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Simulation of fetal heart rate variability with a mathematical model

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ABSTRACT

In the clinic, the cardiotocogram (CTG), the combined registration of fetal heart rate (FHR) and uterine contractions, is used to predict fetal well-being. Amongst others, fetal heart rate variability (FHRV) is an important indicator of fetal distress. In this study we add FHRV to our previously developed CTG simulation model, in order to improve its use as a research and educational tool.

We implemented three sources of variability by applying either 1/f or white noise to the peripheral vascular resistance, baroreceptor output, or efferent vagal signal. Simulated FHR tracings were evaluated by visual inspection and spectral analysis.

All power spectra showed a 1/f character, irrespective of noise type and source. The clinically observed peak near 0.1 Hz was only obtained by applying white noise to the different sources of variability. Similar power spectra were found when peripheral vascular resistance or baroreceptor output was used as source of variability. Sympathetic control predominantly influenced the low frequency power, while vagal control influenced both low and high frequency power. In contrast to clinical data, model results did not show an increase of FHRV during FHR decelerations. Still, addition of FHRV improves the applicability of the model as an educational and research tool.

1. Introduction

The cardiotocogram (CTG) is a commonly used technique to monitor fetal well-being during labor and delivery. The CTG represents the combined registration of fetal heart rate (FHR) and uterine contractions. In clinical practice, fetal condition is based on evaluation of different characteristics of the FHR signal during rest and in response to uterine contractions, such as baseline level, accelerations, decelerations, and baseline variability. The relation between uterine contractions and changes in FHR is very complex. Therefore, previously we developed a mathematical CTG simulation model, describing hemodynamics, oxygenation, and cardiovascular regulation [1,2]. We successfully used the model to investigate the effect of uterine vein and/or umbilical cord occlusions, initiated by uterine contractions, on fetal hemodynamic and oxygen pressures, which via the baro- and chemoreflex lead to changes in FHR. However, the model lacked a description of fetal heart rate variability (FHRV), that is considered to be an important indicator of fetal well-being [3]. FHRV is described as fluctuations in the FHR baseline, which are irregular in amplitude and frequency [4,5]. The presence of FHRV is highly associated with the absence of significant metabolic acidemia, even if the FHR tracing shows decelerations [6]. Decreased FHRV is related to lower Apgar scores and fetal acidosis [7]. Furthermore, loss of FHRV was found to be the most consistent FHR characteristic preceding antepartum fetal death, despite of a usually normal FHR baseline level [8].

In the autonomic control of heart rate (HR), the medulla oblongata of the brain stem, which is part of the central nervous system (CNS), plays an important role [9]. It receives input from baroreceptors, chemoreceptors and respiratory stretch receptors as well as from the hypothalamus and higher brain centers and affects HR via the sympathetic and parasympathetic nerve system [9]. Sympathetic activation increases HR, while parasympathetic activation decreases HR. In the adult different frequency bands can be defined. Very low frequencies (up to 0.04 Hz) are supposed to originate from thermoregulation and humoral systems, and high frequency variations (0.15 to 0.4 Hz) are related to respiration [10]. Low frequency variations (0.04 to 0.15 Hz) are influenced by cardiac sympathetic and parasympathetic nerve activity [10], however,

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no consensus is reached about the relative contribution of these two pathways [11]. Many questions about the source and interpretation of heart rate variability (HRV) remain, and the underlying physiological mechanisms are not completely known [12]. Autonomic control of heart rate in the fetus is even less well understood due to changes in baroreceptor sensitivity [13], cardiovascular sensitivity to neurotransmitters [14], and relative strength of the parasympathetic nervous system with respect to the sympathetic nervous system [14,15] during fetal life.

Since FHRV is an important indicator of fetal distress, aim of this study is to add FHRV to the CTG simulation model to enhance the realism of the model generated CTG tracings. In order to shed more light on the possible sources of FHRV, we investigate the effect of three sources of variability as described by Van Roon et al. [16,17] and Wesseling et al. [18]: autoregulation of the peripheral blood vessels, influence of higher brain centers on the processing of the baroreceptor output in the nucleus tractus solitarius of the medulla oblongata, and the influence of other afferent systems like the heart, lungs and muscles, on the vagal center [16–18]. The enhanced model would be more suitable as an educational tool, both as stand-alone screen-based training of CTG evaluation, and as an intelligent addition to manikins used in team-training, in order to have them automatically respond to the interventions performed by the trainees.

The three sources of variability were implemented in a similar fashion as described by Wesseling et al. [18] by applying a noise source on the peripheral resistance, baroreceptor output and efferent vagal signal. We focus on a normal full term fetus and simulate FHR tracings before labor and during uterine contractions resulting in umbilical cord compression. The simulated FHR tracings are assessed by use of spectral analysis and on FHR bandwidth (BW), defined as the difference between the highest and lowest cardiac frequency in the FHR signal. Spectral analysis gives a quantitative representation of FHRV, and is often used in literature [19]. FHR BW is commonly assessed by visual inspection in the clinic.

2. Material and methods

2.1. Mathematical model

FHRV is added to our mathematical CTG simulation model, that describes feto-maternal hemodynamics, oxygen distribution and fetal regulation [1,2].

In Fig. 1 a simplified schematic overview of the CTG simulation model is shown. A more elaborate description can be found in [1]. The maternal circulation contains a heart (left ventricle) from which blood flows into the arteries. From here blood flows into the intervillous space (IVS), which is modeled explicitly, and into the remainder of the tissues, which are lumped together. Blood flows back into the heart via the veins. In the fetus, the heart is modeled as a combined ventricle, the umbilical and cerebral circulation are modeled explicitly, and the remainder is lumped into the tissues. Oxygenation in the mother takes place in the veins, since the pulmonary circulation is not explicitly modeled. Oxygen is consumed in the maternal tissues and diffuses to the fetus in the IVS of the placenta. In the fetus, oxygen consumption takes place in the brain and tissues. During hypoxia, cerebral artery resistance R_{cera} is reduced via autoregulation in order to increase oxygen transport to the brain. Uterine contractions are modeled through an increase of uterine pressure p_{ut}, acting on the IVS compartment and on all fetal compartments. Additionally, the external pressure on the umbilical cord p_{um} increases during cord compression. These pressure variations result in changes of the resistances of the uterine vein and umbilical blood vessels, causing variations in fetal mean arterial transmural blood pressure $p_{tm,a}$ and arterial oxygen pressure $pO_{2,a}$. These changes are input for the fetal central regulation model. Via the baro- and chemoreceptor these variations are translated into a normalized baro- and chemoreceptor output, r_b and r_c, respectively. Baroreceptor output increases with increasing blood pressure, while chemoreceptor output increases with decreasing oxygen pressure. Via weighting factors these baro- and chemoreceptor outputs are combined into normalized efferent vagal and sympathetic signals, e_v and e_s, respectively. Baro- and chemoreceptor activation both have a stimulating effect on the vagal nervous system. The sympathetic nervous system is stimulated by the chemoreceptor, but inhibited via the baroreceptor (indicated with the minus sign). Stimulation of the vagal pathway leads to increase of heart period T, while stimulation of the sympathetic pathway will decrease T and venous unstressed volume $V_{ven,0}$, but increase cardiac contractility E_{max} and peripheral artery resistance R_{tisa}. The changed effectors are input for the cardiovascular and oxygen model.

For the purpose of the present study, we modified the model [1,2] by removing the baroreceptor low pass filter. We will illustrate the need and the consequences of this modification in the results section.

2.2. Model extension with FHRV

Following Van Roon et al. [17] and Wesseling et al. [18], temporal variations are applied to either the peripheral vascular arterial resistance R_{tisa}, to the baroreceptor output r_b, or to the efferent vagal signal e_v, see Fig. 1. We test the model by using either 1/f noise or white noise as temporal variations. We used 1/f noise because it is considered physiologically realistic [18]. White noise is used to better investigate the transfer function of the system. The dimensionless noise signal $N(t)$ has a mean of 0 and a standard deviation of 1 and is described according to Van Roon et al. [16]:

$$N(t) = \frac{\sum_{k=1}^{n} A \cdot \sin(2\pi f_k t + \phi_k)}{\sqrt{\frac{1}{2}\sum_{k=1}^{n} A^2}}, \begin{cases} A = 1 & \text{white noise} \\ A = \frac{1}{\sqrt{f_k}} & \text{1/f noise} \end{cases} \quad (1)$$

$$\text{with} \quad f_k = k \cdot \Delta f \quad \text{and} \quad \Delta f = \frac{f_{max}}{n}$$

Here, f_{max} represents the maximum frequency taken into account, which is set to 2 Hz in order to include all frequencies from 0.04 to 1.5 Hz that are considered clinically relevant [20,21]. Furthermore, n represents the number of harmonics, which in our model is set to 2000. The phase shift ϕ_k is different for each frequency f_k, and has a uniformly distributed random value between 0 and 2π.

The three sources of variability are obtained by superimposing noise on the corresponding effector or output signal, resulting in new values for the effector $R_{tisa,N}$ or signal $r_{b,N}$ and $e_{v,N}$:

$$\begin{aligned} R_{tisa,N}(t) &= R_{tisa}(t) + m_{R_{tisa}} \cdot N(t) \cdot R_{tisa,0} \\ r_{b,N}(t) &= r_b(t) + m_{r_b} \cdot N(t) \\ e_{v,N}(t) &= e_v(t) + m_{e_v} \cdot N(t) \end{aligned} \quad (2)$$

where m is a dimensionless multiplication factor defining the standard deviation of the changes applied to each of the sources of variability. Since the standard deviation of $N(t)$ equals 1, the value of m represents the signal-to-noise ratio (SNR). $R_{tisa,0}$ is the reference peripheral resistance. For each combination of noise type and source, the value of m was chosen such to obtain an FHR BW (defined as 4 times standard deviation) of 15 ± 1 bpm in steady-state, which, according to the FIGO guidelines [22], is in the normal range for a healthy full-term fetus, while setting m of the other sources to 0.

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