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A mathematical model to simulate the cardiotocogram during labor. Part A: Model setup and simulation of late decelerations

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ABSTRACT

The cardiotocogram (CTG) is commonly used to monitor fetal well-being during labor and delivery. It shows the input (uterine contractions) and output (fetal heart rate, FHR) of a complex chain of events including hemodynamics, oxygenation and regulation. Previously we developed a mathematical model to obtain better understanding of the relation between CTG signals and vital, but clinically unavailable signals such as fetal blood pressure and oxygenation.

The aim of this study is to improve this model by reducing complexity of submodels where parameter estimation is complicated (e.g. regulation) or where less detailed model output is sufficient (e.g. cardiac function), and by using a more realistic physical basis for the description of other submodels (e.g. vessel compression).

Evaluation of the new model is performed by simulating the effect of uterine contractions on FHR as initiated by reduction of uterine blood flow, mediated by changes in oxygen and blood pressure, and effected by the chemoreflex and baroreflex. Furthermore the ability of the model to simulate uterine artery occlusion experiments in sheep is investigated.

With the new model a more realistic FHR decrease is obtained during contraction-induced reduction of uterine blood flow, while the reduced complexity and improved physical basis facilitate interpretation of model results and thereby make the model more suitable for use as a research and educational tool.

1. Introduction

In current clinical practice the cardiotocogram (CTG), the combined registration of fetal heart rate (FHR) and uterine contractions, is used to monitor fetal well-being during labor and delivery. The CTG signals show the input (uterine contractions) and output (FHR) of a complex regulation mechanism, in which amongst others variations in fetal blood pressure and oxygenation play a role. To better understand the underlying physiology, mathematical models can be used. Previously a model for CTG simulation was presented (van der Hout-van der Jagt et al. 2012, 2013a,b). This model included feto-maternal hemodynamics, oxygen distribution, and regulation and was used to simulate different clinical scenarios following uterine flow reduction and umbilical cord compression as induced by uterine contractions. While model results were in line with clinical observations, critical evaluation of the model setup showed room for improvement. For example, since the description of regulation and cardiac function was very detailed while the availability of experimental data was limited, estimation of the many parameter values was ambiguous. Furthermore, the model of hemodynamics focused on the detailed change of arterial pressure during the cardiac cycle, whereas baroreceptor feedback was based on average arterial pressure only, allowing for a less complex model of cardiac function. Also, closure of the uterine and umbilical blood vessels due to uterine contractions was dependent on external vascular pressure, whereas it would be physically more realistic to make it dependent on vascular transmural pressure.

The aim of this study is to improve our previous model for simulation of the CTG, by reducing the complexity of some submodels (e.g. regulation and cardiac function) and thus reducing errors related to ambiguity in parameter estimation, and by improving the physical basis for the description of other submodels (e.g. vessel compression).

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In part A of the paper an overview of the new CTG simulation model is given. Functionality of the model is tested by simulating the effect of uterine flow reduction on FHR in term pregnancy, resulting in FHR changes being known as late decelerations. Late decelerations are characterized as a gradual FHR decrease, meaning that it takes more than 30 s from the onset of the deceleration to the FHR nadir, with the nadir of the deceleration occurring after the contraction peak (Macones et al., 2008; Robinson, 2008). Two different mechanisms are known to be responsible for late decelerations: hypoxic myocardial depression, which plays a role when oxygen delivery to the heart is insufficient, and reflex feedback, which acts via activation of the chemo- and baroreceptor as a result of reduced oxygen pressures induced by uterine contractions (Harris et al., 1982; Martin et al., 1979; Parer, 1981). In this study we focus on the reflex induced late decelerations only. We tested the ability of the model to reproduce experimental data on arterial oxygen pressure, blood pressure and FHR from sheep experiments, in which late decelerations were evoked by means of inflation of a balloon catheter to reduce uterine blood flow (Itskovitz et al., 1982; Parer et al., 1980). In part B of the paper (Jongen et al., 2016b, this issue) we focus on the estimation of all model parameters and we investigate the effect of combined uterine and umbilical flow reduction on FHR, resulting in so-called variable decelerations. Furthermore, in part B model limitations will be discussed.

2. Material and Methods

The model consists of several submodels which describe feto-maternal hemodynamics, oxygenation, fetal regulation, and uterine contractions. Although the general structure of the previous model is maintained (van der Hout-van der Jagt et al. 2012, 2013a,b), changes are applied to the different submodels in order to simplify and enhance the CTG simulation model. Below we describe the setup of the new model. A detailed description of the parameter estimation is given in part B of this paper (Jongen et al., 2016b).

2.1. Feto-maternal hemodynamics

The model of hemodynamics is composed of compartments, representing the storage of blood and oxygen, which are connected via segments that represent convective transport. The fetal circulation consists of a combined ventricle (CV) from where blood flows into the cerebral, umbilical, and tissue circulation (Fig. 1). In the latter circulation, all tissues apart from the brain and fetal placenta (villi) are lumped. In the mother, the heart is represented by the left ventricle (LV) and the uterine circulation is modeled explicitly, while the remainder is lumped into the tissues.

2.1.1. Vascular function

To describe blood storage in the vascular system, we use a linear approximation of the pressure–volume relation around the working pressure of the blood vessel:

$$p_{tm} = \frac{V - V_0}{C} \tag{1}$$

where C represents the compliance of the vessel, V the actual volume, and V_0 the unstressed volume of the vessel at zero transmural pressure. The transmural pressure p_{tm} is defined as:

$$p_{tm} = p - p_{ext} \tag{2}$$

where p represents the absolute pressure in the compartment, and p_{ext} the external pressure acting on the outside. Fetal external pressure is equal to uterine pressure (p_{ut}), while maternal external pressure is set to zero, except for the placental intervillous space (IVS) which is also subjected to p_{ut}, see Fig. 1.

For the IVS that may undergo large volume changes during uterine contractions, a nonlinear pressure–volume relation is used:

$$V_{IVS}(p_{tm}) = V_{max} \cdot f(p_{tm}) \quad \text{with } f(p_{tm}) = \frac{1}{2} + \frac{1}{\pi} \cdot \tan^{-1}\left(\frac{p_{tm} - p_0}{p_1}\right) \tag{3}$$

where V_{IVS} represents the IVS blood volume, V_{max} the maximal IVS blood volume, and p_{tm} the transmural blood pressure of the compartment, while p_0 and p_1 are constants. The function $f(p_{tm})$ was based on a relation between vessel cross-sectional area and transmural pressure (Langewouters et al., 1984).

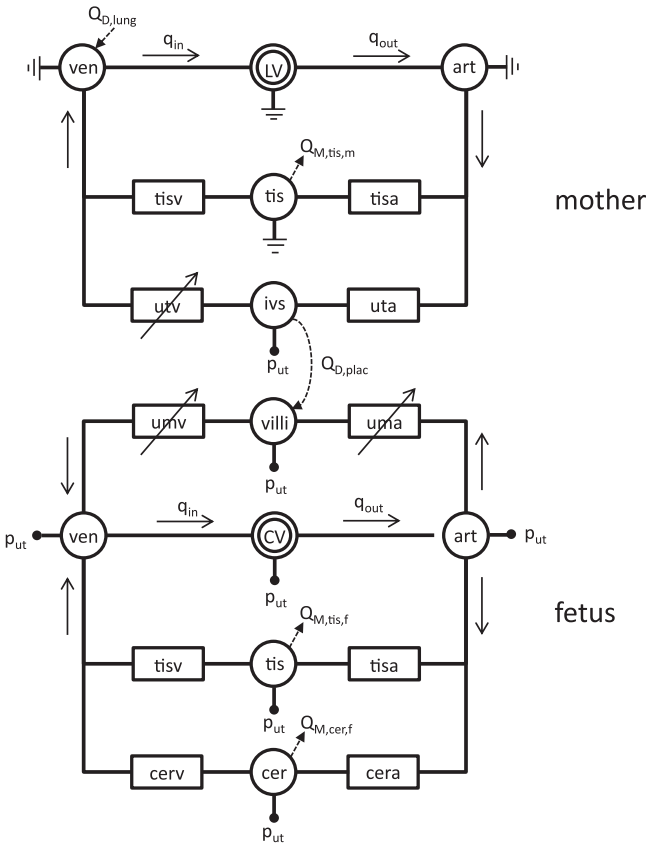

Fig. 1. Schematic overview of the model of feto-maternal hemodynamics and oxygen distribution. The circles represent compartments where storage of blood and oxygen can take place, while rectangles represent segments where blood flows from one compartment to the next. Metabolic and diffusional oxygen flows are indicated by dashed arrows. In the mother blood flows from the left ventricle (LV), via the systemic arteries (art) and the tissue microcirculation arteries (tisa) into the tissue microcirculation (tis). Blood flow into the intervillous space (ivs) takes place via the uterine spiral arteries (uta). Via the microcirculation veins (tisv) and the intramural veins in the uterus (utv) blood flows into the systemic veins (ven) back to the heart. In the fetus, blood flows from the combined ventricle (CV) into the systemic arteries (art). Via the microcirculation arteries (tisa and cera) blood reaches the tissue and cerebral microcirculation (tis and cer, respectively), while blood leaves the microcirculation compartments via the microcirculation veins (tisv and cerv). Via the umbilical arteries (uma) blood flows into the placental villi (villi), and via the umbilical vein (umv) back into the systemic veins (ven). From the veins, blood flows back into the heart. Uterine vein resistance (utv), and umbilical artery and vein resistance (uma and umv, respectively) are variable and change as function of transmural blood pressure as described in (6). In both mother and fetus, q_{in} represents inflow of blood into the heart, while q_{out} represents cardiac outflow. The intervillous space and all fetal compartments experience external uterine pressure p_{ut}. In the mother, oxygen diffuses from the air into the lungs ($Q_{D,lung}$) (modeled as oxygen diffusion into the systemic veins), while oxygen metabolism takes place in the tissues ($Q_{M,tis,m}$). In the placenta, oxygen diffuses from the mother to the fetus ($Q_{D,plac}$). In the fetus, oxygen is consumed in the tissues ($Q_{M,tis,f}$) and the brain ($Q_{M,cer,f}$).

In each compartment, the change in blood volume in time is determined by:

$$\frac{dV}{dt} = q_{in} - q_{out} \tag{4}$$

where q_{in} and q_{out} represent inflow and outflow, respectively.

Blood flow q in between compartments is generally described by:

$$q = \frac{\Delta p}{R} \tag{5}$$

where R represents the resistance of the segment and Δp the (absolute) pressure difference over a segment. The resistance R_{utv} of the uterine vein, which is exposed to large changes in transmural pressure during uterine contractions, is modeled as a function of transmural pressure. Assuming as a first approximation that the flow in this segment follows Poiseuille's law, we model the resistance to be inversely