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A mathematical model to simulate the cardiotocogram during labor. Part B: Parameter estimation and simulation of variable decelerations

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ABSTRACT

During labor and delivery the cardiotocogram (CTG), the combined registration of fetal heart rate (FHR) and uterine contractions, is used to monitor fetal well-being. In part A of our study we introduced a new mathematical computer model for CTG simulation in order to gain insight into the complex relation between these signals. By reducing model complexity and by using physically more realistic descriptions, this model was improved with respect to our previous model.

Aim of part B of this study is to gain insight into the cascade of events from uterine contractions causing combined uterine flow reduction and umbilical cord compression, resulting in blood and oxygen pressure variations, which lead to changes in FHR via the baro- and chemoreflex. In addition, we extensively describe and discuss the estimation of model parameter values.

Simulation results are in good agreement with sheep data and show the ability of the model to describe variable decelerations. Despite reduced model complexity, parameter estimation still remains difficult due to limited clinical data.

1. Introduction

In part A of our paper (Jongen et al., 2016) we gave an overview of a new cardiotocogram (CTG) simulation model. Compared to our previous model (van der Hout-van der Jagt et al., 2012, 2013a, b) the complexity of some submodels was reduced and the physical basis for the description of other submodels was enhanced. It was shown that the model was able to simulate realistic FHR decrease in response to uterine flow reduction as induced by uterine contractions.

In this part the model is used to gain insight into the mechanism of variable FHR decelerations which are caused by umbilical cord compressions, that mostly occur during uterine contractions during labor (Freeman et al., 2012). Variable decelerations are defined as an abrupt FHR decrease of more than 15 bpm, with a maximum time delay of 30 s between onset of the deceleration and FHR nadir, and a duration of less than 2 min (Macones et al., 2008; Robinson, 2008). In addition, the effect of varying amplitude and duration of uterine contractions on the CTG is investigated. We also compare model output with data of sheep experiments in which the umbilical cord was temporarily blocked by use of an occluder (Itskovitz et al., 1983). Although model complexity was reduced, parameter estimation is difficult due to the limited clinical data. Therefore, we will extensively describe and discuss estimation of these parameter values.

The new model is intended to be used to gain insight into the regulation of FHR during labor and delivery. For use as a clinical decision support tool, the model should be made patient-specific. This is a challenging task in view of the limited availability of clinical data and the limited time span for model analysis during labor. Use as an educational tool would be a more realistic next step.

2. Material and methods

The model is extensively described in part A of our study (Jongen et al., 2016). In part B we extend the model in order to simulate combined uterine blood flow reduction and umbilical cord compression induced by contractions. Besides an overview of model parameter estimation is given.

2.1. Model extension

Since during cord compression the umbilical vein and arteries are exposed to large changes in transmural pressure, the corresponding resistances, R_{umv} and R_{uma} respectively, are modeled as function of transmural pressure p_{tm} (part A, Eq. (6)). Parameter values are chosen such that first the umbilical vein will be closed, followed by the umbilical arteries at higher external umbilical pressures, see Table 1.

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Table 1
Umbilical vein and artery resistance parameters.

Parameter	Value	Unit
$R_{0,umv}$	2.05	mmHg · s/ml
$p_{0,umv}$	−17	mmHg
$p_{1,umv}$	10	mmHg
$R_{0,uma}$	2.34	mmHg · s/ml
$p_{0,uma}$	−27	mmHg
$p_{1,uma}$	16	mmHg

The transmural pressure of the umbilical vein $p_{tm,umv}$ and umbilical arteries $p_{tm,uma}$ is determined as the mean absolute pressure of the two neighboring blood compartments minus the external pressure:

$$p_{tm,umv} = \frac{p_{villi}+p_{ven}}{2} - (p_{ut}+p_{um})$$
$$p_{tm,uma} = \frac{p_{villi}+p_{art}}{2} - (p_{ut}+p_{um}) \quad (1)$$

where the external pressure consists of the uterine pressure p_{ut}, that acts on the whole fetus, plus an extra pressure p_{um}, caused by umbilical cord compression.

The degree of cord compression depends on the contraction intensity, fetal position, stage of labor, etc. The effect of these random variables is modeled through a weighting factor w_{um} [–], relating p_{ut} to the external pressure on the umbilical cord p_{um}:

$$p_{um} = w_{um}(p_{ut} - p_{rest}), \quad w_{um} \geq 0 \quad (2)$$

with p_{rest} uterine resting pressure.

2.2. Parameter estimation

Due to the limited available human fetal data, parameter estimation is difficult. For this reason parameter estimation is extensively described. Fetal cardiovascular parameters were obtained from literature and set to values of a 3.5 kg full term human fetus. If human data were not available, fetal sheep data were used to derive the parameters. Some parameter values were set to obtain the desired model responses. Parameter choices are briefly explained below, all parameter values can be found in Tables 1–3 of part A.

2.2.1. Feto-maternal hemodynamics

Fetal combined ventricular output q_{CO} was aimed at 450 ml/min/kg (Kiserud et al., 2006; Parer, 1997; Rudolph, 2009; van Mieghem et al., 2009), ejection fraction *EF* at 0.67 (Schmidt et al., 1995), and heart rate at 135 bpm (part A, Table 1a). Mean arterial transmural blood pressure $p_{tm,a}$ and mean transmural venous blood pressure $p_{tm,v}$ were set to 45 mmHg (Itskovitz et al., 1983; Struijk et al., 2008; Thornburg and Morton, 1986; Unno et al., 1999) and 3 mmHg (Johnson et al., 2000; Rudolph, 2009; Thornburg and Morton, 1986) respectively. Fetal blood volume was reported to be about 75 ml/kg (Linderkamp et al., 1978; Usher et al., 1963; Yao et al., 1969), which is about two third of total feto-placental blood volume (Yao et al., 1969). Therefore, the latter volume was set to 110 ml/kg, which is in accordance with Schwarz and Galinkin (2003). Total microcirculation blood volume was computed from Guyton and Hall (2006) and set to 8% of fetal body blood volume, which was distributed over cerebral (14%) (Cetin et al., 2008; Hofman, 1983) and tissue microcirculation (86%). Average cardiac cavity volume follows from q_{CO}, *EF* and FHR and equals 11.7 ml. The remainder of the body blood volume was distributed over the systemic fetal arteries (1/6) and veins (5/6). Based on geometric considerations (Di Naro et al., 2001; Link et al., 2007; Walker and Pye, 1960) blood volume of the umbilical circulation was divided between the placental villi (65%), umbilical arteries (10%) and vein (25%). Since for the umbilical arteries and vein no separate compartments were included in the model, these blood volumes were added to the systemic arteries and veins respectively.

Maternal cardiovascular parameters were based on pregnancy-related changes as described in literature (part A, Table 1b). Target values for $p_{tm,a}$ and $p_{tm,v}$ were set to 80 mmHg (Clapp and Capeless, 1997; Geva et al., 1997; Katz et al., 1978) and 5 mmHg (Murray, 2007) respectively. During pregnancy, heart rate *HR* increases up to a target value of 80 bpm (Clapp and Capeless, 1997; Geva et al., 1997; Katz et al., 1978; Rubler et al., 1977), while the cardiac output (Abbas et al., 2005; Clapp and Capeless, 1997; Katz et al., 1978; Longo, 1983) and blood volume (Abbas et al., 2005; Longo, 1983) both increase by 40%. In our model cardiac output and total blood volume were set to 7 l/min and 7 l, respectively. Ejection fraction was set to a value of 0.67 (Clapp and Capeless, 1997; Geva et al., 1997; Katz et al., 1978). Intervillous space (IVS) volume was chosen to be 175 ml (Benirschke et al., 2006; Mayhew, 1996; Rainey and Mayhew, 2010), while the volume of the tissue microcirculation was chosen to be 8% of total maternal blood volume (Guyton and Hall, 2006). Average left ventricular blood volume follows from q_{CO}, *EF* and *HR* and equals 87.5 ml. Like in the fetus, the remainder of the blood volume was distributed over systemic arteries (1/6) and veins (5/6). Parameters p_1 and V_{max}, defining the relation between IVS volume V_{ivs} and transmural blood pressure as described by Eq. (3) of part A, were determined by assuming that $p_0 = p_{ref}$, where p_{ref} is the reference transmural IVS blood pressure in steady state. Then it follows that:

$$V_{max} = 2 \cdot V_{ivs}\left(p_{ref}\right)$$

Finally p_1 was determined by assuming that IVS compliance is maximal at p_{ref}, meaning that:

$$p_1 = \frac{V_{max}}{\pi \cdot C_{ivs,max}}$$

For $C_{ivs,max}$ we chose a similar value as for the placental villi (2.4 ml/mmHg).

For both fetus and mother target values of blood flows and pressures were used to estimate resistances and compliances. We chose umbilical cord flow to be 25% of q_{CO}, in agreement with literature data that range from 15% to 34% of q_{CO} (Acharya et al., 2005; Kiserud et al., 2006; Link et al., 2007; Parer, 1997; Rudolph, 2009). The fraction of cardiac output going to the fetal brain was estimated by use of a fractional brain mass of 14% (Cetin et al., 2008; Hofman, 1983) and by the estimation that oxygen metabolism per gram tissue, and thus also blood flow per gram tissue, should be twice as high in brain tissue compared to peripheral tissues. This means that 21% of total cardiac output goes to the brain and 54% to the fetal tissues, which is in accordance with Rudolph (2009). In the mother about 10% of the cardiac output is directed to the uterine circulation (Flo et al., 2010; Parer, 1997; Vorherr, 1975), of which 70–90% is directed to the IVS (Parer, 1997; Rosenfeld, 1984; Wang and Zhao, 2010). Hence we chose 9% of q_{CO} to be directed to the IVS, while 91% is directed to the other maternal tissues.

For the fetal and maternal tissues and fetal brain 95% of the total resistance was assigned to the microcirculation arteries, while 5% was assigned to the microcirculation veins. In the umbilical circulation, the arterial resistance fraction was set to 60%, to obtain a blood pressure of about 20 mmHg in the placental villi (Huikeshoven et al., 1980). In the uterine circulation this fraction was set to 80%, in order to obtain an IVS pressure of about 60–70 mmHg below mean arterial pressure (Ramsey et al., 1959). Except for the placental villi and IVS, compliances were estimated assuming that 70% of the volume in the reference state contributes to the unstressed volume. For the cerebral and tissue microcirculation, unstressed volume fraction was set to 90%. The compliance in the placental villi was set to 2.4 ml/mmHg (Assad et al., 2001; Huikeshoven et al., 1980).

Initial values of V_{ed} and V_{ee} were calculated from target values of q_{CO}, *EF* and FHR. $V_{min,0}$ was chosen to be equal to V_{ee}, while $V_{max,0}$ was set to 0. Finally, E_{max} could be calculated as the slope of a line through the data points (V_{ee}, $p_{tm,a}$) and ($V_{max,0}$, 0), while E_{min} was calculated as the slope of a line through (V_{ed}, $p_{tm,v}$) and ($V_{min,0}$, 0).

2.2.2. Oxygen distribution

The oxygen diffusion coefficient in the placenta was set to 0.082 ml O_2/(s · mm Hg) (part A, Table 2) such that in steady state a fetal umbilical arterial oxygen pressure of 18.5 mmHg was obtained (Acharya and Sitras, 2009; Link et al., 2007; Sjöstedt et al., 1960). Fetal oxygen metabolism was set to be 8 ml O_2/(min · kg) (Acharya and Sitras, 2009; Bonds et al., 1986) and divided over cerebral metabolism (28%) and tissue metabolism (72%). We chose a threshold value of 5 mmHg for cerebral oxygen metabolism ($pO_{2,th,cer,f}$) (Jones et al., 1977) and 10 mmHg for the peripheral tissues ($pO_{2,th,tis,f}$), where the latter value corresponds to about 50% of the steady-state oxygen concentration, based on Sá Couto et al. (2002).

Maternal oxygen consumption was set to 600 ml O_2/min. The oxygen pressure in the air was set to 160 mmHg, while target maternal arterial oxygen pressure was set to 98 mmHg. Combination of this oxygen pressure difference and total feto-maternal oxygen metabolism yielded a pulmonary oxygen diffusion coefficient of 0.169 ml O_2/(s · mm Hg). Since in the current study maternal oxygenation was kept constant, an oxygen metabolism threshold was irrelevant for the maternal model.

Fetal and maternal parameter values defining the relation between cO_2 and pO_2 were chosen as described by Sá Couto et al. (2002).

2.2.3. Regulation

Cerebral autoregulation: For the cerebral autoregulation the value of γ, indicating how well the cerebral resistance can adapt to variations in arterial oxygen content, was estimated by use of Peeters et al. (1979) and set to a value of 0.5. The cerebral resistance can maximally decrease by 50%, which means that cerebral blood flow can increase with a factor of 2. Finally, the time constant $\tau_{R_{cera}}$ was chosen to be 10 s according to Ursino and Magosso (2000).

Central regulation: For the baroreceptor and chemoreceptor outputs (part A, Eq. 21) the parameters η_1 and η_2 follow from the condition that $r(y = y_{ref}) = 0$ and from the (desired) slope at the reference point ($y = y_{ref}$):

$$\eta_1 = \ln\left(\frac{-r_{min}}{r_{max}-r_{min}}\right) \quad (3)$$

$$\left.\frac{dr^*(y)}{dy}\right|_{y=y_{ref}} = \eta_2 \cdot \eta_1 e^{\eta_1}(r_{max}-r_{min}) \quad (4)$$

Baroreceptor parameters were obtained by scaling the relation as described by