Patient-specific modeling for the assessment of circulatory adaptation in fetal growth restriction

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Abstract— **Fetal growth restriction (FGR) is one of the major contributors to adverse perinatal outcome. However, the diagnostic tools currently used for estimating the fetal hemodynamic status are still limited. In this study we developed a methodology for estimating fetal hemodynamic parameters. The method is based on a mathematical model of the fetal circulation, an optimization algorithm and measurements of power-Doppler ultrasound. The model estimates parameters of the fetal circulation that are not possible for direct measurement. The method was tested on a cohort of 20 normal and 22 growth-restricted fetuses. In each fetus, power-Doppler velocity waveforms were measured in large number of sites of the fetal circulation. Three-dimensional volume-flow measurements were performed in the placenta to evaluate its resistance to blood flow. Model predictions indicated significant changes in the circulation of FGR fetuses compared to normal fetuses. In the FGR group, the model predicted significant reduction in fetal cardiac output and decreased cardiac output distribution towards the placenta. In FGR fetuses that showed adverse outcome, the model indicated significant increase in cardiac output distribution towards the brain and in the degree of blood shunted by the ductus venosus, indicating severe brain-sparing state in these fetuses. We conclude that patient-specific modeling may be useful in personalizing and optimizing the treatment options in pregnancies complicated by fetal growth-restriction.**

Keywords— **Fetal growth restriction, Patient-specific modeling, Brain-sparing effect, Mathematical model, Placental resistance to blood flow, Power Doppler ultrasonography.**

I. Introduction

Fetal growth restriction (FGR) refers to failure of a fetus to achieve its genetically growth potential. FGR affects up to 5–10% of pregnancies and is associated with significant adverse perinatal outcomes [1]. Growth restriction may result from a number of origins such as genetic disorders or congenital infections, leading to placental insufficiency, reduced placental blood supply and reduced oxygenation. These pathological conditions may evolve into hypoxia and acidemia, resulting in adverse pregnancy outcome.

When the fetus is subjected to hypoxia, it elicits a sequence of compensatory actions, referred as the 'brain-sparing effect'. These mechanisms operate to maintain the supply of oxygen and nutrients to the brain and to the heart, at the expense of other less vital organs. In the first stages of FGR the brain-sparing effect successfully maintains the supply of substrates and oxygen to the brain and heart despite the absolute reduction in placental oxygen transfer. However, when the brain-sparing effect reaches its limit, fetal deterioration may occur rapidly and the fetus may be subjected to cerebral hypoxia.

The main clinical challenges in the management of FGR pregnancies are the evaluation of the fetal hemodynamic status and the determination of timing of delivery. In the clinical practice, evaluation of fetal hemodynamics is performed by serial measurements of Doppler flow-velocity waveforms (FVWs), combined with functional testing such as the biophysical profile and fetal heart rate monitoring. Although Doppler indices reflect the degree of fetal compromise, they suffer from significant variability between fetuses that is expressed by large variance in the Doppler reference tables.

To better understand the hemodynamic state of the growth-restricted fetus, a patient-specific model should be used. Since the measurement of hemodynamic quantities such as blood pressure and flow is not possible in-utero, the use of mathematical modeling may be beneficial in the assessment of fetal well-being. The subject of this study was to develop a methodology for patient-specific modeling of the fetal circulation. This method was used to identify the degree of circulatory compromise in fetuses diagnosed as FGR.

II. Methods

A mathematical model of fetal circulation was developed using a set of parameters that provided accurate fit to a variety of physiological indices such as cardiac output, cardiac output distribution and velocity waveforms in the major blood vessels. This nominal model was designed to

M. Long (Ed.): World Congress on Medical Physics and Biomedical Engineering, IFMBE Proceedings 39, pp. 453–456, 2013.
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describe normal fetal circulation for a wide spectrum of gestational ages. To describe the circulation of a specific fetus as measured by Doppler FVWs of major site of its circulation, a parameter estimation procedure was developed. This parameter estimation process was designed to minimize the difference between the model calculated flow waveforms and the measured velocity waveforms. The process was tested on a set of normal and FGR fetuses.

A. The mathematical model of fetal circulation:

A mathematical model was developed based on the structure of the feto-placental circulation in singleton pregnancies, while emphasizing the most relevant components. A diagram of the model is illustrated in Fig. 1.

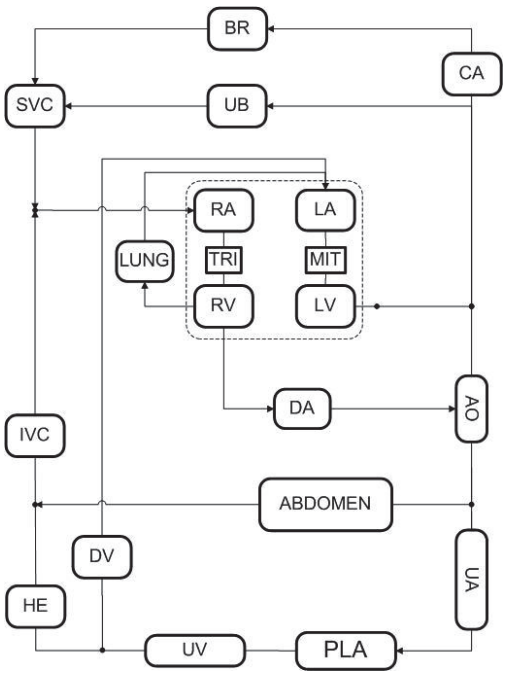

Fig. 1. Block diagram of the fetal circulation. BR: Brain, CA: Carotid arteries, UB: Upper body extremities, SVC: Superior Vena Cava, RA: Right Atrium, RV: Right Ventricle, TRI: Tricuspide valve, MIT: Mitral valve, LV: Left Ventricle, DA: Ductus Arteriosus, AO: Aorta, IVC: Inferior Vena Cava, UA: Umbilical arteries, UV: Umbilical vein, DV: Ductus Venosus, HE: Hepatic.

B. The model of the fetal heart and circulation:

During the systolic phase, the relation between blood pressure *P(t)* and volume *V(t)* in the chambers of the fetal heart were modeled by time-variant elastance, according to Suga and Sagawa [1]. Vessel segments were modeled based on a reduced Navier-Stokes equations, assuming rigid cylindrical tube, laminar flow, incompressible Newtonian fluid, neglecting nonlinear components. Volume to pressure relationship in the internal organs was modeled by an exponential function.

Four hemodynamic indices were calculated as estimates of the fetal hemodynamic state: (a) combined cardiac output (in mL min^{-1} Kg^{-1}); (b) placental blood flow (in mL min^{-1} Kg^{-1}); (c) cerebral blood flow (in % of total cardiac output); and (d) Degree of blood shunt in the DV.

C. Scaling of model parameters:

The model was designed to describe the fetal circulation between 21 to 40 weeks of gestation. In this period, fetal weight increases from 400 grams to 3400 grams. Scaling of model parameters, such as the volume of the fetal heart chambers, resistance of blood vessels, blood vessel inertance and the compliance of internal organs was based on the results of Dawson [2] regarding scaling of vascular networks in mammals, according to eq. 1:

$$P = P_0^{\,S} \qquad (1)$$

where P is the parameter value, P_0 is the nominal value for a 1500 grams (30 weeks of gestation) fetus and S is a scaling factor. Fetal blood volume (in mL) was set as 0.1×(fetal weight) [3] where fetal weight was in grams.

D. *Experimental data collection*

The study included women with normal and FGR pregnancies from 23 to 40 weeks of gestation. Doppler flow-velocity waveforms were measured using a Voluson E8 (GE Healthcare) ultrasound machine, equipped with a 3.5-MHz curvilinear abdominal transducer. Doppler FVWs were measured at the UA and MCA. In these vessels, pulsatility index (PI) [4] was calculated. On the venous side of the fetal circulation, FVWs were recorded at the ductus venosus (DV), where peak velocity index for veins (PVIV) [5] was calculated. Intra-cardiac flows were measured at the tricuspid (TRI) and mitral (MIT) valves. Placental vascular indices were measured using the Virtual Organ Computer-aided AnaLysis (VOCAL) software (3D SonoView, GE Medical Systems). The vascularization index (VI) of the placental tissue was calculated [6, 7].

E. Inverse solution: estimation of model parameters

Inputs for the estimation process were the set of Doppler velocity recordings (v), placental 3D indices and the estimated fetal weight. A nominal model was created for describing a normal fetus of the same weight with normal FVWs.

To estimate model parameters we used nonlinear optimization minimizing the residual between the computed and measured (noted by superscript ^). To this end, vectors v and $\hat{v}$ were defined, spanning all the measured FVWs and calculated flow waveforms, respectively.

$$v = \left[v^{\mathrm{UA}}, v^{\mathrm{MCA}}, v^{\mathrm{DV}}, v^{\mathrm{TRI}}, v^{\mathrm{MIT}} \right]^T \qquad (2)$$

$$\hat{v} = \left[\hat{v}^{\mathrm{UA}}, \hat{v}^{\mathrm{MCA}}, \hat{v}^{\mathrm{DV}}, \hat{v}^{\mathrm{TRI}}, \hat{v}^{\mathrm{MIT}} \right]^T \qquad (3)$$

where v and $\hat{v}$ consisted of calculated flow or measured velocity waveforms of the umbilical artery, middle cerebral artery, ductus venosus, tricuspid valve and mitral valve, respectively. The residual vector ($\hat{R}$) was defined to describe the error between the calculated and measured waveforms, as follows.

$$\hat{R} = \left[v - \hat{v} \right]^T \quad (4)$$

A cost-function J was therefore defined as an averaged mean squared error (MSE) between the velocity and flow waveforms:

$$J = \hat{R}^T \hat{R} \quad (5)$$

Thus the estimation problem was presented as the search of the parameter set that minimizes J in the least-squares sense. This process continued iteratively until the mean squared error between the model waveforms and the measured FVWs was less than a predefined threshold value. In each iteration, values of model parameters were restricted to physiological range. Placental resistance was estimated by the morphology of the umbilical artery FVW. Placental compliance (C_{pla}) depended on the (normalized) vascularization index (VI) according to eq. 6:

$$C_{pla} = C_{pla,0} \cdot VI^P \quad (6)$$

where $C_{pla,0}$ is the nominal value of placental compliance, P is a scaling factor and VI is the measured vascularization index, normalized between 0 and 1.

III. Results

The technique was tested on 42 pregnant women (20 had normal pregnancy and 22 had pregnancy complicated by FGR). Maternal age and number of primiparas were not different between the study and control groups. Gestational age at delivery, birth weight and birth weight percentile were significantly lower in the FGR group, as expected from the study design. In the FGR group two intrauterine fetal deaths (9%) occurred, three neonates (14%) developed respiratory complications, yielding overall five neonates (23%) with composite adverse outcome.

Fig. 2 presents a representative example of the algorithm results in normal and FGR patients. The figure shows the measured Doppler velocity waveform and the model calculated flow waveforms.

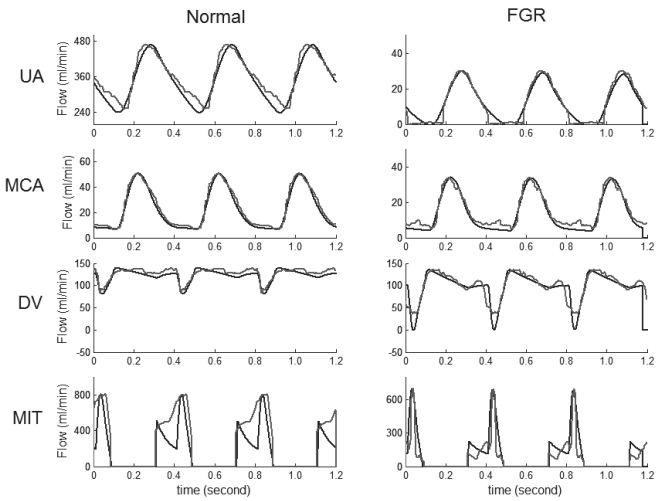

Fig. 2. Calculated waveforms (solid lines) and measured Doppler flow-velocity waveforms (dashed lines) of the umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV) and mitral valve (MIT) in normal and FGR patients

The results of the patient-specific indices of the cardiac output, placental blood flow, cerebral blood flow and percentage of cerebral cardiac output are shown in Table 1 Data presented as (mean±SD).

Table 1: Patient-specific hemodynamic indices calculated by the mathematical model.

Parameter	Units	Nornal	FGR	Adverse
Cardiac output	mL/min/Kg	419±68	354±55‡	342±18†
Pla.blood flow	mL/min/Kg	182±30	149±52†	100±44‡
Cerebral blood flow	%	8.0±2	9.1±3	10.8±2‡
Blood shunt in DV	%	42+15	44+19	65+19‡

FGR: fetal growth-restriction, adverse: adverse outcome, Pla: placental, DV: ductus venosus, †: P-value<0.05 compared to the normal group, ‡ P-value<0.01 compared to the normal group

The added value of the patient-specific hemodynamic indices in relation to presently used Doppler indices was assessed by binary logistic regression analysis (Table 2). Diagnostic performance was evaluated by the model sensitivity and specificity for the detection of FGR. Two subsets of Doppler signals were analyzed: subset (A): {UA, MCA}; and (B): {UA, MCA, DV, MIT, TRI}. Subset A represented fetal FVWs that are routinely measured during fetal assessment, whereas subset B consisted of all FVWs that were included in the parameter estimation process. The hemodynamic indices showed the best diagnostic performance, with sensitivity of 85% and specificity of 78%.

Table 2: Regression deviance, sensitivity and specificity for different subsets of Doppler flow-velocity waveforms and the patient-specific hemodynamic indices

Signal subset	Deviance	Sensitivity (%)	Specificity (%)
Subset A	54.2	60	57
Subset B	29.3	65	78
Hemodynamic indices	38.3	85	78
Subset A + hemo.indices	37.5	85	78
Subset B + hemo. indices	27.9	70	74

IV. CONCLUSIONS

We presented a theoretic methodology for estimating fetal hemodynamic parameters. The technique is based on a patient-specific, age-dependent mathematical model of the fetal circulation and an algorithm for model parameter estimation. The method was tested on a cohort of normal and growth-restricted fetuses. In FGR fetuses, the model predicted cardiac output and placental blood flow significantly below normal. Fetuses showing adverse outcome were identified to have significant increase in cardiac output distribution towards the brain and in the degree of blood shunt by the ductus venosus (Table 1).

Currently there is no single test that indicates the degree of fetal oxygenation or fetal well-being. The decision regarding the time of delivery in FGR fetuses is therefore based on a relatively simple analysis of Doppler FVWs, combined with functional testing such as biophysical profile and fetal heart rate. The rationale behind the development of methodology for patient-specific modeling of the fetal circulation (Fig. 1) is threefold: first, the current analysis of Doppler waveforms does not utilize the entire information that exists in the signal. The use of simple indices such as the PI or S/D ratio for arteries and PVIV for veins ignores the morphology of the entire signal and uses only the maximum and minimum points of the velocity profile or its average value. Second, the integration of information from multiple sites of the fetal circulation may reveal hidden insights regarding the mutual effects between venous flow, cardiac contractility and afterload during the compensated stage of FGR. Third, the use of statistical reference ranges of normal Doppler indices is of limited clinical use since these tables suffer from large standard.

The method presented in this study was shown to be more sensitive than conventional Doppler indices for the identification of FGR pregnancies. This may be attributed to several factors. First, for the purpose of system identification, FVWs were recorded in a large number of sites in the fetal circulation, even in locations not routinely used in standard fetal examination. Second, the model used the entire morphology of the FVW. Third, the integration of data into one coherent cardiovascular system enabled the analysis of the interface between the arterial, cardiac and venous flow. As a result of this analysis, the model was able to estimate hemodynamic indices such as cardiac output and cardiac output distribution that could not have been measured with Doppler ultrasound. Indeed, the model was shown to add significant information above the traditional analysis of the Doppler waveforms (Table 2). Both sensitivity and specificity of the patient-specific hemodynamic indices were higher than those acquired by Doppler indices. These results support the methodology presented in this study and demonstrate the power of the identification method proposed for the fetal circulation.

To conclude, the technique presented in this study for patient-specific estimation of fetal hemodynamic parameters may be useful in optimizing and personalizing the treatment options in pregnancies complicated by FGR.

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