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Correlation analysis of PRSA-based parameters during labor: a simulation study

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***Abstract*—During labor, a fetus might suffer considerable stress due to uterine contractions (UCs). Based on results obtained on a near-term pregnant sheep model, UCs mimicked as complete umbilical cord occlusions (UCOs) significantly activate vagal response, making the fetal inter-beat time interval (FRR) to display a sawtooth-like shape, which can be modeled using a pair of exponential functions (for the growing and decaying fronts, respectively). In addition, acceleration and deceleration capacities (AC/DC) and deceleration reserve (DR) computed through Phase-Rectified Signal Averaging (PRSA) technique proved to be sensitive to acid/base balance (for a wide range of their parameters T and s). In this preliminary study, we used a mathematical model linking UCOs and FRR response to investigate, using synthetic series, whether AC, DC, and DR are correlated with the time constants of the exponential models. Also we verified how this relation is affected by different values of the parameter T (with $s = T$). We found that DC and DR were strongly correlated with the time constant describing the increase of FRR after the onsets of UCOs in the range $5-11$ (strongest correlation for DC was -0.87 at $T = 8$, while for DR -0.92 at $T = 10$, $p < 0.05$). AC was instead not significantly correlated with the decay time constant (likely to due the limited sample size available). This study motivates further investigations on PRSA related quantities and on the reasons behind their alterations during hypoxemia and metabolic acidosis.**

***Keywords*—Fetal Heart Rate Variability (HRV) analysis, Labor, Phase-Rectified Signal Averaging (PRSA), Deceleration Reserve (DR)**

I. Introduction

During labor, a fetus might suffer considerable stress due to uterine contractions (UCs) and head compression passing through the pelvic cavity, resulting in vagal stimulation and alterations of the fetal heart rate (FHR) [1]. The cardiotocography (CTG) is the most used monitoring system during labor to identify fetal compromise, and it is based on Doppler signal. However, CTG has some main limitations: 1) the low sampling frequency and the averaging process preclude finer analysis of FHR variability (FHRV); 2) although there is a strong association between some FHR patterns and the state of hypoxia/acidosis, overall CTG has low specificity and low positive predictive value to detect hypoxemia and/or metabolic acidosis; 3) finally, and of important clinical significance, CTG presents high intra and inter-observer variability and lack of quantitative assessment [2]. These limitations impact the rate of unnecessary interventions on one hand (cesarean sections or instrumental delivery), and lack of reduction of cerebral palsy and other labor-complications on the other side, representing, thus, an unresolved problem. The assessment of FHRV is the best available proxy of the autonomous nervous system (ANS) functional state. The nutrient deprivation and hypoxemia can pound on the ANS regulation of the cardiovascular system, affecting FHRV [3].

PRSA is a new methodology, proposed by Bauer *et al.* [4], capable of extracting quasi-periodic oscillations more resistant to non-stationarities, signal loss and artifacts. It provides two measures that quantify the average cardiac acceleration (AC) and deceleration (DC) capacity from a inter-beat time interval series (RR). This technique proved to be effective in the context of fetal monitoring when applied to CTG signals or fetal RR series (FRR). Our recent study [5] found that in fetal sheep exposed to repetitive umbilical cord occlusions (UCOs) - to mimic UCs - there is a high correlation between AC and DC and acid-base balance; particularly, AC and DC progressively increased during UCOs phases, suggesting an activation of ANS. AC and DC also achieved promising results in FHR monitoring, being capable to differentiate healthy fetuses and those with growth restriction [6], [7], [8].

Dissimilarities in AC and DC values arise when asymmetric increasing/decreasing trends appear in the signal, which is common during labor. Motivated by this consideration, we introduced the deceleration reserve (DR), a new and more predictive metric of measure for risk stratification during labor [9]. DR is given by the difference between DC and AC.

Regarding the mentioned animal model [5], we also found that at the beginning of each UCO, FRR increased progressively to quickly recover when pressure was released. Similarly, during an UC during labor, FRR increases analogously, as shown in Fig. 1(a). In [5], FRR response was modeled using an exponential model for both UCO and recover phases. These models were characterized by time constants, describing the speed of FRR adaptation (the higher the time constant is, the lower is the adaptation speed). Despite the remarkable results achieved by the aforementioned PRSA's parameters, it is not known yet what AC, DC, and DR actually measure. In this preliminary study, we hypothesized that AC, DC, and DR might estimate the time constants of the increasing and decreasing trends of heart rate response to UCO, and thus

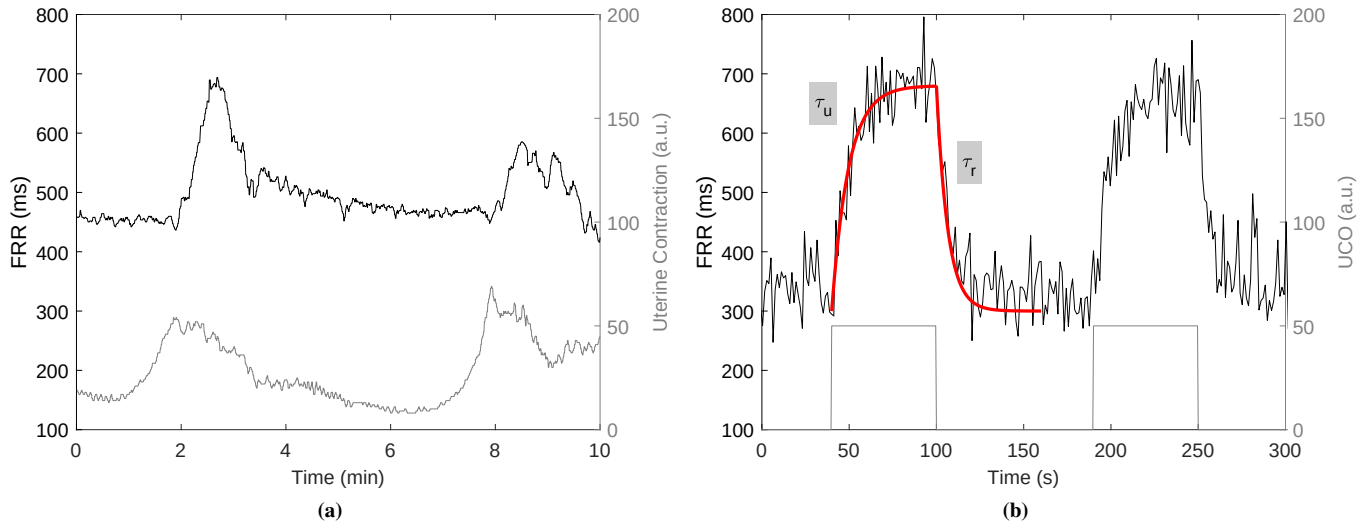

Fig. 1: Panel (a): Example of intrapartum human CTG-derived FRR series and its corresponding UC (light grey). Panel (b): Example of synthetic FRR series, UCO (light grey) and FRR response model (red).

characterize the response of the fetus to maternal contraction during labor.

II. Methods

A. Background on PRSA and derived parameters

A complete description of the PRSA algorithm can be found in [4], [9]. Briefly, anchor points are first identified on the time series $x[k]$. Each time index k, where the sample $x[k]$ satisfies the condition

$$\frac{1}{T}\sum_{i=0}^{T-1} x[k+i] > \frac{1}{T}\sum_{i=1}^{T} x[k-i], \tag{1}$$

is inserted in the DC anchors' point list (for AC, the inequality sign must be flipped). Second, all the windows of $2L$ elements centered on each anchor point are aligned (anchor points are located at the $L+1$ sample) and then averaged, obtaining the PRSA series (a series of $2L$ elements).

From the PRSA series, AC and DC are then derived with

$$\text{DC (or AC)} = \sum_{i=1}^{s} \frac{\text{PRSA}[L+i]}{2s} - \sum_{i=0}^{s-1} \frac{\text{PRSA}[L-i]}{2s}. \tag{2}$$

DR is instead defined [9] as the sum of DC and AC (note that AC is a negative quantity for RR series).

B. The model

Synthetic FRR series were generated by adding White Gaussian Noise $w(t)$ to $y(t)$, the theoretical FRR response to the UCO $u(t)$, as in [10]. In particular, $y(t)$ was modeled with the following ordinary differential equation

$$\dot{y}(t) = -\tau_r^{-1} y(t) - (\tau_r^{-1} - \tau_u^{-1}) u(t) y(t) + u(t), \tag{3}$$

where t is time, τ_u and τ_r the time constants of the growing and decreasing trends, respectively. When, $u(t)$ assumes only the values 0 or 1, the solution of (3) is the exponential function

$$y(t) = u(t)(1 - e^{-\frac{t}{\tau_u}}) + (1 - u(t)) e^{-\frac{t}{\tau_r}}. \tag{4}$$

Finally, FRR is modelled with $x[k]$, which was built with

$$x[k] = 400 y[k] + w[k] + 400, \tag{5}$$

where $y[k]$ and $w[k]$ are the discrete versions of $y(t)$ and $w(t)$, respectively. The variance of $w[n]$ was selected so that the signal-to-noise ratio was 10 db.

Fig. 1(b) shows a synthetic FRR signal and the corresponding UCO. The exponential model is superimposed.

C. The dataset

Seven 4-hour long FRR series were generated using the model described in sec. II-B. The UCO signal $u(t)$ was set to be a periodic square wave. In particular, 60 s of stimulation ($u(t) = 1$) followed by 90 s of rest ($u(t) = 0$) were repeated for the entire duration of the simulation.

Values of τ_u and τ_r were taken from [5], where the two time constants were estimated from an animal model of labor. Briefly, seven near-term pregnant sheep underwent to repetitive and complete UCOs. Occlusions were meant to mimic the fetal stress during the labor and lasted 60 s, then followed by a resting period of 90 s. The protocol ended when pH$<$ 7.00 (measured through periodic blood samples) or up to 2 hours of stimulation. Fetuses were defined healthy prior the beginning of the stimulation protocol. Each UCO induced a heart rate deceleration resembling the time series reported in Fig. 1(b). From such time series, the two time constants τ_u and τ_r were estimated using a least square approach.

Given the fact the AC, DC, and DR are linearly dependent on the standard deviation of the input signal, we normalized the series to have unitary variance as in [9].

D. Statistical analysis

Correlation analysis was performed between AC vs τ_r, DC vs τ_u, and DR vs $\tau_u - \tau_r$, for T values in the range $1-50$, $s = T$, and $L = 50$. Correlations were considered statistically significant for p-values < 0.05.

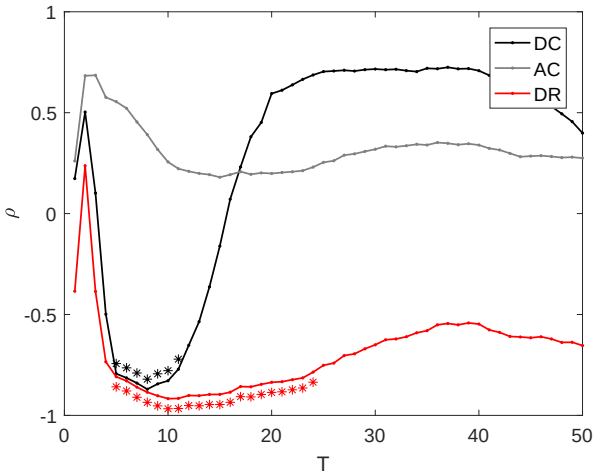

Fig. 2: Pearson's correlation coefficient ρ of AC vs τ_r, DC vs τ_u, and DR vs $\tau_u - \tau_r$. $*$ refers to statistically significant correlations ($p < 0.05$).

III. Results

Figure 2(c) reports the Pearson's correlation coefficient ρ of the correlation analysis described in sec. II-D. We found that DC had a high statistically significant correlation with τ_u in the range $5 - 11$ of T ($s = T$), while DR had a larger span of significant correlations with $\tau_u - \tau_r$ in the range $5 - 24$. AC had no significant correlation with τ_r (likely due to the limited sample size).

IV. Conclusions

In this preliminary study, we determined that DC, DR, computed using PRSA were strongly correlated with the time constants of the FRR response to uterine contractions, for a wide range of T values.

Although the significant range for T we found was similar to the ones reported in [5], [6], further investigation is needed to determine the potential advantage of the use of these time constants in risk stratification along with PRSA's based parameters. The evaluation of the performance of these new metrics in identifying compromised fetuses during labor is still underway.

The main limitations of the study were two. First, the time constants available in the animal model were only seven, thus limiting the observation of further significant correlations (as in case of AC). Second, the sheep model comprised only normoxic fetuses. Extending the analysis to an hypoxic animal model might help in better guiding the selection of the T and s parameters, when DC or DR are used for risk stratification.

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