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Vectorial analysis of the electrohysterogram for prediction of preterm delivery: a preliminary study

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Abstract— **Electrophysiological measurement of uterine contractions, referred to as electrohysterogram (EHG), is potentially more informative than methods currently used during pregnancy for timely recognition of complications such as preterm labor. Unfortunately, EHG measurement and interpretation remain challenging. Recently, some attention has been dedicated to the analysis of the EHG propagation, which is hypothetically predictive of the delivery time. This hypothesis, though physiologically reasonable, has not been investigated yet. A dedicated maximum likelihood (ML) method has been proposed and validated for identifying the conduction velocity vector of single EHG spikes. This validated ML method is here employed for comparing the conduction velocity vector in two groups of pregnant women with uterine contractions that were prospectively classified as productive or unproductive contractions. The estimated conduction velocity vector showed significant differences in the two groups. The spikes extracted from those contractions eventually classified as unproductive showed a significantly lower conduction velocity amplitude (CV= 4.89 ± 1.19 cm.s^{-1} *vs* CV= 8.63 ± 2.92 cm.s^{-1}) and a higher occurrence of upward propagation relative to productive contractions. These results suggest that productive and unproductive uterine contractions are associated to significantly different properties of the conduction velocity vector, which is likely to be proven fundamental in predicting preterm delivery.**

I. INTRODUCTION

Preterm delivery, i.e., delivery before completing the 37$^{\text{th}}$ week of gestation, is still a major cause of infant mortality and morbidity. In the majority of cases, the obstetric precursor is spontaneous preterm labor in the form of preterm uterine contractions [1]. Most obstetric interventions to reduce the incidence of spontaneous preterm delivery focus on inhibiting contractions by tocolytic agents in order to temporarily delay delivery. However, the effectiveness of tocolytic agents requires early introduction of the therapy. Therefore, timely recognition of the process leading to labor is of prime importance to discriminate preterm physiological contractions that are unproductive, i.e., will not soon lead to delivery, from productive contractions, i.e., contractions that will induce a progressive cervical dilatation and soon lead to delivery.

Besides symptomatic self monitoring and cervical change evaluation, current methods employed in clinical practice during pregnancy are based on uterine contraction monitoring. The use of biomarkers, such as fibronectin, has also been recently proposed as a screening test for preterm labor prediction.

Unfortunately, none of current methods can reliably discriminate between unproductive and productive uterine contractions [2]. Quantitative information on the myometrium (uterine muscle) can be derived from the noninvasive measurement of its electrical activity, referred to as electrohysterogram (EHG). Several techniques have been proposed for the analysis of the EHG. Some authors have developed methods for the noninvasive estimation of the intrauterine pressure [3], while other authors could distinguish between two different EHG frequency components [4] or observe a shift in the frequency content of the EHG signal as delivery approaches [5], possibly being able to predict the course of pregnancy. The ultimate goal and main challenge remains the prediction of preterm delivery.

While the reported techniques are invariably based on single channel measurements [5], we believe that multichannel EHG recording can convey additional important information for monitoring and predicting the progress of pregnancy. Our hypothesis is that different propagation properties of the EHG signal underly unproductive and productive uterine activity. In order to test this hypothesis, we present here a preliminary study aimed at estimating and comparing the EHG signal propagation in 22 pregnant women with uterine contractions that, based on the delivery time, were prospectively classified as productive or unproductive. We estimated direction and amplitude of the conduction velocity vector of single EHG spikes within each uterine contractions. Contractions were automatically and noninvasively detected from the EHG using an adapted version of the method we presented in [3]. Amplitude and direction of the conduction velocity vector were derived for each spike using a validated method [6].

II. METHODOLOGY

Here, a synthetic overview of the methodology used for the analysis is given. For further details we refer to [3] and [6].

A. Background

The contractile element of the uterus is the myometrium, which is composed of smooth muscle cells. The sequence of contraction and relaxation results from a cyclic depolarization and re-polarization of the cells in the form of action potentials (AP). APs occur in bursts; they arise in cells that act as pacemakers and propagate from cell to cell through gap junctions, which are low-resistance electrical

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connections [7]. Differently from skeletal muscles, which are striated and present an anatomical direction of propagation parallel to the fiber orientation, the direction of propagation of the myometrium intracellular AP is *a priori* unknown [4]. Due to lack of evidence [8], many authors concluded that no classical linear propagation of single APs could be assumed for the myometrium, and that only global propagation of the whole burst envelop could be measured [4] [8]. However, more recently, measurements of the electrical activity of the guinea pig uterus using a grid of extracellular electrodes clearly demonstrated that also for the myometrium, similarly to the myocardium, a linear propagation of single APs can be measured [9].

B. Dataset

The measurements were performed at the Máxima Medical Center in Veldhoven (the Netherlands) after approval by the ethical committee of the hospital. After signing an informed consent, 22 women admitted to the hospital with contractions were enrolled into the study. The recorded uterine contractions were prospectively classified as productive contractions, if delivery occurred within 24 hours from the recording, and unproductive uterine contractions, if delivery occurred more than 24 hours after the measurements. The gestational age of the recorded women ranged from 26 to 41 weeks. Six of the analyzed women were preterm.

The sensors were placed as described in Fig. 1 after skin preparation for contact impedance reduction. The EHG was recorded using a Refa system (TMS International, Enschede, the Netherlands), comprising a multichannel amplifier for electrophysiological signals and a grid of 64 high-density (HD) electrodes (1 mm diameter, 4 mm inter-electrode distance). Due to the *a priori* unknown AP direction of propagation, the bi-dimensional arrangement of the electrodes on the grid (8x8) permits to estimate all the possible conduction velocity directions along the abdominal plane parallel to the abdominal surface.

The HD electrode grid was placed on the mid-line of the lower abdomen immediately below the umbilicus. On the two hips we placed the common reference (REF) for the monopolar EHG signals recorded by the HD electrode and the ground (GRD) electrode. The external tocogram, simultaneously recorded due to medical prescription, was employed to support the assessment of the contraction period. An accelerometer was fixed on the HD electrodes to detect movements and exclude from the analysis signal segments affected by motion artifacts.

A bipolar signal was also measured by a couple of standard bipolar electrodes (1 cm diameter, variable interelectrode distance) to allow recording other signals (such as the fetal ECG). The bipolar signal was eventually employed to derive the contraction timing and trigger the conduction velocity vector estimation. The HD electrode grid could also be suitable, but the larger surface of the bipolar sensors offered better results for this specific purpose.

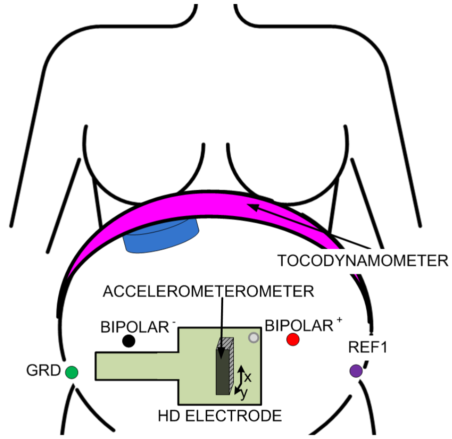

Fig. 1. Sensor placement on the abdomen.

C. Contraction detection

The conduction velocity vector was identified during the contraction periods. We automatically detected onset and duration of the contractions based on an estimate of the internal uterine pressure (IUP) [3]. The IUP estimate was derived from the bipolar EHG signal by calculating the unnormalized first statistical moment $\Psi(t)$ of the Spectrogram, $\rho(t,f)$, in a selected frequency band, $[f_{min}, f_{max}]$,

$$\Psi(t) = \int_{f_{min}}^{f_{max}} f\,\rho(t,f)\,df. \tag{1}$$

The selected frequency band was [0.3 Hz, 0.8 Hz].

Differently from our previous work [3], no modeling was used to improve the estimation accuracy of the IUP amplitude. A more accurate estimation of the IUP, which was out of the scope of the present work, would not significantly improve the accuracy of the thresholding procedure used to assess onset and duration of the uterine contraction [10].

D. Conduction velocity vector identification

The conduction velocity vector was identified in two dimensions in overlapping two-second segments (1.5 s overlap) within the contraction period. A validated maximum likelihood (ML) method was employed.

Following the schematic representation of Fig. 2, we describe the EHG propagation by a conduction velocity vector $\underline{v}$. The conduction velocity vector has an amplitude CV and an incidence angle θ ($\theta \in [-\pi,\pi]$) with respect to the vertical axis of the electrode grid. The signal is detected by N_r rows and N_c columns of electrodes. Assuming that the same signal shape $s(n)$ is measured at each channel, the signal x_{rc} measured at the channel (r,c) in the r^{th} row ($r \in [1,2,...,N_r]$) and c^{th} column ($c \in [1,2,...,N_c]$) of the electrode grid can be modeled as

$$x_{rc}(n) = s(n-(r-1)\,\tau_r-(c-1)\,\tau_c)+w_{rc}(n), \tag{2}$$

where n indicates the time samples ($n \in [1,2,...,N]$) and $w_{rc}(n)$ is the white Gaussian noise with variance σ^2_{rc} which is present at the channel (r,c). As from (2), we assume linear propagation of the AP, i.e., in each channel (r,c)

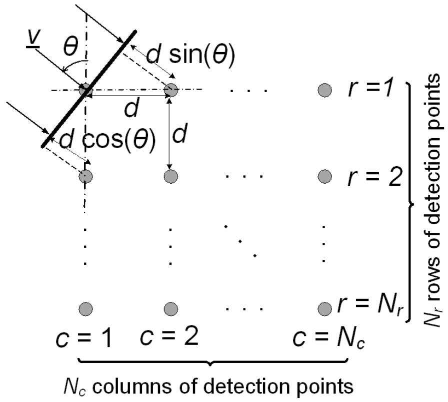

Fig. 2. Schematic description of the model used for estimating the conduction velocity vector.

the reference signal shape $s(n)$ is delayed by τ_r and τ_c time samples relative to the previous row and column, respectively.

Identification of the vector $\underline{v}$ requires estimation of (τ_r, τ_c), which we obtain using a maximum likelihood (ML) approach, i.e., by maximization of the probability density function $p((\tau_r, \tau_c)|x_{rc}(n), s(n))$. In the frequency domain, where τ_r and τ_c can be estimated without resolution limits, and under the assumption of white Gaussian noise, the ML approach is equivalent to the minimization of the cost function

$$E^2(\tau_r, \tau_c) = \frac{2}{N} \sum_{r=1}^{N_r} \sum_{c=1}^{N_c} \sum_{f=1}^{N/2} \Big[X_{rc}(f) + \\ -S(f) e^{-j2\pi f[(r-1)\tau_r + (c-1)\tau_c]} \Big]^2. \quad (3)$$

In (3), indicated by f the discrete frequency, $X_{rc}(f)$ and $S(f)$ are the Fourier transform of the signal recorded at the channel (r, c) and of the reference shape, respectively.

Following the description in Fig. 2, for an inter-electrode distance equal to d it follows that τ_r and τ_c are related to the conduction velocity amplitude CV and to the incidence angle θ by

$$\tau_r = \frac{d \cdot cos(\theta)}{CV} \\ \tau_c = \frac{d \cdot sin(\theta)}{CV}. \quad (4)$$

The use of different weighting strategies of the derived cost function was introduced in [6] to deal with poor inter-channel signal similarity due to the presence of noise. The weights $a_{rc} \in \mathbb{R}^+$, are inversely proportional to the estimated channel noise. Of the different weighting strategies proposed in [6], we chose the weighted cost function with the best estimation accuracy, $\widehat{E}^2_{a^w}(\tau_r, \tau_c)$, where

$$\widehat{E}^2_{a^w}(\tau_r, \tau_c) = \frac{2}{N} \sum_{r=1}^{N_r} \sum_{c=1}^{N_c} \sum_{f=1}^{N/2} \Big[a^w_{rc} \Big(X_{rc}(f) + \\ -\widehat{S}_w(f) e^{-j2\pi f[(r-1)\tau_r + (c-1)\tau_c]} \Big) \Big]^2. \quad (5)$$

The estimate $\widehat{S}_w(f)$ of the reference shape $S(f)$ in (3) can be calculated as the weighted average of the signals $X_{rc}(f)$,

$$\widehat{S}_w(f) = \sum_{r=1}^{N_r} \sum_{c=1}^{N_c} a^w_{rc} \cdot X_{rc} e^{j2\pi f[(r-1)\tau_r + (c-1)\tau_c]}, \quad (6)$$

while the weights are recursively derived as

$$a^w_{rc} = \frac{A}{\frac{2}{N}\sqrt{\sum_{f=1}^{N/2} X_{rc}(f) \cdot X^*_{rc}(f) - \sum_{r=1}^{N_r} \sum_{c=1}^{N_c} (a^w_{rc})^2 \cdot X_{rc}(f) X^*_{rc}(f)}}. \quad (7)$$

For the minimization of the cost functions, the Nelder-Mead Simplex search method was used [11]. The values of τ_r and τ_c were initialized according to the average values reported in the literature for the uterine AP CV [9].

III. RESULTS

Of the enrolled subjects, 11 delivered within 24 hours from the recordings (labor group) and 11 delivered after more than 24 hours (pregnancy group). Both groups include three patients with preterm contractions (6 in total). From each subject, a minimum of one and a maximum of three contractions were identified and analyzed. In total, 33 contractions were processed for the labor group and 31 for the pregnancy group. APs with CV values above 30 cm.s^{-1}, which are significantly higher than the physiological values reported in the literature [4], [9], were considered as outliers and excluded from the analysis.

In Fig. 3, the average estimated conduction velocity amplitude, CV, is indicated, for each contraction, separately for the two groups. We also indicate those contractions recorded on preterm women, but, due to the limited statistics, we do not separately analyze those cases. In Fig. 3, the average value of all the analyzed APs within a contraction is used to provide a measure which is independent of the number of the segments analyzed.

The amplitude, CV, of the conduction velocity vector was significantly ($p < 0.02$) different in the two groups. We estimated average values of conduction velocity amplitude, CV= 8.63 ± 2.92 cm.s^{-1}, CV= 4.89 ± 1.19 cm.s^{-1} for the labor group and for the pregnancy group, respectively.

The incidence angle showed a high variability among the analyzed APs even within the same contraction. However, on average, different values of incidence angle were found in the two groups ($\theta = 17 \pm 41$ in labor *vs.* $\theta = -9 \pm 26$ in pregnancy). The lower angle of incidence of the pregnancy group is due to a higher number of retrograde waves ($\theta < 0$).

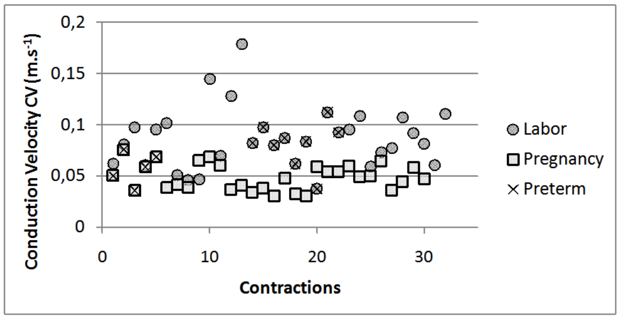

Fig. 3. Average CV value for each contraction analyzed in the two populations. Crossed symbols indicate contractions measured preterm.

IV. DISCUSSION AND CONCLUSIONS

Previous studies formulated the hypothesis that the conduction properties of the EHG could provide important information for the prediction of delivery and the discrimination between productive and unproductive uterine contractions. However, no previous study investigated this hypothesis in women.

For the first time, based on dedicated methodology which we have previously validated, we present here a study aimed at identifying and comparing the conduction velocity vector in pregnant women. These women were admitted at the hospital due to the presence of uterine contractions that were prospectively classified as productive (labor) and unproductive (pregnancy).

From our results, significantly different properties of the conduction velocity vector emerge from the two evaluated groups. Relative to the pregnancy group, for the labor group we found, in fact, a higher conduction velocity amplitude and an increased prevalence of anterograde waves, i.e., propagating downward.

These results support the hypothesis that an increased level of electrical activity propagation at the myometrium is a key factor for the onset of a productive contraction. The prevalence APs propagating downward in the labor group, previously observed also on the whole burst during labor [12], is in agreement with the logical conclusion that a preferred anterograde propagation might be associated with the effectiveness of a contraction. When analyzing the propagation of APs within a burst, the angle of incidence has a high variability even within the same burst. This may suggest that analyzing the single spikes rather than the whole burst, may convey further and more specific information.

From the clinical standpoint, a possible limitation of the study is the size of the analyzed groups relative to the variety of the encountered clinical situations in terms of gestational age, use of medications, and possible co-morbidity due, for example, to infection. Further clinical validation is required to correlate all these situations with the properties of the identified conduction velocity vector.

Noteworthy, for accurately identifying the conduction velocity vector, propagation must be linear. We excluded from the analysis spikes propagating non linearly as we expected those cases to be outliers, i.e., to have a propagation velocity outside the physiological range reported by previous literature. While it is reasonable to hypothesize that the linearity of the propagation could be itself a discriminative parameter for contraction efficiency, several aspects related to the evolution from pregnancy to labor are not yet fully understood.

Therefore, future study should focus on investigating the physiological origin of these outliers in relation to the linearity of the EHG propagation. The linearity of EHG propagation may contribute, in fact, possibly in combination with other parameters derived from the EHG, to provide a comprehensive assessment of the contraction efficiency.

In conclusion, this paper integrates and evaluates dedicated methods for assessing the clinical use of the EHG conduction velocity vector characteristics as a prognostic tool for preterm delivery. This study opens the way to future research in this direction and represents a promising perspective for clinical applications.

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REFERENCES

[1] R. Goldenberg, J. Culhane, J. Jams, and R. Romero, "Epidemiology and causes of preterm birth," *Lancet*, vol. 371, pp. 75–84, 2008.
[2] R. Garfield, H. Maul, L. Shi, W. Maner, C. Fittkow, G. Olsen, and G. Saade, "Methods and devices for the management of term and preterm labor," *Ann. NY Acad.Sci.*, vol. 943, pp. 203–224, 2001.
[3] C. Rabotti, M. Mischi, J. van Laar, S. Oei, and J. Bergmans, "Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals," *Physiol. Meas.*, vol. 29, pp. 829–41, 2008.
[4] D. Devedeux, C. Marque, S. Mansour, G. Germain, and J. Duchêne, "Uterine electromyography: a critical review," *Am. J. Obstet. Gynecol.*, vol. 169, pp. 1636–1653, 1993.
[5] M. Vinken, C. Rabotti, S. Oei, and M. Mischi, "Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature," *Ob. Gyn. Survey*, vol. 64, pp. 529–541, 2009.
[6] C. Rabotti, M. Mischi, S. Oei, and J. Bergmans, "Noninvasive estimation of the electrohysterographic action-potential conduction velocity," *Biomedical Engineering, IEEE Transactions on*, vol. 57, no. 9, pp. 2178 –2187, 2010.
[7] T. Chard and J. Grudzinskas, *The uterus*. Cambridge University Press, 1994.
[8] J. Duchêne, C. Marque, and S. Planque, "Uterine EMG signal: propagation analysis," in *IEEE EMBS Proc. Int. Conference*, 1990, pp. 831–832.
[9] W. Lammers, H. Mirghani, B. Stephen, S. Dhanasekaran, A. Wahab, and M. Al Sultan, "Patterns of electrical propagation in the intact guinea pig uterus," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 294, pp. R919–R928, 2008.
[10] K. Horoba, J. Jezewski, J. Wrobel, and S. Graczyk, "Algorithm for detection of uterine contractions from electrohysterogram," in *IEEE EMBS Proc. Int. Conference*, 2001, pp. 2161–2164.
[11] J. Lagarias, J. Reeds, M. Wright, and P. Wright, "Convergence properties of the Nelder-Mead simplex method in low dimensions," *SIAM J. Optim.*, vol. 9, pp. 112–147, 1998.
[12] C. Rabotti, M. Mischi, J. van Laar, S. Oei, and J. Bergmans, "Inter-electrode delay estimators for electrohysterographic propagation analysis," *Physiol. Meas.*, vol. 30, pp. 745–761, 2009.