3.5 system, and this output provided FHR signals at a fixed rate of 4 Hz. The Omniview-SisPorto® 3.5 system was used to convert this data into Excel® files for subsequent analysis, which passed through the pre-processing algorithm described by Gonçalves et al [10] to deal with episodes of signal loss and artifacts.

An example of a FHR and a MHR signal in the last two hours of labour is given in Figure 1. The mean duration of tracings was 331 min (SD=183 min) and the average MHR and FHR signal losses were, respectively, 8.2% (SD=11.0%) and 12.2% (SD=10.3%).

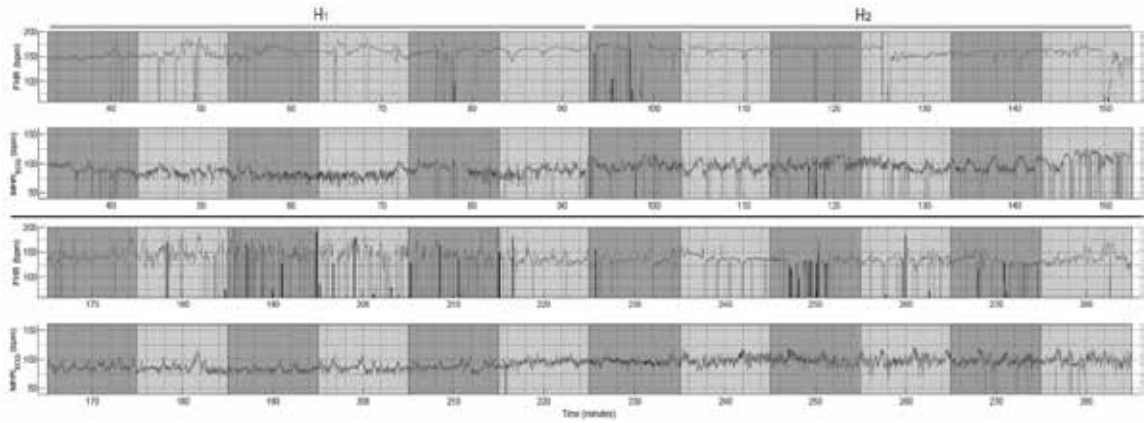

Figure 1: Examples of simultaneous acquired FHR and MHR signals in the last two hours of labour H_1 and H_2 (before pre-processing). FHR and MHR presented in the *first* and *second* rows correspond to a fetus born with UAB pH ≥7.20; FHR and MHR presented in the *third* and *fourth* rows correspond to a fetus born with UAB pH <7.15.

Heart rate analysis

The last hour of each tracing (H_2) and the one before that (H_1) were used for analysis, considering segments S_i of 10-min length (i=1,…,6) within H_1 and H_2. Each of these segments was analyzed using linear (time- and frequency-domain) and nonlinear indices. An overview of the methods used in the individual FHR and MHR analysis, as well as in the analysis of their interaction, is provided in Figure 2.

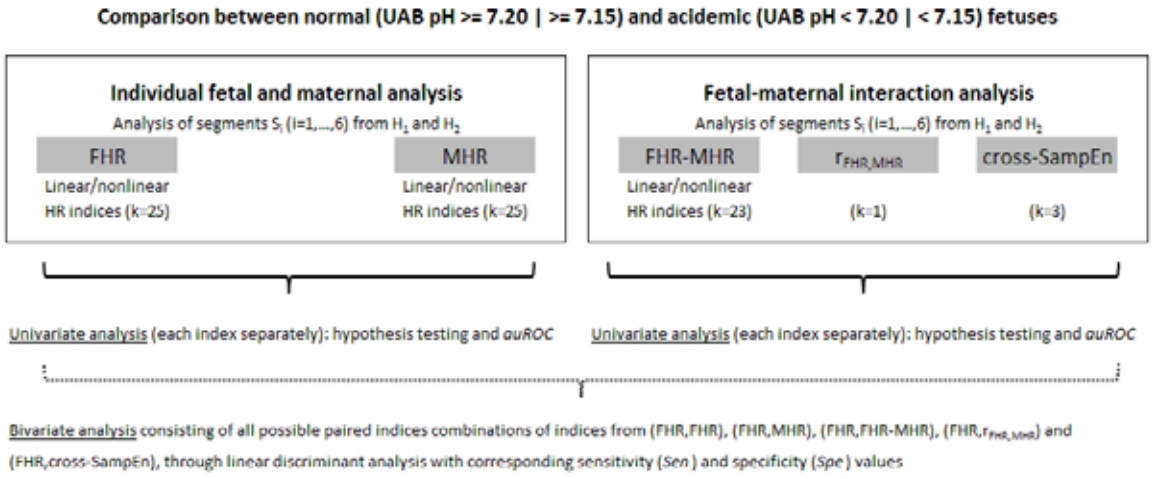

Figure 2: Overview of the methods used in the comparison between normal and acidemic fetuses, based on the individual analysis of FHR and MHR, and on the fetal-maternal interaction analysis. *k:* number of indices; *UAB pH*: umbilical artery blood pH; *auROC*: area under the ROC curve; *Sen*: sensitivity; *Spe*: specificity.

For time domain linear analysis, the following indices were calculated: mean heart rate (mHR), standard deviation of HR (sdHR), long-term irregularity (LTI), Delta HR (Δ), short-term variation (STV) and interval index (II). All but II reflect gross changes in HR average and variability, whereas II assesses short-term HR variability taking into account long-term variability [10]. The frequency domain analysis was based on the nonparametric estimation of the spectrum, based on a procedure previously described in detail [10]. The following frequency bands were considered: very low frequency (VLF) at 0–0.04 Hz for MHR and at 0-0.03 Hz for FHR; low frequency (LF) at 0.04–0.15 Hz for MHR and at 0.03-0.15 Hz for FHR; medium frequency at 0.15-0.50 Hz for FHR; and high frequency (HF) at 0.15–0.40 Hz for MHR and at 0.50-1.00 Hz for FHR. The VLF band is of difficult interpretation, appearing to reflect thermoregulatory and slow regulating systems of peripheral vessels [33] and occurs prominently when autonomic activity is strongly suppressed, as in sinusoidal patterns [32]. LF and HF are mainly associated with activity of the sympathetic and parasympathetic systems, respectively. LF_{norm} and HF_{norm} were also computed for MHR by normalizing each absolute value by (TP-VLF). Due to the spectral division of FHR into LF, MF and HF bands, LF_{norm} and HF_{norm} are not usually computed for FHR. The LF/HF index, which reflects the balance between the autonomic nervous system branches, as well as total power (TP, i.e., all the spectrum area), were also considered for MHR and FHR. The balance LF/(MF+HF) was also evaluated for FHR.

For non-linear analysis, approximate entropy [24] - ApEn(m,r) - and sample entropy [27] - SampEn(m,r) - were calculated, considering values 0.1xSD, 0.15xSD and 0.2xSD for *r* and value 2 for *m* [25], while *N* was 2400 points (10-min HR segments at 4Hz). The criterion for the selection of the threshold parameter *r* proposed in Lu et al [19] was also considered. Entropy indices have been associated to complex cortical nervous system activity [25]. Another set of commonly used nonlinear indices computed from the Poincaré plot, SD_1 (short-term variability), SD_2 (long-term variability) and their ratio SD_1/SD_2, were also considered [33].

Interaction between MHR and FHR was assessed with respect to its linear and nonlinear components. The linear component was assessed by the linear HR indices computed from the signals difference FHR-MHR and by the signals correlation ($r_{FHR,MHR}$). The nonlinear component of the interaction was assessed by the non-linear HR indices computed from the signals difference FHR-MHR, as well as through cross-SampEn(m,r), which is a technique for

assessing the degree of asynchrony or dissimilarity between two different time series (FHR and MHR). Both time series (FHR and MHR) were normalized to have zero mean and SD=1, prior to cross-SampEn computation, due to the amplitude difference between MHR and FHR signals (which leads to a high number of non-defined computations). The same parameters *m* and *r* defined for ApEn and SampEn were considered. Cross-SampEn is preferable over cross-ApEn because it is always defined and is not direction dependent [27].

Statistical analysis

For each index, the difference between the last two hours of labour (H_1 and H_2) and between the fetuses born with UAB pH < 7.20 (n=12) and ≥ 7.20 (n=39) , and < 7.15 (n=5) and ≥ 7.15 (n=46), was evaluated using 95% bootstrap (B=1000) percentile confidence intervals (95% CI) for the median and nonparametric Mann–Whitney (normal versus acidemic) and Wilcoxon (H_1 versus H_2) statistical tests, setting significance at $p<0.05$ [7,20]. The correlation between FHR and MHR was computed through the Spearman correlation coefficient. The auROC was computed to assess the capacity of each HR index of discriminating between normal and acidemic cases in the univariate analysis, accomplished by the sensitivity and specificity associated with the point of the ROC curve closest (considering the Euclidean distance) to the optimum. The discrimination between normal and acidemic fetuses in the bivariate analysis was performed using the Fisher linear discriminant analysis , for which sensitivity (*Sen*) and specificity (*Spe*) were computed based on whole points, as well as based on the leave-one-out method (Sen_{LOO} and Spe_{LOO}) [7,11].

RESULTS

Progression of labour was associated with a significant increase in most MHR and FHR linear indices, whereas entropy indices decreased, both in fetuses born with an UAB pH < 7.20 or ≥ 7.20 (Table 2), an in those with UAB pH < 7.15 or ≥ 7.15 (data not shown). A significant increase from H_1 to H_2 in the short- and long-term variability was also identified by the SD1 and SD2 indices (Table 2). The mother´s sympatho-vagal balance increased significantly as labor progressed, whereas the opposite was observed in the fetus (Table 2).

On univariate analysis, indices computed from FHR and from the FHR-MHR signal achieved the highest auROC values for prediction of newborn acidemia, with 0.76 and 0.88 for the UAB thresholds of 7.20 and 7.15, respectively (Table 3; Fig. 3). The inclusion of the MHR signal on bivariate analysis (with FHR-MHR indices, correlation or cross-entropy) clearly improves the results, particularly in the initial segment of H_2, with highest sensitivity and an improvement in specificity, achieving respectively the values of 100.0% and 89.1% when combining LTI from FHR with SampEn from FHR-MHR (Table 4; Fig. 4).

Table 2. MHR and FHR indices in the form of 95% confidence intervals, during the last two hours of labor (H_1 and H_2), in normal (UAB pH ≥7.20) and acidemic (UAB pH <7.20) fetuses.
Statistical significance ($p < 0.05$): [a] MHR_{Normal} versus $MHR_{Acidemic}$ in H_1; [b] FHR_{Normal} versus $FHR_{Acidemic}$ in H_1; [c] MHR_{Normal} versus $MHR_{Acidemic}$ in H_2; [d] FHR_{Normal} versus $FHR_{Acidemic}$ in H_2; [1] H_1 versus H_2 in MHR_{Normal}; [2] H_1 versus H_2 in FHR_{Normal}; [3] H_1 versus H_2 in $MHR_{Acidemic}$; [4] H_1 versus H_2 in $FHR_{Acidemic}$.

	H1				H2				P-value	
	UAB pH ≥ 7.20		UAB pH < 7.20		UAB pH ≥ 7.20		UAB pH < 7.20		UAB pH	H1 vs H2
	MHR	FHR	MHR	FHR	MHR	FHR	MHR	FHR		
mHR	82.88-85.92	142.8-145.4	81.86-85.42	137.6-146.2	89.08-94.25	140.3-145.4	84.14-89.95	132.1-138.9	d	1,2,3,4
sdHR	6.10-6.68	7.22-8.97	5.52-6.64	7.73-10.22	7.64-8.69	12.51-16.57	6.98-8.41	12.40-24.67	d	1,2,3,4
LTI	10.96-11.92	8.84-10.21	9.37-12.20	9.94-12.37	12.92-15.51	13.44-17.33	12.93-16.62	16.92-38.80	b,d	1,2,3,4
Δ	22.03-23.93	21.64-24.70	20.04-23.83	23.91-28.55	26.68-29.65	33.30-40.13	24.66-29.80	34.65-56.40		1,2,3,4
STV	3.62-3.97	2.89-3.32	3.40-4.16	3.11-4.13	4.17-4.70	4.39-5.41	3.98-5.43	4.75-8.50	d	1,2,3,4
II	0.56-0.61	0.37-0.40	0.54-0.68	0.38-0.44	0.54-0.59	0.37-0.40	0.53-0.64	0.34-0.41	b	1
TP	20.33-23.42	27.18-39.19	18.27-23.26	32.14-51.80	28.23-37.84	79.01-149.1	27.30-40.97	76.20-274.2		1,2,3,4
VLF	6.77-7.93	8.75-14.80	5.64-8.34	11.24-18.95	9.61-13.09	28.07-44.77	9.27-14.56	25.08-78.02		1,2,3,4
LF	7.50-8.55	14.06-19.55	6.64-8.64	16.38-26.48	9.52-12.30	38.59-73.04	9.22-13.92	42.10-116.5		1,2,3,4
LF_{norm}	56.67-61.98	-	58.99-66.61	-	59.66-67.24	-	57.35-64.82	-		1
MF	-	1.89-3.23	-	1.76-3.68	-	9.17-16.60	-	6.07-33.27		2,4
HF	3.02-4.09	0.28-0.54	2.53-3.90	0.15-0.59	3.66-5.20	1.78-3.76	3.55-7.62	1.02-6.49		1,2,3,4
HF_{norm}	25.38-29.94	-	23.94-29.64	-	21.34-26.19	-	22.26-29.00	-		1
LF/(MF+HF)	-	5.01-5.70	-	6.40-8.49	-	3.51-4.32	-	3.21-4.98	b	2,4
LF/HF	1.92-2.45	30.62-41.43	1.83-2.74	44.37-85.30	2.19-3.05	19.52-24.52	1.99-2.74	19.19-35.16	b	1,2,4
ApEn(2,0.1)	0.93-0.99	0.53-0.62	0.93-1.00	0.54-0.64	0.88-0.94	0.41-0.45	0.87-0.97	0.39-0.49		1,2,4
ApEn(2,0.15)	0.77-0.85	0.36-0.43	0.76-0.85	0.36-0.44	0.73-0.78	0.29-0.33	0.71-0.79	0.28-0.33		1,2,3,4
ApEn(2,0.2)	0.62-0.68	0.26-0.30	0.63-0.70	0.28-0.31	0.61-0.66	0.23-0.25	0.58-0.69	0.23-0.28		1,2,4
SampEn(2,0.1)	0.81-0.88	0.38-0.45	0.77-0.91	0.38-0.50	0.79-0.86	0.27-0.32	0.77-0.83	0.24-0.35		1,2,4
SampEn(2,0.1	0.64-0.74	0.26-0.31	0.63-0.73	0.25-0.32	0.61-0.68	0.18-0.21	0.57-0.65	0.16-0.22		1,2,3,4
SampEn(2,0.2)	0.50-0.56	0.18-0.22	0.51-0.58	0.19-0.24	0.47-0.54	0.14-0.16	0.44-0.55	0.14-0.17		1,2,3,4
r_{Lu}	0.13-0.14	0.09-0.10	0.12-0.14	0.09-0.10	0.11-0.13	0.11-0.12	0.12-0.14	0.10-0.11		1,2,4
$ApEn_{Lu}$	0.86-0.91	0.54-0.66	0.87-0.94	0.59-0.71	0.80-0.87	0.36-0.42	0.80-0.87	0.38-0.47		1,2,3,4
$SampEn_{Lu}$	0.75-0.80	0.39-0.49	0.75-0.80	0.43-0.55	0.70-0.77	0.22-0.28	0.66-0.77	0.21-0.34		1,2,3,4
SD_1	1.19-1.40	0.87-1.21	1.05-1.31	0.79-1.35	1.42-1.64	1.99-2.80	1.27-1.94	1.58-3.86	a	1,2,3,4
SD_2	8.48-9.31	10.19-12.69	7.59-9.32	10.87-14.86	10.55-12.19	17.53-23.18	9.70-11.82	17.42-34.80	d	1,2,3,4
SD1/SD2	0.14-0.16	0.09-0.10	0.13-0.16	0.08-0.10	0.12-0.14	0.10-0.12	0.13-0.17	0.09-0.11		1,2,4

Table 3. Univariate analysis for the comparison between normal and acidemic fetuses using individual indices from the FHR and MHR and from their interation analysis.

Analysis	H_1|H_2	S_i	p-value	auROC	Sen	Spe
UAB pH threshold = 7.20						
FHR: LF/HF	H_1	S_1	0.007	0.76	83.3	76.9
FHR: LF/HF	H_1	S_5	0.008	0.76	66.7	87.2
FHR-MHR: LF/HF	H_1	S_1	0.007	0.76	83.3	76.9
FHR-MHR: LF/HF	H_1	S_5	0.007	0.76	66.7	87.2
FHR-MHR: LTI	H_2	S_1	0.009	0.75	83.3	66.7
FHR-MHR: LTI	H_2	S_4	0.012	0.74	75.0	76.9
FHR: STV	H_1	S_3	0.016	0.73	83.3	61.5
FHR: LF/(MF+HF)	H_1	S_1	0.020	0.72	91.7	66.7
FHR: LTI	H_2	S_4	0.027	0.71	66.7	79.5
MHR: ApEn(2,r_{Lu})	H_1	S_1	0.034	0.71	75.0	61.5
UAB pH threshold = 7.15						
FHR: Delta	H_2	S_1	0.006	0.88	80.0	91.3
FHR-MHR: Delta	H_2	S_1	0.006	0.88	89.1	80.0
FHR-MHR: LF	H_2	S_1	0.006	0.88	80.0	93.5
FHR-MHR: SampEn(2,r_{Lu})	H_2	S_1	0.006	0.88	100.0	76.1
FHR: LF	H_2	S_1	0.007	0.87	80.0	93.5
FHR-MHR: sdHR	H_2	S_1	0.007	0.87	80.0	89.1
FHR-MHR: SD_2	H_2	S_1	0.007	0.87	80.0	87.0
FHR-MHR: TP	H_2	S_1	0.009	0.86	80.0	93.5
FHR-MHR: ApEn(2,r_{Lu})	H_2	S_1	0.010	0.86	80.0	71.7
FHR: sdHR	H_2	S_1	0.010	0.86	80.0	95.7

The table presents the ten situations with the higher auROC, considering the umbilical artery blood pH (UAB pH) thresholds of 7.20 and 7.15. S_i represents the different segments *i* within H_1 or H_2. auROC = area under the ROC curve; Sen = sensitivity; Spe = specificity.

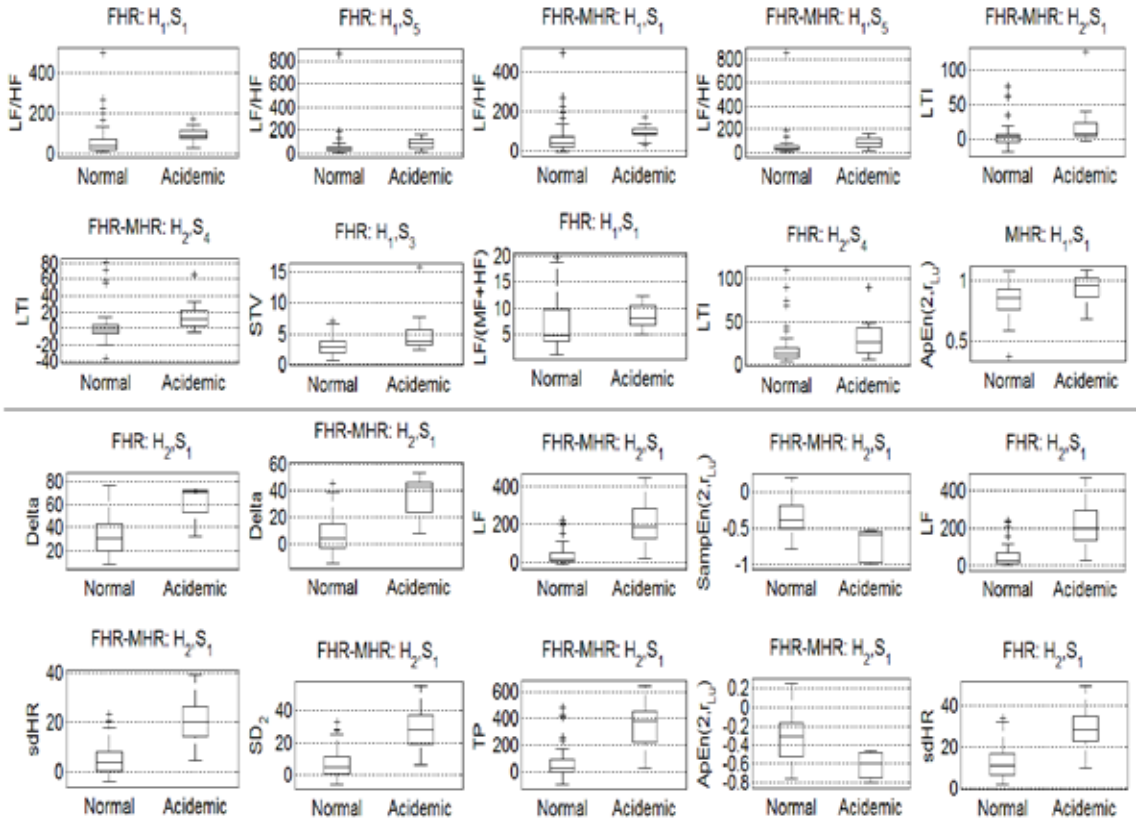

Figure 3. Boxplots pertaining to the univariate statistical analysis presented in Table 3, regarding the comparison between normal and acidemic fetuses. The *first two lines* correspond to the UAB pH threshold of 7.20, whereas the *third* and *fourth lines* correspond to the threshold of 7.15

Table 4. Bivariate analysis for the comparison between normal and acidemic fetuses using individual indices from the FHR and MHR and from their interaction analysis

LDA: xx-axis (FHR)	LDA: yy-axis	$H_1\|H_2$	S_i	Sen	Spe	Sen_{LOO}	Spe_{LOO}	a	b
UAB pH threshold = 7.20									
II	FHR: SampEn(2,0.2)	H_1	S_3	83.3	71.8	75.0	71.8	2.08	-0.60
II	FHR: ApEn(2,0.2)	H_1	S_3	83.3	69.2	75.0	66.7	2.11	-0.53
ApEn(2,r_{Lu})	MHR: LF/HF	H_2	S_6	83.3	66.7	75.0	66.7	19.2	-4.11
LF/HF	MHR: HF	H_1	S_1	83.3	66.7	75.0	59.0	0.05	-0.20
SD_1	FHR-MHR: Delta	H_1	S_1	91.7	61.5	83.3	61.5	19.2	-20.3
ApEn(2,r_{Lu})	FHR-MHR: Delta	H_1	S_2	83.3	71.8	83.3	69.2	-63.3	44.6
SampEn(2,0.2)	$r_{FHR,MHR}$	H_2	S_4	75.0	66.7	50.0	43.6	-1.89	0.26
ApEn(2,0.2)	$r_{FHR,MHR}$	H_1	S_6	75.0	64.1	66.7	64.1	1.69	-0.50
r_{Lu}	cross-SampEn(2,0.1)	H_1	S_1	83.3	61.5	66.7	59.0	6.40	0.12
SD_1/SD_2	cross-SampEn(2,0.1)	H_1	S_1	83.3	61.5	66.7	56.4	4.04	0.36
UAB pH threshold = 7.15									
ApEn(2,0.2)	FHR: SampEn(2,0.1)	H_2	S_1	100.0	78.3	80.0	78.3	0.84	0.11
ApEn(2,0.1)	FHR: ApEn(2,0.15)	H_2	S_1	100.0	73.9	80.0	73.9	2.45	-0.73
Delta	MHR: SampEn(2,0.15)	H_2	S_1	100.0	84.8	100.0	84.8	-0.04	2.51
Delta	MHR: SampEn(2,r_{Lu})	H_2	S_1	100.0	87.0	80.0	87.0	-0.02	1.76
LTI	FHR-MHR: SampEn(2,r_{Lu})	H_2	S_1	100.0	89.1	80.0	87.0	0.01	-0.88
LTI	FHR-MHR: SampEn(2,0.1)	H_2	S_1	100.0	87.0	100.0	87.0	0.01	-0.95
VLF	$r_{FHR,MHR}$	H_2	S_6	100.0	65.2	100.0	65.2	0.003	-0.22
TP	$r_{FHR,MHR}$	H_2	S_1	80.0	87.0	80.0	87.0	-0.01	1.44
SampEn(2,0.1)	cross-SampEn(2,0.2)	H_2	S_1	100.0	71.7	100.0	67.4	1.76	-0.16
TP	cross-SampEn(2,0.2)	H_2	S_1	80.0	91.3	100.0	91.3	-0.003	1.07

The table presents the two combinations of indices from (FHR,FHR), (FHR,MHR), (FHR,FHR-MHR), (FHR,$r_{FHR,MHR}$) and (FHR,cross-SampEn), corresponding to the highest values of sensitivity (Sen) and specificity (Spe). Results are presented for the UAB pH thresholds of 7.20 and 7.15. S_i: represents the different segments within hours 1 or 2 (H_1 or H_2); auROC is the area under the ROC curve; Sen_{LOO} and Spe_{LOO}: sensitivity and specificity values based on the leave-one-out (LOO) method; coefficients *a* and *b*: slope and intercept of the linear discriminant analysis (LDA).

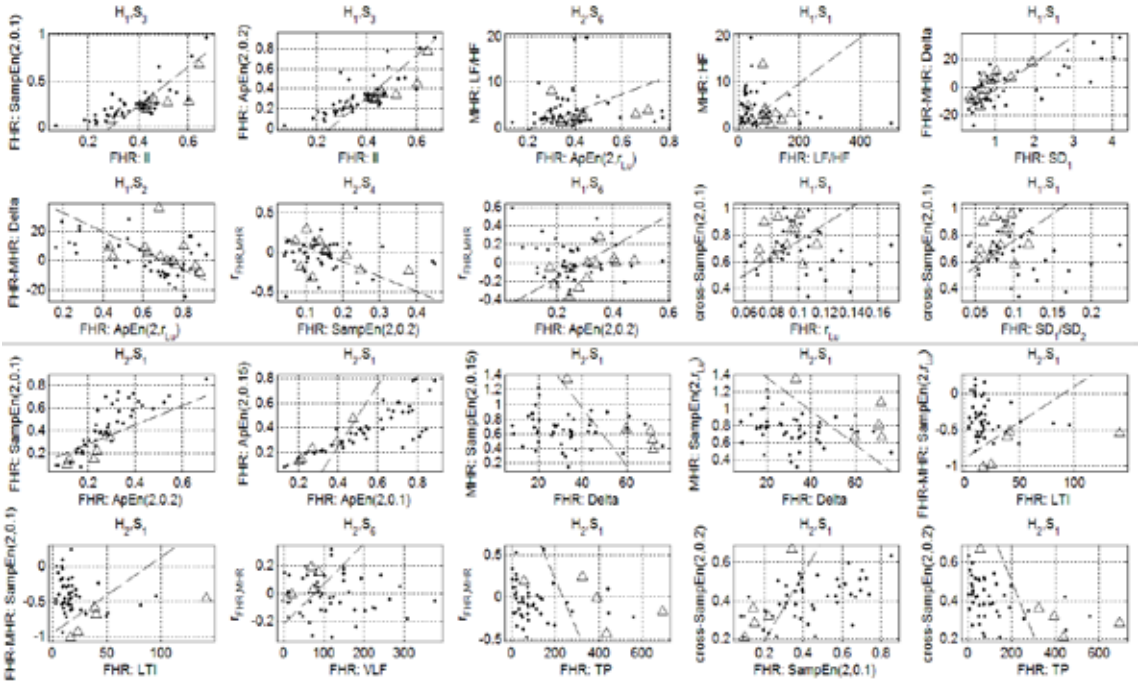

Figure 4. Scatterplots with the pairs of indices that led to the best discrimination between normal (represented by dots) and acidemic (represented by triangles) fetuses, according to the results presented in Table 4. The first two lines correspond to the UAB pH threshold of 7.20, whereas the third and fourth lines correspond to the threshold 7.15.

DISCUSSION

This study showed that linear and non-linear analysis of simultaneous MHR and FHR recordings may improve the identification of fetal academia during labor, when compared with FHR analysis alone.

The results obtained with FHR analysis alone were consistent with those reported in previous studies [11], showing that progression of labor courses with an increased activity of the fetal autonomous nervous system, decreased sympatho-vagal balance and decreased activity of more complex heart rate control systems. Additionally, a significantly higher sympatho-vagal balance was observed in the acidemic fetuses in H_1, which is in agreement with the findings of Kwon et al [18] in term fetuses.

The novel findings in this study were that changes were also present in MHR, with progression of labor and with fetal acidemia. Most linear time domain and spectral MHR indices increased, except in acidemic fetuses, while entropy indices decreased, although in lesser magnitude than for the FHR. These findings suggest that the mother also increases the activity of her autonomous nervous system and decreases the activity of more complex heart rate control systems, but contrary to the fetus, also increases in sympatho-vagal balance were observed with progression of labor except in acidemic cases. The results associated with the progression of labor are not surprising, as they represent responses to stress that have been previously described in laboratory and human studies [11-13], characterized by an increase followed by a decrease in sympatho-vagal imbalance. Those associated with fetal acidemia may denote a moderate response to stress on the maternal side, while the fetus has a more marked reaction associated with lower pO_2 values and higher hemodynamic instability. To our knowledge, similar evaluations of MHR features have not been previously conducted, and the only reported

change has been an increase in MHR baseline and number of accelerations during labor [26,30].

The changes found with simultaneous FHR-MHR analysis, reflect the individual findings described for isolated MHR and FHR. Progression of labor and fetal acidemia were associated with a significant increase in most linear and entropy FHR-MHR absolute paired differences, which were more pronounced than the described isolated MHR or FHR changes.

Although the study sample included only a small number of fetuses born with UAB pH < 7.20, it was already possible to obtain significant differences, as occurred with isolated FHR analysis in a previous study with a similar sample size [11,14]. It is recognized that UAB pH threshold of 7.20, although representing the tenth percentile of fetuses with normal outcomes [6], and used has the main outcome measure in other studies [18], it is a clinically weak criterion for adverse newborn outcome [8,34]. However, the finding that significant results could also be obtained when the UAB pH threshold of 7.15 suggests that there is consistency in these findings. Nevertheless, larger series with more cases of low UAB pH are needed to confirm these findings, as the use of the 7.15 threshold to classify newborns as acidemis can still be considered clinically weak.

The separate analysis of the 2h preceding birth provided an idea of the evolution of fetal and maternal indices during labour, as well as a comparison between normal and acidemic fetuses- however, in previous studies on FHR analysis related to acidemia, it was found that this was more effective when performed on a segment basis, in particular at the start of the last hour of labour [10,11], probably because of a lower signal quality in the last segments. Therefore, the univariate and bivariate analysis in the present work was performed on a segment basis, with the first 10-min segment of H_2 providing the best discrimination between normal and acidemic fetuses, in agreement with previous findings [10,11].

The interaction between the MHR and FHR signals was assessed using well-known linear and nonlinear methods to analyze coupling in a dynamic system [29]. However, despite the large amount of available methods, such as mutual information, cross entropy or symbolization approaches, the obtained results do not convey a clear message. Analysis with a larger variety of methods is recommendable in controlled conditions, but human labor goes well beyond this. Nevertheless, the methods used to assess maternal-fetal interaction provided interesting results for the detection of newborn acidemia using bivariate analysis.

The inclusion of MHR analysis improved the identification of fetal acidemia, particularly in the first 10-min segment of the last hour. On univariate analysis, the indices computed from the FHR-MHR signal were among those with highest auROC values, better results than entropy indices applied to isolated FHR. When including the MHR signal on bivariate analysis - in the form of the MHR indices, FHR-MHR indices or cross-SampEn – it was observed a comparable or even increase in sensitivity and a clear improvement on specificity. The latter is important to avoid the important aspect of unnecessary intervention during labor. The use of multivariate analysis could lead to even better results, but a larger sample is required for this.

CONCLUSION

This exploratory study suggests that simultaneous analysis of MHR and FHR during labor can improve the identification of fetal acidemia, when compared with FHR alone, namely in the last hour of labor. Further studies are warranted to assess the clinical usefulness of combined MHR and FHR analysis in the prediction of the maternal and fetal condition.

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CHAPTER 6

ELECTROCARDIOGRAPHY VERSUS PHOTOPLETHYSMOGRAPHY IN THE ASSESSMENT OF MATERNAL HEART RATE VARIABILITY DURING LABOR

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ELECTROCARDIOGRAPHY VERSUS PHOTOPLETHYSMOGRAPHY IN ASSESSMENT OF MATERNAL HEART RATE VARIABILITY DURING LABOR

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ABSTRACT

Purpose

Evaluation of maternal heart rate (MHR) variability provides useful information on the maternal-fetal clinical state. Electrocardiography (ECG) is the most accurate method to monitor MHR but it may not always be available, and pulse oximetry using photoplethysmography (PPG) can be an alternative. In this study we compared ECG and PPG signals, obtained with conventional fetal monitors, to evaluate signal loss, MHR variability indices, and the ability of the latter to predict fetal acidemia and operative delivery.

Methods

Both signals were simultaneously acquired in 51 term pregnancies during the last two hours of labor (H_1 and H_2). Linear time- and frequency-domain, and nonlinear MHR variability indices were estimated, and the dataset was divided into normal and acidemic cases, as well as into normal and operative deliveries. Differences between ECG and PPG signals were assessed using non-parametric confidence intervals, hypothesis testing, correlation coefficient and a measure of disagreement. Prediction of fetal acidemia and operative delivery was assessed using areas under the receiver operating characteristic curve (auROC).

Results

Signal loss was higher with ECG during the first segments of H_1, and higher with PPG in the last segment of H_2, and it increased in both signals with labour progression. MHR variability indices were significantly different when acquired with ECG and PPG signals, with low correlation coefficients and high disagreement for entropy and fast oscillation-based indices, and low disagreement for the mean MHR and slow oscillation-based indices. However, both acquisition modes evidenced significant differences between H_1 and H_2 and comparable auROC values were obtained in the detection of fetal acidemia and operative vaginal delivery.

Conclusions

Although PPG captures the faster oscillations of the MHR signal less well than ECG and is prone to have higher signal loss in the last 10-min preceding delivery, it can be considered an alternative for MHR monitoring during labor, with adaptation of cut-off values for MHR variability indices.

INTRODUCTION

Computerized analysis of maternal heart rate (MHR) recordings obtained by electrocardiography (ECG) may help in the assessment of different clinical maternal-fetal conditions, during the antepartum period [1-7] and in the detection of MHR-fetal heart rate (FHR) ambiguities during labor [8-11].

In clinical practice, however, it is not always possible to obtain MHR recordings with ECG during labour, because many fetal monitors do not incorporate this technology, and some healthcare professionals and laboring women think it is unnecessary and interferes with the physiological experience of childbirth. Alternatively, MHR can be obtained with a pulse oximetry sensor and photoplethysmography (PPG), using monitors that have been integrated or are coupled to fetal monitors. Continuous monitoring of maternal oxygen saturation is required in some clinical situations during labor, and some women find it more comfortable than chest electrodes. Moreover, some fetal monitors have recently incorporated pulse oximetry into the tocodynomometer sensor, so MHR can be obtained with no extra equipment. However, there is no data on whether MHR analysis is equivalent when obtained with ECG or PPG.

MHR acquired either by ECG or PPG is transmitted to fetal monitors, which store FHR and MHR simultaneously, typically at a same regular time basis, by means of signal interpolation [12]. However, the heart rate (HR) obtained with PPG is less accurate than that acquired with ECG [13], particularly during exercise [14]. Similarly, this may also happen in other situations of increased physical effort, namely during labor.

The accuracy of PPG appears to be suitable for the analysis of the HR of newborn infants in the delivery room [15], in the neonatal intensive care unit [16], and in the study of obstructive sleep apnea syndrome, using spectral analysis [17] or entropy methods [18], or in the detection of FHR decelerations, in the intrapartum period [19]. In addition, artifacts that contaminate PPG waveforms can be automatically rejected using methods based on waveform morphology analysis [20].

To date, no studies have evaluated whether PPG is as accurate as ECG for MHR acquisition during labour. In addition, no studies have compared signal loss when using the two methods.

The objective of this study was to compare simultaneously-acquired ECG and PPG signals for the detection of MHR rate during labour. The following parameters were evaluated in both signals: signal loss, variability indices as evaluators of signal characteristics, and the ability of the latter to predict fetal acidemia and operative delivery. The rationale for MHR to be able to predict fetal acidemia and operative delivery, comes from the knowledge that many situations of fetal hypoxia/acidosis and abnormal labor progression (with its surrogate indicator of operative delivery) are associated with an anomalous pattern of uterine contractions [21], and the latter is related with maternal sympatho-vagal activity [22-23]. MHR variability could thus provide an early sign of fetal academia and/or labour dystocia, by means of the autonomic changes associated with altered uterine contraction dynamics.

METHODS

Data acquisition

A total of 51 MHR recordings, pertaining to 51 different laboring women, were obtained simultaneously with ECG and PPG during the last two hours before delivery (H_1 and H_2). All signals were acquired in uneventful singleton term pregnancies, and all women were under epidural analgesia. The study was approved by the hospital's Ethics Committee and all mothers gave informed consent to participate.

In order to assess the capacity of ECG and PPG signals in the classification of fetal acidemia and operative vaginal delivery, the dataset was divided into normal and acidemic groups - considering an umbilical artery blood (UAB) pH threshold of 7.15 – and into normal and operative vaginal deliveries. The main maternal and perinatal characteristics of the study groups are presented in Table 1.

MHR obtained with ECG was acquired with two unipolar chest electrodes placed on three classical locations (2nd right and left intercostal spaces and 5th left intercostal space in the medioclavicular line) linked to a conventional STAN®31 fetal monitor (Neoventa, Gothemburg, Sweden). The monitor amplifies the signals, digitalises them at a sample rate of 1600 Hz with a 12-bit precision, and then applies a filter. A heart period is calculated from the RR interval and converted to the nearest integer, in beats per minute [12].

MHR obtained by PPG was acquired using a conventional pulse oximetry infrared finger probe, linked to the VitalCare 506DN3 Vital Signs Monitor (Criticare Systems, Inc., Wisconsin, USA), which was connected to the STAN® 31 fetal monitor. The HR period is derived from analysis of the dual wavelength LED waves, representing arterial blood volume changes, and is transmitted to the fetal monitor at a sampling rate of 1 Hz with an accuracy and resolution of ±1 bpm [24].

Both ECG and PPG signals were exported from the STAN monitor at a sampling rate of 4Hz, via its RS232 port, into the Omniview-SisPorto® 3.5 program (Speculum, Lisbon, Portugal) for storage and subsequent offline analysis. After the application of a pre-processing algorithm described by Gonçalves *et al* [25], with an adaptation to scale, the signals were resampled at a frequency of 2Hz considering only the odd samples, which mitigates the repetition of MHR values, keeping them below the Nyquist frequency (the spectrum of interest is ≤ 0.4Hz). Figure 1 displays an example of MHR signals simultaneously acquired by ECG and PPG, where it is patent that the PPG signal smoothens the abrupt oscillations occurring in very short time periods, and thus delays baseline shifts, although this is compensated afterwards.

Table 1: Main maternal and perinatal characteristics of the study population, with the subdivisions into normal versus acidemic groups, and normal versus operative vaginal deliveries.
Values within brackets in the header correspond to the number of cases. P-value <0,05 is in italic

	Fetuses born with UAB pH ≥ 7.15 (n=45)	**Fetuses born with UAB pH < 7.15 (n=6)**	**p-value**	**Normal deliveries (n=28)**	**Vaginal operative deliveries (n=19)**	**p-value**
Maternal data, median (IQR)						
Age (years)	28 (3.5)	27 (10)	0.597	28 (8.0)	28 (9.0)	0.550
Parity	0 (1)	0 (1)	0.853	0 (1)	0 (0)	**0.001**
Gestational age (weeks)	39.9 (1.3)	39.8 (2.5)	0.578	39.7 (1.1)	39.9 (1.1)	0.415
Delivery, n (%)			0.693			-
Vaginal, normal	25 (56%)	3 (50%)		-	-	
Vaginal, operative	17 (37%)	2 (33%)		-	-	
Cesarean section	3 (7%)	1 (17%)		-	-	
Epidural analgesia, n (%)	45 (100%)	6 (100%)	-	28 (100%)	19 (100%)	-
Newborn data, median (IQR)						
Birthweight (grams)	3190 (393)	3078 (381)	0.255	3160 (350)	3200 (405)	0.871
1 minute Apgar score	9 (1)	9 (0)	0.679	9 (1)	9 (1)	0.957
5 minute Apgar score	10 (0)	10 (0)	0.679	10 (0)	10 (0)	0.687
UAB pH	7.27 (0.09)	7.10 (0.06)	**0.000**	7.27 (0.10)	7.22 (0.09)	0.109
Gender, n (%)			0.191			0.246
Males	24 (53%)	1 (17%)		11 (39%)	11 (58%)	
Females	21 (47%)	5 (83%)		17 (61%)	8 (42%)	

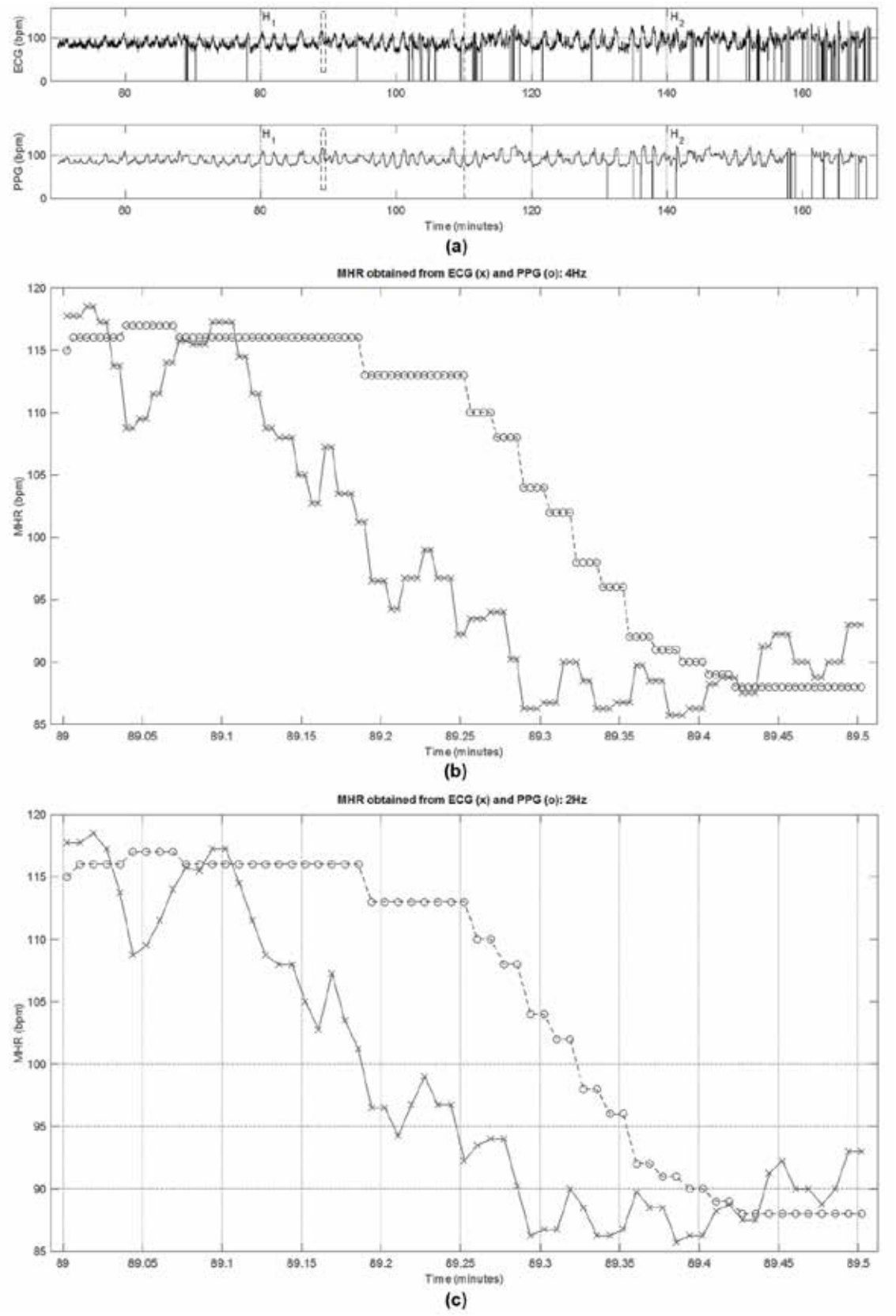

Fig. 1 An example of a MHR tracing obtained with ECG (*upper plot*) and PPG (*lower plot*) for H_1 and H_2 (**a**). The rectangle between *vertical dashed lines* in **a** represents the 30-s segment shown in **b** and **c**, obtained respectively at 4 and 2 Hz sampling rates, with ECG (*marked with a cross*) or PPG (*marked with a circle*) signals

MHR analysis

MHR recordings were evaluated using linear (time- and frequency-domain) and nonlinear methods, applied to 10-minute segments. The segment-based analysis mitigates the possible effect of non-stationarity. Segments with more than 15% signal loss (the percentage of MHR values equal to 0) before the pre-processing operation, in one or both of the acquisition modes (ECG or PPG), were excluded from the analysis.

For time domain linear analysis, the following indices were calculated: mean MHR (mHR); standard deviation of MHR (sdHR); long-term irregularity index, assessed by the inter-quartile range of the squared root of the sum of consecutive pairs of squared samples (LTI); Delta MHR representing the average amplitude within a minute (Δ); short-term variation (STV); and interval index (II). All but II reflect gross changes in MHR average and variability, whereas II assesses short-term MHR variability taking into account long-term variability [25]. For frequency domain analysis, the following frequency bands were considered: very low frequency (VLF) at 0–0.04 Hz, low frequency (LF) at 0.04–0.15 Hz and high frequency (HF) at 0.15–0.40 Hz [26]. Nonparametric spectrum estimation was performed according to a procedure previously described in detail [25]. The whole spectrum area corresponds to the total power (TP). The VLF band appears to reflect thermoregulatory and slow regulating systems of peripheral vessels [26] and occurs prominently when autonomic activity is strongly suppressed. LF is associated with the activity of both the sympathetic and parasympathetic branches of the autonomic nervous system, whereas HF is mainly associated with the parasympathetic branch. LF_{norm} and HF_{norm} were also computed by normalizing each absolute value by TP-VLF. The LF/HF index, which reflects the balance between the autonomic nervous system branches, was also considered.

For non-linear analysis, approximate entropy (ApEn) [27], and sample entropy (SampEn) [28] were calculated, considering values 0.1 SD, 0.15 SD and 0.2 SD for r and value 2 for m [29], while N was 1200 points (corresponding to 10-min MHR segments). The criterion for selection of the threshold parameter r proposed by Lu *et al* [30] was also considered. Entropy indices have been associated with complex cortical nervous system activity [29]. The Poincaré plot is one of the most popular techniques for analysis of HRV variability [31]. It is formed from the representation of each RR interval against its previous RR interval. The most commonly used HR variability indices based on the Poincaré plot are SD1, SD2, and the ratio SD1/SD2, where SD1 and SD2 are related to fast beat-to-beat and longer-term variability, respectively [31]. These three nonlinear measures were also considered, and the Poincaré plot was constructed.

Statistical analysis

The ECG and PPG signals were compared by evaluating the percentage of signal loss, the percentage of MHR values obtained from ECG and PPG differing less than or equal to 5 bpm (HR_m) [32-33] and the previously described MHR variability indices in the six 10-min segments of H_1 and H_2. Statistical inference was based on 95% bootstrap (B=1000) percentile confidence intervals for the median, Spearman correlation of coefficient and nonparametric Mann-Whitney statistical test with significance level set at $p<0.05$ [34-35]. Disagreement was assessed through the information-based approach dAB [36], ranging between 0 and 1 (from lowest to highest disagreement). The ability of each MHR variability index to predict newborn acidemia and operative vaginal delivery was determined using areas under receiver operating curve (auROC).

RESULTS

The percentage of MHR signal loss for the ECG and PPG signals increased as labor progressed, from H_1 to H_2, as displayed in Figure 2. Median signal loss with ECG was significantly higher than with PPG in the first four segments of H_1 (1% versus 0%), exhibiting a pronounced positively skewed distribution (Figure 2). Median signal loss with PPG was significantly higher than with ECG in the last segment of H_2 (10% versus 20%). A total of 38 segments in H_1 (12.7%) and 113 segments in H_2 (36.9%) were excluded from analysis due to signal loss higher than 15% in ECG and/or PPG signals (Figure 2). MHR values differing less than or equal to 5 bpm between ECG and PPG signals (HR_m), had a median of 76.4% (inter-quartile range of 17.5%) in H_1, and 71.5% (inter-quartile range of 22.6%) in H_2.

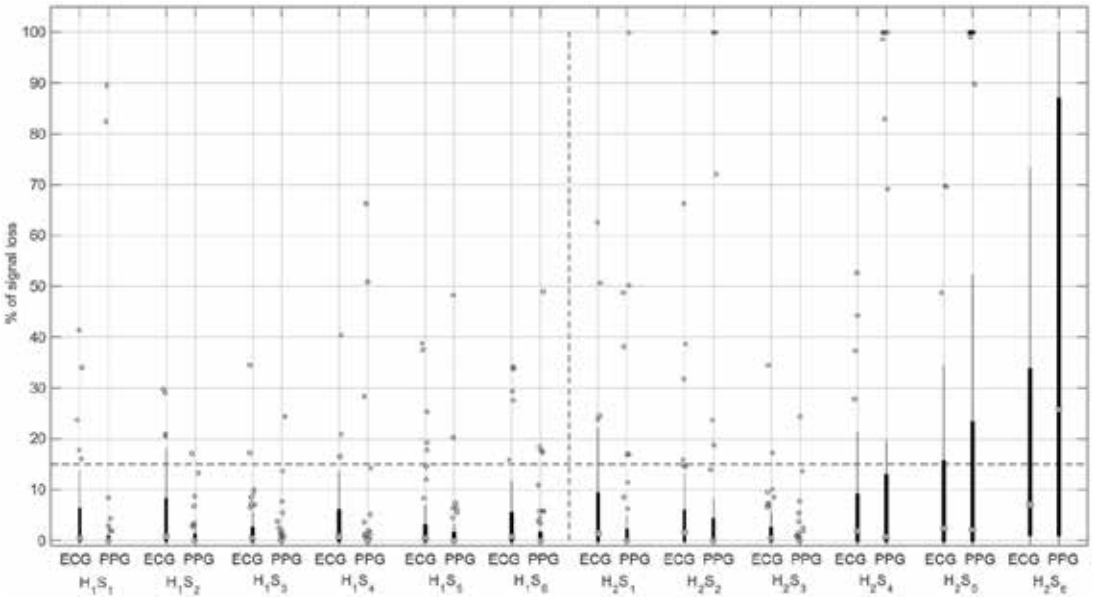

Fig. 2 Percentage of signal loss with ECG and PPG across all the 10-min segments S_i (i=1,…,6) of H_1 and H_2 , represented as *boxplots*. The *horizontal dashed line* corresponds to the 15% signal loss threshold used to exclude segments from analysis of MHR variability indices

MHR variability indices obtained from PPG signals were significantly lower than those obtained from ECG signals, with the exception of LF_{norm} and LF/HF (Table 2). The lower values of short-term variability and entropy indices are likely to be due to the inability of PPG to capture faster signal oscillations, as showed in Figure 1. Most linear indices and SD_2 obtained with the two methods were highly correlated, with values ranging between 0.60 and 1.00, whereas LF_{norm}, HF_{norm}, LF/HF and the remaining non-linear indices had lower correlations, ranging between 0.07 and 0.59 (Table 2).

Progression of labor (from H_1 to H_2) was associated with a significant increase in SD_1, SD_2 and most linear indices (excluding II, LF_{norm}, HF_{norm} and LF/HF) and with a decrease in entropy indices (Table 2). This was generally observed with both acquisition modes, with the exception of most entropy-based indices in PPG signals.

	H_1				H_2				H_1 vs H_2	
	95% CI				95% CI				p	
	ECG	PPG	p	r	ECG	PPG	p	r	ECG	PPG
mHR	83.09-85.59	83.19-85.64	**0.002**	1.00	86.29-93.13	86.64-93.32	**0.016**	0.99	**0.000**	**0.001**
sdHR	5.99-6.55	4.35-5.11	**0.000**	0.90	6.66-7.97	5.11-5.99	**0.000**	0.92	**0.000**	**0.000**
LTI	10.53-11.67	8.13-9.19	**0.000**	0.92	12.37-14.33	9.19-11.31	**0.000**	0.90	**0.000**	**0.000**
Delta	21.42-23.33	10.16-11.44	**0.000**	0.71	24.19-27.13	11.30-13.78	**0.000**	0.81	**0.000**	**0.000**
STV	3.53-3.89	0.94-1.03	**0.000**	0.60	3.85-4.41	1.05-1.18	**0.000**	0.71	**0.001**	**0.000**
II	0.56-0.63	0.19-0.21	**0.000**	0.74	0.55-0.60	0.18-0.21	**0.000**	0.72	0.177	0.573
TP	25.82-30.27	11.42-14.32	**0.000**	0.83	33.50-44.59	14.05-21.23	**0.000**	0.89	**0.000**	**0.000**
VLF	8.53-10.57	7.53-9.49	**0.000**	0.95	11.13-15.57	8.88-13.56	**0.000**	0.94	**0.000**	**0.001**
LF	6.67-8.12	3.20-4.01	**0.000**	0.88	8.16-10.87	4.14-5.47	**0.000**	0.90	**0.000**	**0.000**
LF_{norm}	45.28-50.38	90.90-92.56	**0.000**	0.44	43.29-49.99	91.69-92.76	**0.000**	0.41	0.926	0.643
HF	4.70-5.61	0.16-0.20	**0.000**	0.71	5.90-7.69	0.21-0.27	**0.000**	0.73	**0.000**	**0.000**
HF_{norm}	28.33-32.18	4.70-5.49	**0.000**	0.45	28.03-32.48	4.66-5.55	**0.000**	0.45	0.805	0.958
LF/HF	1.47-1.69	16.67-19.56	**0.000**	0.48	1.35-1.67	16.48-19.73	**0.000**	0.46	0.944	0.981
ApEn(2,0.1)	1.21-1.24	0.55-0.60	**0.000**	0.23	1.16-1.21	0.57-0.61	**0.000**	0.22	**0.010**	0.276
ApEn(2,0.15)	1.15-1.20	0.52-0.56	**0.000**	0.43	1.10-1.15	0.48-0.56	**0.000**	0.47	**0.023**	0.371
ApEn(2,0.2)	0.98-1.04	0.26-0.45	**0.000**	0.51	0.96-1.02	0.24-0.34	**0.000**	0.53	0.163	0.620
SampEn(2,0.1)	1.52-1.62	0.38-0.45	**0.000**	0.38	1.41-1.54	0.40-0.46	**0.000**	0.59	**0.039**	0.524
SampEn(2,0.15)	1.16-1.29	0.33-0.39	**0.000**	0.38	1.06-1.16	0.31-0.38	**0.000**	0.46	**0.001**	0.336
SampEn(2,0.2)	0.91-0.99	0.20-0.28	**0.000**	0.51	0.87-0.96	0.18-0.22	**0.000**	0.58	0.062	0.479
r_{Lu}	0.13-0.13	0.06-0.06	**0.000**	0.48	0.12-0.13	0.06-0.06	**0.000**	0.36	0.074	0.286
ApEn(2,r_{Lu})	1.20-1.24	0.57-0.61	**0.000**	0.18	1.15-1.21	0.60-0.63	**0.000**	0.12	**0.007**	**0.003**
SampEn(2,r_{Lu})	1.33-1.39	0.40-0.46	**0.000**	0.08	1.22-1.32	0.43-0.49	**0.000**	0.07	**0.000**	0.052
SD_1	1.57-1.74	0.37-0.39	**0.000**	0.47	1.68-2.17	0.40-0.46	**0.000**	0.44	**0.004**	**0.000**
SD_2	8.21-9.06	6.13-7.22	**0.000**	0.91	9.17-10.94	7.21-8.46	**0.000**	0.93	**0.000**	**0.000**
SD_1/SD_2	0.19-0.21	0.06-0.06	**0.000**	0.48	0.17-0.19	0.05-0.06	**0.000**	0.36	0.078	0.308

Table 2: MHR variability indices, obtained with ECG and PPG in H_1 and H_2, presented as 95% confidence intervals (95% CI), with the corresponding p-values and correlation coefficients. The last two columns display the p-values of the comparison between H_1 and H_2.

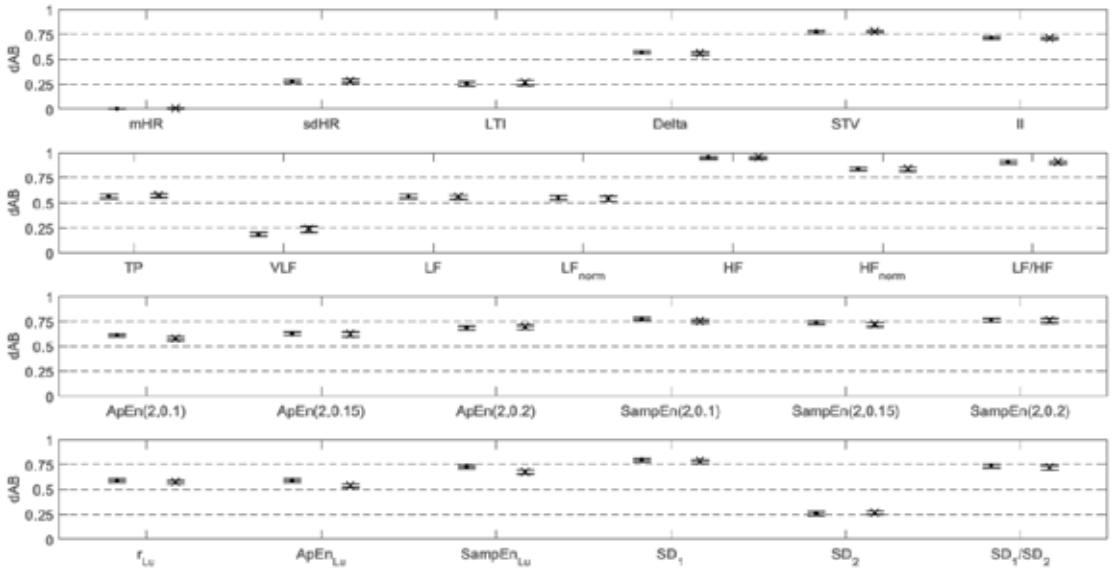

Fig. 3 Disagreement (d_{AB}) between the MHR variability indices obtained with ECG and PPG, for liar time-domain indices (*first row*), linear frequency-domain indices (*second row*), entropy indices (*third row*) and Poincaré plot indices (*fourth row*). Disagreement was assessed for the initial (H_1, *dot*) and final (H_2, *cross*) 10-min tracing segments (*error bars* represents the 95% CI). Note that the zero value corresponds to the minimum.

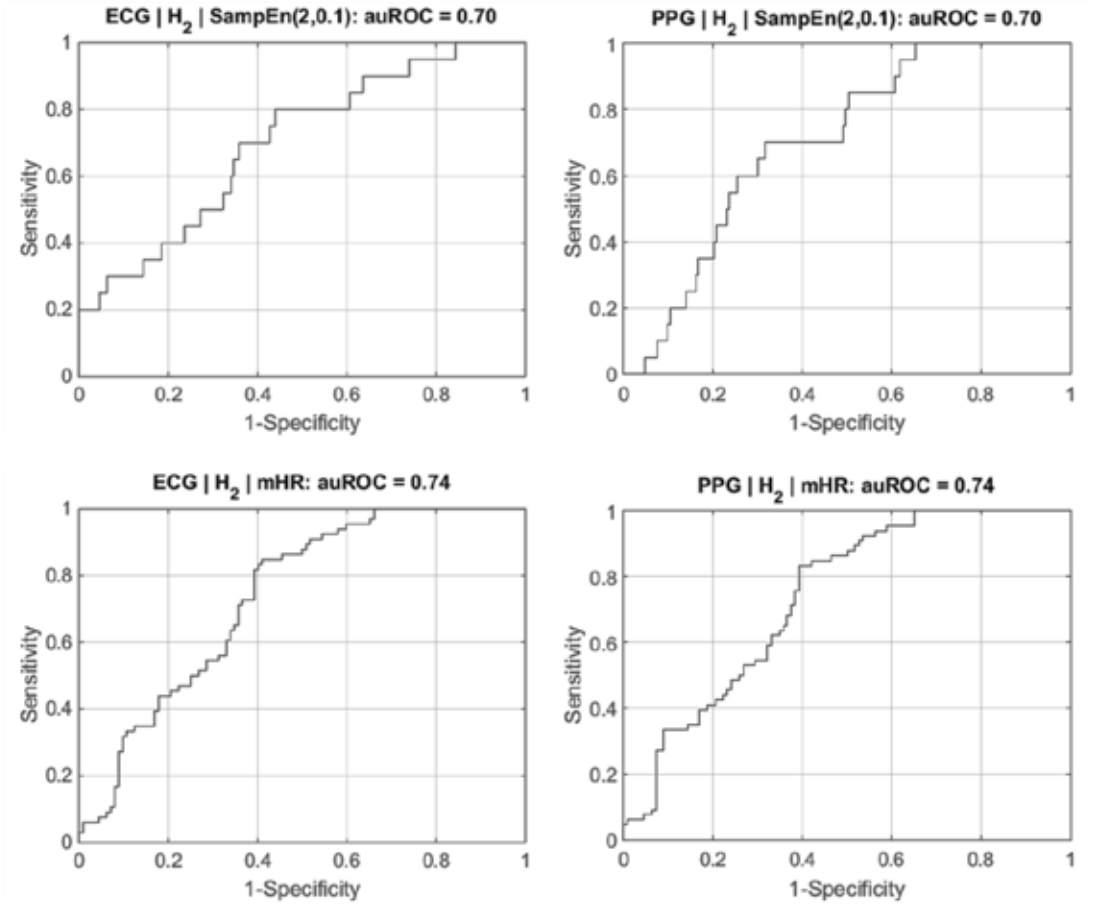

Fig. 4 Receiver operating characteristics curves for the detection of fetal acidemia in H_2 (top plats) using SampEn(2,0.1), with ECG (left plot) and PPG (right plot), both associated with an auROC of 0.70. A similar analysis for the detection of operative delivery is given in the lower plots, for wich an auROC of 0.74 was achieved using mHR in H_2

MHR indices related with short-term variability or faster oscillations had the highest disagreements between ECG and PPG recording modes, namely the linear time-domain indices Delta, STV and II, the linear frequency-domain indices, excluding VLF, and the non-linear indices, excluding SD_2, for which d_{AB} was in the range 0.57-0.96 (Figure 3).

Considering the analysis of normal versus acidemic newborns, MHR variability indices obtained with ECG or PPG were not significantly different between both groups in H_1. However, there were significant differences in H_2, both with ECG and with PPG. The highest auROC values were obtained with SampEn(2,0.1) in H_2, with similar auROC values of 0.70 for ECG and PPG (Figure 4).

There were also significant differences between normal and vaginal operative deliveries in several MHR indices in H_1 and H_2, both with ECG and PPG signals. The highest auROC value was 0.74, obtained with mHR in H_2 for ECG and PPG (Figure 4).

DISCUSSION

To our knowledge, this is the first study to compare linear and non-linear MHR variability indices obtained with ECG and PPG during labor. The main objective was to determine whether PPG can be used as an alternative to ECG, as the latter may not always be available.

The clinical scenarios chosen to perform our comparison between MHR variability indices derived from signals obtained with ECG or PPG were progression of labor, fetal acidemia and operative vaginal delivery, as these are conditions related with different maternal balances between cortical and autonomic nervous system activities [5,26].

The percentage of signal loss with the PPG signal was similar to that of the ECG during the final segments of labour, and was only significantly higher in the last 10-min segment (S_6) of H_2. This may have happened because of maternal movements and inadvertent temporary removal of the pulse oximeter in this more stressful period. In addition, the percentage of signal loss of the PPG signal was significantly lower than the ECG in the first four segments of H_1. Therefore, the use of PPG is not compromised because of signal loss in the last two hours before delivery, with the exception of the final 10-min segment.

The similarity of MHR variability indices calculated with ECG and PPG signals was not the same for all indices. Those related with faster oscillations and entropy were poorly correlated and exhibited high disagreement. Linear indices related with baseline and long-term variability (e.g. mHR, VLF and SD_2) were highly correlated and had low disagreement. These findings corroborate the different visible characteristics of the ECG and PPG signals (Figure 1).

Visual analysis of the PPG signal suggests an absence of the high frequency component, supported by considerably lower absolute values of HF than the ECG signal. Although to a lesser extent, TP, VLF and LF indices derived from the PPG signal were also lower than their ECG counterparts. LF_{norm} was approximately twice, HF_{norm} was smaller to a larger extent and LF/HF was much higher in PPG signals. In spite of this, a consistent trend from H_1 to H_2 was observed with both ECG and PPG signals (Table 2). We can therefore conclude that, although spectral indices derived from the two signals are significantly different, if appropriate reference ranges are used, PPG signals may be used as an alternative to the ECG for traditional HRV spectral analysis.

A possible explanation for the difference between ECG and PPG signals is related with the HR extraction technique. A beat detection approach is usually employed in the ECG signal, whereas spectral analysis is commonly used with PPG signals. The narrower shape of the peak

in the ECG signal may lead to a higher resolution. Unfortunately, access to the raw PPG signal data was not possible in this study, nor could detailed information on this extraction technique be obtained from the manufacturers. It should be noted that the differences between ECG and PPG signals may also be related to the inherently different nature of these signals: the PPG signal depends on the detection of blood ejected from the heart measuring changes in light absorption, whereas ECG signals evaluate electrical activity of the heart. These two signals should naturally have the same periodicity for healthy subjects, but they can differ in subjects with cardiac dysrhythmias. Patients with atrio-ventricular block or atrial fibrillation can exhibit an electro-mechanical cardiac dysynchrony. While these situations are unlikely to occur in a population of healthy women with uneventful pregnancies, such as the one in the present study, they may appear in higher-risk pregnancies. Bizarre and noisy MHR signals obtained by the ECG are typically associated with the most significant and persistent cardiac disrythmias [37].

Progress of labor was associated with an increase of most MHR linear indices and a decrease of entropy indices, with both acquisition methods. This is consistent with a previously described increase in autonomic nervous system activity throughout labor, both from the maternal and fetal sides [3,38]. PPG signals seem to be as good as ECG ones for establishing the evolution of slow oscillation-based MHR indices throughout labour.

Similar auROC values were obtained in the discrimination between acidemic and normal fetuses, and between normal and vaginal operative deliveries, when using ECG and PPG signals. The highest observed value of 0.70 using SampEn(2,0.1) in H_2 regarding fetal acidemia, and of 0.74 using mHR in H_2 in the detection of operative vaginal delivery, opens the possibility of single or combined use of MHR and FHR indices, in the identification of these situations. The discriminatory capacity of these indices may be higher for detection of fetal acidemia when considering a multivariate approach [39]. However, the objective of maximizing discriminatory performance was not under the scope of the present study.

Further refinement of pre-processing and processing algorithms may optimize the results reported in this study, regarding clinical applications. Conventional fetal monitors supply MHR at 4Hz intervals, whereas the frequency bands of interest in human adults are in the range 0-0.4Hz. Accordingly, 80% of the spectrum corresponding to the interval between 0.4Hz and the Nyquist frequency (2Hz) is of little interest. Therefore, signal acquisition or resampling at 2Hz rather than 4 Hz may be considered, as in the present study, and this may allow a reduction in computation time without compromising results. However, particular care must be taken when analyzing MHR signals at other untested sampling frequencies (smaller than 2Hz or beat-to-beat), as this has been shown to influence the results of variability indices [40]. Additionally, the sampling frequency, presence of noise and the filtering procedure of the original signal, and different equipment from the one considered in this study, must be carefully evaluated.

CONCLUSION

In conclusion, although PPG capture faster oscillations of the MHR signal less well than ECG and is prone to have higher signal loss in the last 10-min preceding delivery, it can be considered an alternative for MHR monitoring during labour, when appropriate MHR variability indices are used with a proper adaption of cut-off intervals. Further studies are warranted to confirm whether access to the PPG raw signal data or more detailed information on the extraction method will improve performance, and whether linear and entropy analysis of MHR, alone or in combination with FHR, may be clinically useful.

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CHAPTER 7

GENERAL DISCUSSION

MAIN CONCLUSIONS

FUTURE PROSPECTS

GENERAL DISCUSSION

In this closing chapter, we present a general discussion regarding the results, the strengths, and the weaknesses of each study and suggestions for further developments.

As described in **Chapter 1**, a bibliographic search conducted at the outset of this thesis showed that few studies have evaluated the relationship between MHR and FHR, and most have focused on the occurrence of MHR-FHR ambiguities. The bibliographic search strategy was not easy to define. Several searches using the keywords “maternal” or “mother” and “fetal” or “fetus” and “heart rate” provided thousands of articles that were unrelated to the comparison between MHR and FHR recordings. After extensive electronic and manual searches, we consistently verified that all eligible articles contained these keywords in their title or abstract; therefore, we decided to adopt a search strategy limited to those fields. The consistency of this strategy has been confirmed throughout the course of this thesis; thus, we propose it for future studies in this area. An updated search conducted at the time of the final writing of this thesis has added four more articles to our initial bibliographic search, besides the five published by us. Two of the articles were on technical aspects related to MHR and FHR recording [1,2], and the other two were on the physiology of MHR-FHR interactions [3,4]. This suggests that our thesis provides a significant contribution to an area of continuing interest for the research and clinical communities.

Development and evaluation of an algorithm for computer analysis of MHR during labor

Chapter 2 provides a description of a unique algorithm for computerized MHR and FHR analysis. When compared with a consensus of experts, it provided good to excellent agreement and reliability. It was also possible to detect MHR changes associated with labor progression, namely a well-defined basal MHR and accelerations, which are significantly more frequent in the last hour of labor. With a better tracing storage and retrieval, the computer analysis overcame the imprecise visual interpretation of recordings, allowing a more accurate method to understand the complexity of maternal-fetal pathophysiologic interactions and emerge as a possible valid tool for on-line intrapartum maternal-fetal monitoring. However, this study was confined to a small case series obtained during the final hours of labor, a limitation partially justified by the difficulty of acquiring good maternal and fetal signals during active pushing efforts. More extensive studies are warranted for improvement of the algorithm and its assessment in different clinical scenarios, both in the ante- and intrapartum periods and using alternative methods for simultaneous and continuous acquisition of maternal and fetal signals coupled in the same device.

Development and validation of an algorithm to detect and delete MHR-FHR ambiguities during labor

Chapter 3 describes a unique algorithm developed to detect and delete MHR-FHR ambiguities. Our results strongly reinforce that MHR-FHR ambiguities during the last hour of labor are much more frequent and subtle than initially suspected, and these ambiguities could result in either unnecessary interventions or failure to timely intervene. To date, only two retrospective studies [5,6] and one prospective observational study [7] examining the presence of maternal and fetal signal ambiguity have been published, mainly focused on the different methods of acquiring maternal and fetal signals and the incidence of MHR-FHR ambiguities. However, none has reported the subtraction of maternal from fetal heart rate. In our study, the application of this

algorithm to FHR tracings recorded during labor resulted in a significant improvement in tracing classification, and constitutes a strong motivation for more extensive studies in different clinical settings and in search of optimized technical solutions having the same purpose. However, several limitations have to be considered in the analysis of these results and future research. First, the need of inclusion of more cases of higher-risk populations, as the few number of cases with umbilical artery pH less than 7.15 has limited clinical significance. Second, a more systematic evaluation and refinement of the criterion used for the exclusion of MHR-FHR ambiguities, tested with other methods of acquiring maternal and fetal signals.

Exploration of the clinical application of the developed algorithms for combined conventional computerized analysis of MHR and FHR recordings in the assessment of labor progression, acidemia, and maternal-fetal attachment

In **Chapter 4**, we explore the application of combined computer analysis of MHR and FHR recordings in the assessment of labor progress, fetal acidemia, and maternal-fetal attachment. To our knowledge, this was the first study to evaluate such associations. The progression of labor was linked with a significant increase in MHR accelerations and FHR decelerations, not only in non-acidemic fetuses, as observed in the study presented in *Chapter 3*, but also in mildly acidemic fetuses (UAB pH < 7.20). Moreover, there was an increase in MHR-FHR correlations and differences in accelerations and decelerations in acidemic fetuses, indicating an increase in maternal-fetal attachment in those situations. This suggests that maternal-fetal attachment may be a way to protect fetuses that are born acidemic, and provides new data to be considered in subsequent studies in infant survival and future development of theories in this topic. To our knowledge, there are no other studies regarding these features in this context, and this preliminary study proposed that MHR-FHR respond differently during labor with signs of increased maternal-fetal attachment during labor progression in the acidemic fetus. However, these results must be interpreted with caution as they pertain to a small number of fetuses with mild-to-moderate acidemia and with modest auROC. Nevertheless, the results suggest that more discriminative results can be achieved with optimized mathematical algorithms, testing easier ways of simultaneous MHR and FHR recording and using larger datasets with more acidemic cases, to overcome the overlapping of clinical outcomes that occurred in this study.

Exploration of the clinical application of combined non-conventional spectral and entropy analysis of MHR and FHR recordings in the assessment of labor progression and acidemia

In **Chapter 5,** non-conventional computer analysis (spectral and entropy analysis) of MHR-FHR signals was evaluated for the prediction of labor progression and newborn acidemia (UAB pH < 7.15). Progression of labor was associated with a significant increase in most MHR and FHR linear indices, whereas entropy indices decreased, both in acidemic and non-acidemic fetuses. Whereas results obtained with FHR analysis alone were consistent with those reported in previous studies, namely the significantly higher sympatho-vagal balance observed in acidemic fetuses, the novel findings in this study were that changes were also present in MHR with progression of labor and with fetal acidemia. Whereas the mother´s sympatho-vagal balance increased significantly as labor progressed, the opposite was observed in the fetus. The inclusion of MHR in bivariate analysis achieved high sensitivities and specificities in the prediction of newborn acidemia, providing encouraging results for this approach. However, limitations exist in respect to the small number of fetuses born with UAB pH less than 7.20 included in the study sample.

Exploration of the use of pulse oximetry as an alternative to electrocardiography for the acquisition of MHR signals

In **Chapter 6,** motivated by the need of further development of continuous and simultaneous MHR and FHR monitoring, the use of pulse oximetry was for the first time compared with ECG for the acquisition of MHR signals during labor**,** as an easier and alternative method of acquiring MHR signals. The percentage of MHR signal loss for the ECG and PPG signals increased as labor progressed, and during the final segments of labor, namely in the last 10-minute segment before delivery, was similar in PPG and ECG acquisition. Maternal movements, discomfort, and inadvertent removal of the maternal finger probe were the main reasons for signal loss using PPG. However, as PPG had lower signal loss during the first four segments of H_1, and had better performance than the ECG signal regarding signal loss of MHR estimation during labor, it can be considered an alternative for MHR monitoring during labor, as long as a proper adaptation of cut-off intervals is set up.

MAIN CONCLUSIONS

- Although there is an intimate relationship between the mother and the fetus, few studies have evaluated the interaction between MHR and FHR during labor.
- Most publications evaluating MHR-FHR interactions are related with misinterpretation of the MHR as FHR during labor, and only a few explore pathophysiologic issues.
- Visual analysis of MHR tracings is subject to poor observer agreement and reliability, similarly to that reported for FHR analysis.
- Computer analysis of MHR is now possible with a mathematical algorithm developed as part of the work of this thesis.
- MHR-FHR ambiguities occurring in FHR recordings acquired during labor may now be detected and deleted with an algorithm developed and validated as part of the work of this thesis, resulting in an improvement in FHR tracing classification.
- Combined computer analysis of MHR and FHR recordings appears to be a promising method to evaluate labor progress, fetal acidemia, and maternal-fetal attachment.
- Non-conventional (spectral and entropy) computer analysis of MHR and FHR signals using spectral and entropy models appears to be a promising method for the evaluation of labor progress and detection of fetal acidemia.
- Although pulse oximetry captures the faster oscillations of the MHR signal less well than does ECG, it can be considered an alternative for MHR monitoring during labor.

FUTURE PROSPECTS

This thesis was based on original exploratory studies that have opened new perspectives for future developments and research. Here, we summarize some future prospects.

- Improvement and implementation of the novel mathematical algorithm for MHR analysis, as well as the criterion used for exclusion of MHR-FHR ambiguities.

- Larger studies to confirm the impact of the proposed combined computerized MHR-FHR analysis on the diagnostic accuracy of intrapartum cardiotocography and decrease the unnecessary intervention associated with false-positive yellow-red alarms in non-acidemic fetuses, without compromising sensitivity.

- Further assessment of the developed algorithms for MHR-FHR analysis in different clinical scenarios and using alternative methods for simultaneous and continuous acquisition of maternal and fetal signals, namely using maternal pulse oximetry and fetal ECG.

- Further assessment in larger clinical studies of MHR-FHR analysis using the non-conventional spectral end entropy heart rate indices explored in this thesis.

- Exploration of MHR analysis is prediction of labor progression and dystocia. This has not been done in this thesis, but an initial promising study has already been performed and presented at a conference meeting [8] using HR indices related with the estimation of the maternal sympatho-vagal balance associated with labor dynamics.

Although many questions remain to be answered, this thesis evidenced that MHR and FHR analysis may be powerful tools accessible to systematic study, which could lead to scientific and technologic progress and improve maternal-fetal clinical knowledge, namely the pathophysiologic interactions, the overall maternal-fetal conditions, and perinatal outcome.

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