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ORIGINAL RESEARCH

Parasympathetic tone variations according to umbilical cord pH at birth: a computerized fetal heart rate variability analysis

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Abstract Non-reassuring fetal heart rate tracings reflect an imbalance between the parasympathetic and sympathetic nervous systems. In this situation, fetal asphyxia can be suspected and may be confirmed by metabolic measurements at birth like low pH or high base deficit values. The objective of this study was to determine whether fetal asphyxia during labor is related to parasympathetic nervous system activity. This is a retrospective study of a database collected in 5 centers. Two hundred and ninety-nine fetal heart rate tracings collected during labor were analyzed. Autonomic nervous system, especially the parasympathetic nervous system, was analyzed using an original index: the FSI (Fetal Stress Index). The FSI is a parasympathetic activity evaluation based on fetal heart rate variability analysis. Infants were grouped based on normal or low pH value at birth. FSI was measured during the last 30 min of labor before birth and compared between groups. The minimum value of the FSI during the last 30 min before delivery was significantly lower in the group with the lower umbilical cord arterial pH value. In this pilot study during labor, FSI was lower in the group of infants with low arterial pH at birth.

Keywords Acidemia · Autonomic nervous system · Fetus · Heart rate variability · Umbilical cord pH

1 Introduction

During pregnancy and labor the fetus can be deprived of an adequate supply of oxygen. When fetal asphyxia is suspected it can be confirmed by metabolic measurements at birth like a low pH or a high base deficit in umbilical cord arterial blood [1]. Since the central nervous system and cardiovascular system are very sensitive, small changes in oxygen levels can result in severe neurosensory disorders like cerebral palsy, or even death of the newborn [2].

One serious consequence of anoxia in the fetus is metabolic acidosis which alters fetal heart rate (FHR) and fetal heart rate variability (HRV) [3] including heart rate pattern reductions in variability, decelerations, bradycardia, or tachycardia [4, 5]. Visual inspection of FHR by medical professionals during labor is the most common clinical assessment to evaluate the risk of acidosis. The American College of Obstetricians and Gynecologists (ACOG), the International Federation of Gynecology and Obstetrics (FIGO) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommend a grid classification system based on FHR visual interpretation [6–8]. However, visual analysis is subject to a poor inter- and intra-observer agreement [9–11].

Several authors investigated computerized HRV analysis methods for fetal autonomic state evaluation and showed significant changes fetal HRV when fetal acidemia occurred [12–16]. As such, our first objective was to

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develop a non-invasive HRV based-technology for measurement of parasympathetic activity in fetuses. Based on work done with adults, this technology allows quick computation of an index that reflects parasympathetic activity variations. In brief, during a stressful situation such as pain, the index falls as parasympathetic activity decreased [17, 18]. Changes in parasympathetic activity measured with our index can predict the intensity of postoperative pain [19] and can be used in conscious patient for pain and/or stress assessment [20, 21]. Recently, this technology has been adapted to the particular context of newborn infant wellbeing monitoring. The index was significantly reduced in newborns presenting significant behavioral postoperative pain [22, 23], and was increased after a nursing care known to activate the parasympathetic activity in neonates (handling and listening to human voice) [24]. The aim of this study was to investigate the fetal parasympathetic activity by computerized HRV analysis relative to fetal acidemia. We hypothesized that fetuses with low pH values will present low parasympathetic activity evaluated by our HRV method.

2 Methods

2.1 Population

This study used a database of 299 FHR records obtained for routine medical purposes in 5 centers (Lille, Valenciennes, Saint Vincent de Paul, Robert Debré, Poissy-St-Germain, France) from November 2003 to February 2005.

For the database records, after informed consent, women in labor were connected to cardiotocograph (CTG; Philips[TM] series 50, Philips Medical Systems[TM], Böblingen, Germany) for continuous FHR recording using ultrasound probes. Inclusion criteria were singleton pregnancies between 36 and 42 weeks of gestation with cephalic presentation. The FHR recordings obtained were issued from Philips[TM] series 50 CTG connected to a personal computer (Toshiba Satellite Pro, Toshiba[TM], Japan) for data acquisition and storage. All fetal heart rate tracing were performed by ultrasound Doppler. All the records from this database showed a good signal quality. Maternal parameters including age, parity, gestational age, mode of delivery, and expulsion duration (period between the beginning of expulsive efforts and birth), were collected. Neonatal parameters including birth weight and Apgar score were also reported. Blood samples were collected from the umbilical cord artery and vein at birth in order to determine pH values, pO_2, pCO_2, and Base Deficit (BD blood). Data were sourced from medical chart. This study was approved by the French committee of obstetrics and gynaecology research ethics (CEROG OBS 2015-11-18).

2.2 Description of the FHR analysis method

HRV is mediated by the parasympathetic and sympathetic nervous system. High frequency FHR variations (>0.15 Hz) [25, 26] correspond to parasympathetic activity only whereas low frequency FHR variations (0.04–0.15 Hz) are related to both parasympathetic and sympathetic activity. The very low frequency variations (<0.04 Hz) are related to thermoregulatory and endocrine activities [27–30]. Our HRV based technology is already validated in adults and newborn infants [17–24] and was recently adapted for the evaluation of parasympathetic activity changes in fetuses.

Most of the published methods are based on a spectral analysis of HRV [31–33]. Our analysis consists of a filtering method followed by a continuous analysis of the filtered signal magnitude in the time domain. The following paragraph describes this technology adaptation for the calculation of fetal HRV named FSI (Fetal Stress Index).

The FSI index is based on continuous FHR analysis. FHR values are transformed into time interval in millisecond.

$$T_i = 60000/FHR_i$$

The time series are then re-sampled at an 8 Hz sampling frequency and isolated in a 64 s moving window. The time series is then mean centered:

$$T_i' = T_i - \frac{1}{N}\sum_{i=1}^{N}(T_i)$$

and normalized:

$$T_i'' = T_i' / \sqrt{\sum_{i=1}^{N}(T_i')^2}$$

The resulting T_i'' series is then high pass filtered in order to isolate oscillations above 0.15 Hz.

We then obtain a time series representative of the FHR parasympathetic variations as shown in Fig. 1.

Local maximum and minimum are detected on this filtered signal and the lower and upper envelopes are plotted
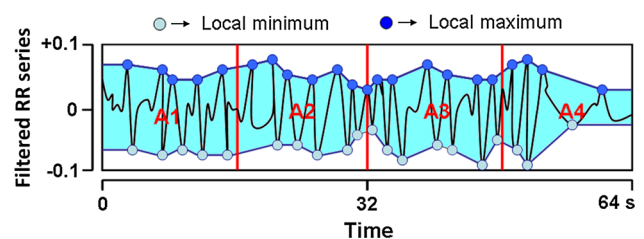

Fig. 1 FSI computation. Normalized and filtered RR Series (black curve). A1, A2, A3 and A4 are computed between lower and upper envelopes (area in blue). Lower area (A_{min}) is then selected and FSI is computed

in order to compute the areas between envelopes A1, A2, A3 and A4 in four 16 s sub-windows. A_{min} is defined as the lowest of this 4 areas.

$$A_{min} = min(A1, A2, A3, A4)$$

FSI is computed from A_{min} as: $FSI = 100 \times (5.1 \times A_{min} + 1.2)/12.8$ in order to obtain a 0–100 numerical value reflecting the visual aspect of the filtered time series. Continuous computation is assumed by sliding the moving window with a 1 s moving period.

High FSI values (near 100) correspond to an important parasympathetic activity, whereas a decrease of FSI corresponds to a decrease of the parasympathetic activity.

2.3 Data analysis

The minimum, maximum and mean values of FSI (respectively FSI_{min}, FSI_{max} and FSI_{mean}) were computed for the last 30 min before delivery.

Kitlinski et al. [34] demonstrated a physiological linear decline of umbilical cord arterial pH with gestational age and propose gestational age-adjusted pH thresholds. For this study, we therefore decided to group infants based on low or normal umbilical cord arterial pH values using the gestational age-adjusted pH thresholds (pH_{GA}) proposed by Kitlinski et al. [34].

2.4 Statistical analysis

All data are presented as median (1st–3rd quartile). We used non parametric Mann–Whitney tests to compare each parameter and χ^2 or Fisher tests were performed for binary parameters. Probability values less than $P < 0.05$ were considered significant. Data were analyzed using SPSS 20.0 (IBM, Armonk, NY, USA).

3 Results

3.1 Description of the population

All maternal characteristics (birth weight, parity, gestational age, delivery mode…) were similar between the groups (Table 1). The proportion of newborns with an Apgar score ≤ 7 at 1 min was significantly higher in the group $pH \leq pH_{GA}$ ($P = 0.006$) but no difference was observed for Apgar scores at 5 min.

3.2 FSI variations

FSI_{min} and FSI_{mean} were significantly lower in the low pH values group [$P = 0.018$ and $P = 0.031$, (Table 2)].

4 Discussion

We compared the FSI maximum, minimum, and mean values computed 30 min before delivery between groups with low and normal pH values. We found that both the minimum and mean values of the FSI were significantly lower for the low pH group. This suggests that low high frequency variations measured with FSI_{min} and FSI_{mean} are consistent with fetal acidemia. The fetus can develop metabolic mechanisms in order to compensate oxygen deficit. During the first steps of hypoxia, chemoreceptors are activated and a bradycardia may be observed following a vagal response [35]. At the same time, the activation of α-adrenergic receptors induces a peripheral vasoconstriction that results in a redistribution of blood flow to brain, heart, and adrenals; and generated a hypertension. Then, baroreceptors are stimulated in order to decrease heart rate. Catecholamines are secreted in response to the sympathetic stimulation, heart rate is increased and glycogenolysis is activated. If the lack of oxygen increases, because of the anaerobic metabolism used in cells, a metabolic acidosis can appear. It causes an important activation of the sympathetic nervous system. The sensitivity of chemoreceptors and baroreceptors is decreased, the role of the autonomic nervous system is reduced (intensity of sympathetic and parasympathetic messages is mitigated) resulting in late heart rate decelerations and slower recuperation [36]. HRV is dramatically reduced [37, 38] and the fetus presents a high risk of sequelae. As pO_2 modifications exist, fetuses engage physiological adaptation mechanisms that will have an effect on the heart rate via the autonomic nervous system. In this study, we evaluated the relative parasympathetic activity using an index between 0 and 100. Our main result is a decrease of FSI during the last 30 min of labor for fetuses born with low arterial umbilical cord pH values. In other words, the drop in FSI were more pronounced for fetuses with $pH \leq pH_{GA}$. We can assume that these data reflect the decreasing intensity of autonomic nervous system caused by a lack of oxygen.

HRV analysis methods have been used for fetal acidosis diagnosis. These methods are based on time or frequency domain analysis of fetal HRV [39]. Ayres-de-Campos et al. [40] estimated short term and long term variability (STV and LTV) in the time domain to predict neonatal outcome. They demonstrated that both STV and LTV varied with newborns with low arterial pH and low Apgar scores. Furthermore, Galazios et al. [41] found a decreased STV in the low umbilical arterial pH at birth group. When using frequency domain analysis methods there is inconsistency in the literature. Some authors found a decrease in the low frequencies [12], or a decrease in very low, low and high frequencies [31] and others did not find any modifications

Table 1 Maternal and neonatal characteristics

	pH > pH$_{GA}$ $n = 287$	pH ≤ pH$_{GA}$ $n = 12$	P value
Maternal characteristics			
Age (y)	28 (24–32)	29.5 (22–36)	0.562
Parity	2 (1–3)	1 (1–2)	0.593
Gestational age (wk + d)	39 + 6 (38 + 6 − 40 + 5)	40 + 0 (39 + 1–41 + 1)	0.094
Spontaneous vaginal delivery	242/287 (84%)	8/12 (67%)	0.115
Caesarean section	18/287 (6%)	0/12 (0%)	0.468
Vacuum	5/287 (2%)	0/12 (0%)	0.814
Forceps	23/287 (8%)	3/12 (25%)	0.076
Expulsion duration (min)	10 (5–15)	12.5 (9.5–21.25)	0.130
Meconial amniotic fluid	34/287 (12%)	1/12 (8%)	0.579
Neonatal parameters			
Birth weight (g)	3320 (3010–3602)	3420 (2990–3560)	0.712
Apgar ≤ 7 1 min	17/287 (6%)	4/12 (33%)	0.006
Apgar ≤ 7 5 min	10/287 (3%)	0/12 (0%)	0.660
Arterial pH	7.24 (7.19–7.29)	7.04 (7.02–7.07)	<0.0001
Arterial pCO2 (mmHg)	57 (48–64)	88 (84–89)	<0.0001
Arterial base deficit (mmol/L)	−3 [(−6)–(−1)]	−12 [(−12.5)–(−9.5)]	0.001
Venous pH	7.34 (7.30–7.37)	7.16 (7.08–7.19)	<0.0001
Venous pCO2 (mmHg)	40 (36–45)	56 (52–62)	<0.0001
Venous base deficit (mmol/L)	−3 [(−5)–(−2)]	−9 [(−10)–(−7.5)]	0.001

Values are presented as median (1st–3rd quartile) or ratio and percentage. Groups were defined according to umbilical cord arterial pH at birth: pH > pH$_{GA}$ or pH ≤ pH$_{GA}$. pH$_{GA}$ corresponds to the pH threshold according to gestational age [34]. Mann–Whitney tests were used to compare numerical parameter. χ^2 or Fisher tests were performed for binary parameters

$P < 0.05$ were considered significant

Table 2 FSI values

	pH > pH$_{GA}$ $n = 287$	pH ≤ pH$_{GA}$ $n = 12$	P value
FSI$_{max}$	60 (56–64)	56 (52–62)	0.142
FSI$_{min}$	36 (33–39)	32 (28–37)	0.018
FSI$_{mean}$	46 (44–49)	42 (38–48)	0.031

Values are presented as median (1st–3rd quartile) or ratio and percentage. Groups were defined according to umbilical cord arterial pH at birth: pH > pH$_{GA}$ or pH ≤ pH$_{GA}$. pH$_{GA}$ corresponds to the pH threshold according to gestational age [34]. Mann–Whitney tests were used to compare numerical parameter

$P < 0.05$ were considered significant

[13]. In several studies, an increase of low frequencies and a decrease of high frequencies were observed in case of fetal acidemia [15, 16, 32]. Our data support these results and are consistent with our hypothesis that lower FSI are found in infants with low pH at birth.

The comparisons between FHR analysis methods should be interpreted carefully because FHR signal acquisition and processing techniques vary widely. For example, Siira et al. [32] investigated fetal HRV through a spectral analysis using invasive fetal scalp electrodes whereas Chung et al. [31] performed a spectral analysis on the FHR signal issued from the Doppler ultrasound CTG. Doppler ultrasound CTG does not provide beat-to-beat FHR recordings; and FHR is usually averaged over 3 beats and sampled at 4 Hz. According to Van Laar et al. [25] FHR high frequency spectral analysis is only reliable if FHR is acquired on a beat-to-beat basis and issued from direct ECG signal obtained with a scalp electrode suggesting results using FHR that are averaged should be interpreted with caution. Other authors described time domain signal processing methods allowing the use of FHR signal issued from the Doppler ultrasound CTG [40, 41]. As our method is also based on a time domain analysis, we hypothesized that Doppler ultrasound CTG signal will be suitable for our analysis.

One limitation of our study is that we only listed one case of severe acidosis with an arterial pH at birth under 7.00 (6.91) and 12 newborns with pH values lower than the gestational age adapted threshold. However, despite this low number of severe acidosis, we showed a reduction of the FSI in the case of low pH values.

Though, this pilot study demonstrated the feasibility of computing the FSI non-invasively from FHR issued from CTG, other studies need to be performed in order to compare FSI computed from FHR issued from a CTG to FSI computed from FHR acquired on a beat-to-beat basis issued from a fetal scalp electrode. Our data showed that parasympathetic tone, illustrated by the HRV-based index FSI, is reduced during labor when a low arterial pH at birth was found. We are currently working on improving our technology sensitivity using sheep instrumented models and we will perform a prospective study in a larger population in order to detect more precisely fetuses with potential distress during delivery.

Compliance with ethical standards

Conflict of interest JDJ and RL are shareholders and LB was a team member of Mdoloris Medical Systems (that commercializes ANI and NIPE monitors which are based on the presented technology). The remaining authors report no conflict of interest.

Ethics approval The present retrospective study was approved by the French committee of obstetrics and gynaecology research ethics (CEROG OBS 2015-11-18).

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