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Patient-specific estimates of vascular and placental properties in growth-restricted fetuses based on a model of the fetal circulation☆

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ABSTRACT

Introduction: Intrauterine growth restriction (IUGR) due to placental insufficiency is associated with blood-flow redistribution in order to maintain perfusion to the brain. However, some hemodynamic parameters that might be more directly related to staging of the disease cannot be measured non-invasively in clinical practice. For this, we developed a patient-specific model of the fetal circulation to estimate vascular properties of each individual.

Methods: A lumped model of the fetal circulation was developed and personalized using measured echographic data from 37 normal and IUGR fetuses to automatically estimate model-based parameters. A multivariate regression analysis was performed to evaluate the association between the Doppler pulsatility indices (PI) and the model-based parameters. The correlation between model-based parameters and the placental lesions was analyzed in a set of 13 IUGR placentas. A logistic regression analysis was done to assess the added value of the model-based parameters relative to Doppler indices, for the detection of fetuses with adverse perinatal outcome.

Results: The estimated model-based placental and brain resistances were respectively increased and reduced in IUGR fetuses while placental compliance was increased in IUGR fetus. Umbilical and middle cerebral arteries PIs were most associated with both placental resistance and compliance, while uterine artery PI was more associated with the placental compliance. The logistic regression analysis showed that the model added significant information to the traditional analysis of Doppler waveforms for predicting adverse outcome in IUGR.

Discussion: The proposed patient-specific computational model seems to be a good approach to assess hemodynamic parameters than cannot be measured clinically.

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1. Introduction

Intrauterine growth restriction (IUGR) from placental insufficiency is one of the leading causes of perinatal mortality/morbidity [1,2]. It is associated with blood-flow redistribution that involves several vessels of the feto-placental circulation, such as the aortic isthmus (AoI), middle cerebral artery (MCA) and the umbilical artery (UA). This blood-flow redistribution due to IUGR is thought to be caused by the increase in the placental and peripheral resistances and the decrease of brain resistance due to cerebral arteries vasodilation, and is associated with worse perinatal, neurodevelopmental and cardiovascular outcome [3–7]. In clinical practice, these fetal hemodynamic changes are evaluated by quantifying the Doppler flow-velocity waveforms using empirical pulsatility indices (PI). However, in some small for gestational age (SGA) fetuses, placental histological changes compatible with placental under-perfusion, defined as any maternal and/or fetal vascular pathology, were identified without changes in the Doppler indices [8,9]. Moreover, signs of placental under-perfusion have been associated with an increased risk of neonatal morbidity [10,11] and abnormal neurodevelopmental outcome [8].

It is commonly believed that an increase in the pulsatility of the arterial flow is caused by an increase in vascular resistance. Several studies in an IUGR sheep model [12–16], or using an electrical-analog model of the placental circulation [14,16–19], have evaluated the association between different alterations in vascular structures and beds with the Doppler in the UA and uterine artery (UtA). These studies supported that the UA–PI is directly related to high placental and low UA resistance or a combination of high placental resistance and UA wall abnormalities. However, in other studies, using vasoactive agents to increase resistance, a poor correlation between pulsatility and resistance was found. In the UtA, similarly to the UA, some fetal sheep studies [15] demonstrated that when the placental microcirculation was occluded, resistance was increased and abnormal Doppler waveforms were observed. However, UtA Doppler is also influenced by maternal factors [20], and therefore abnormal patterns could not be explained only by the changes in placental vasculature. Thus, there are several hemodynamic factors that can lead to abnormal Doppler waveforms in both UA and UtA, and not all changes originate from an increase in placental resistance.

All theses studies were performed in animal models or using electrical equivalent models. However, it is not feasible to study, in-vivo and non-invasively, the underlying hemodynamic determinants of the Doppler-waveforms in different vessels in human fetuses and alternative approaches need to be used. To better understand hemodynamic remodeling, a patient-specific model of the fetal circulation can be used to estimate different vascular and hemodynamics properties of each patient that cannot be assessed during the ultrasonography evaluation. Despite that several models of the fetal circulation have been developed, only few of them were patient-specific [21,22]. Our purpose was to use a lumped model of the fetal circulation to estimate patient-specific vascular and placental properties of normal and IUGR fetuses. This might help in the understanding of IUGR and its underlying mechanisms and to compare the diagnostic performance of those variables for prediction of increased risk of adverse perinatal outcome.

2. Methods

2.1. Study population

Ultrasonographic data from IUGR and normally grown fetuses (controls) were used to fit the computational model. IUGR and control fetuses were selected from singleton pregnancies who attended for routine hospital visit in the third trimester of pregnancy at the Maternal-Fetal Medicine Department at BCNatal in Barcelona between January 2010 and April 2014. Eighty percent of the fetuses included were already included in previous studies from our group [23,24]. IUGR was defined as an estimated fetal weight (EFW) and confirmed birthweight below the 10th centile according to local reference curves [25] together with a pulsatility index (PI) in the UA above 2 standard deviations [26]. Controls were selected among non-complicated pregnancies with EFW and birthweight above 10th centile [25]. Pregnancies with structural/chromosomal anomalies or evidence of infection were excluded. The study protocol was approved by the local Ethics Committee and parents provided written informed consent.

In all fetuses, biometrics and feto-placental Doppler, including flow velocities in the UA, UtA, MCA, AoI and right and left ventricle (RV and LV) outflow tracks were performed using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA). Details on the ultrasonographic evaluation can be found in the Supplementary Methods.

At delivery, gestational age (GA), birth weight, birth weight centile, mode of delivery, Apgar scores, umbilical pH, presence of preeclampsia and length of stay at the neonatal intensive care unit were also recorded. Adverse perinatal outcome was defined as the presence of at least one of the following: umbilical artery pH < 7.15, 5 min APGAR score <7.0, admission to neonatal care unit for a period of at least 25 days or intervention for fetal distress.

2.2. Patient-specific modeling

2.2.1. Lumped model of the fetal circulation

An improved version of our previous model of the fetal circulation [22] was implemented. New arterial segments and vascular beds of the downstream fetal circulation were included. Specifically, the descending aorta was replaced by the thoracic and abdominal aorta, two iliac and two UA. The peripheral vascular bed was replaced by two kidneys, two lower body and placental vascular beds. The model consisted of 19 arterial segments and 12 vascular beds as shown in Fig. 1.

As described in Garcia-Canadilla et al. [22], the equivalent lumped model was constructed by interconnecting two different building blocks: (1) the arterial segment, which included a capacitor (C), a resistor (R) and an inductor (L), representing arterial compliance, resistance of blood flowing in the arterial segment and blood inertia respectively; and (2) the vascular bed, consisting of a three-element Windkessel model, which included a resistor and a capacitor representing the vascular bed resistance and compliance respectively. The equivalent lumped model of the fetal circulation consists of a total of 94 electrical components and 2 inputs, and was implemented in MATLAB (2013b, The MathWorks Inc., Natick, MA).

2.2.2. Patient-specific input data

Patient-specific blood velocity waveforms from RV and LV outflow tracks (V_{RV} and V_{LV}), AoI (V_{AoI}), MCA (V_{MCA}) and UA (V_{UA}) were obtained by manual delineation of the envelope of the respective Doppler profiles. The corresponding blood-flows: Q_{LV}, Q_{RV}, Q_{AoI}, Q_{MCA} and Q_{UA} were calculated. Details on the blood-flow calculation are described in Supplementary Methods. The GA and EFW were used to calculate the different electrical components of the equivalent circuit. The detailed description of the calculation of the electrical components of the model is described in Supplementary Methods.

2.2.3. Patient-specific fitting

A diagram of the patient-specific fitting algorithm is shown in Fig. 2. The input of the model was the set of the patient-specific