Understanding Prenatal Brain Sparing by Flow Redistribution Based on a Lumped Model of the Fetal Circulation

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Abstract. Intrauterine Growth Restriction due to placental insufficiency leads to cardiac dysfunction in utero which can persist postnatally. Brain sparing by flow redistribution is an adaptive mechanism used by the restricted fetus to ensure delivery of oxygenated blood to the brain. The quantification of reversed flow in the aortic isthmus is used in clinical practice to detect signs of brain sparing. Two parameters are used to quantify reversed flow: pulsatility index and isthmic flow index. We developed a simplified 0-D lumped model of the fetal circulation to simulate brain-sparing for better understanding this compensatory mechanism and its influence on the mentioned parameters. We were able to reproduce the clinical phenomenon and to quantify the effect of brain sparing on pulsatility and isthmic flow indexes. Therefore, our model seems to be a good approximation of the fetal circulation and offers potential to study hemodynamic changes in intrauterine growth restricted fetuses.

1 Introduction

Cardiovascular disease is the leading cause of mortality in developed countries. Besides the already known risk factors related to lifestyle and genetics, there is growing evidence that in some cases cardiovascular disease has its origin during prenatal life [1]. Historical cohort studies [1] and animal models [2] have shown a clear association between low birth weight and increased cardiovascular mortality in adulthood. There are many fetal conditions that can lead to fetal cardiac dysfunction in utero which often persists postnatally [3]. Intrauterine growth restriction (IUGR) is defined as a low estimated fetal weight and it is mostly due to placental insufficiency resulting in a reduction of oxygen and nutrients suply to the fetus. In order to cope with this chronic restriction, some adaptive

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mechanisms are triggered. One of these mechanisms consists of a redistribution of the arterial blood flow in order to maintain an adequate level of oxygenation to key organs such as heart and brain. This compensatory mechanism is called the "brain-sparing" effect and results in an increment of blood flow through the brain circulation and, consequently in a reduction in the peripheral one. Also, AoI flow has been correlated with the postnatal neurodevelopmental outcome in IUGR fetuses [4, 5].

During prenatal life the aortic isthmus (AoI) plays an important role because it connects the two parallel ventricular outputs and maintains an adequate balance between upper body and lower body / placental circulation. Under normal conditions, the flow in the AoI is anterograde (from heart to periphery) during the whole cardiac cycle. However, under altered conditions, such as IUGR, reversed blood flow can be observed during diastole and late-systole in the AoI [6] (see Fig.1). In clinical practice, blood flow waveforms have been quantified with the pulsatility index (PI), calculated as PI=(max velocity - min velocity)/mean velocity. However, in obstetrics there is a preference to use the Isthmic Flow Index (IFI) to quantify Doppler velocity flow in the AoI [5]. IFI reflects the amount and direction of the blood through this vascular segment and it is calculated as: IFI=(systolic + diastolic)/systolic velocity integrals.

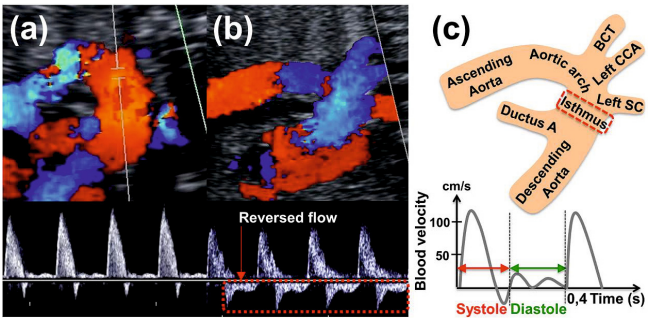

Fig. 1. Typical normal (a) and abnormal (b) aortic isthmus Doppler flow velocity with reversed blood flow, both from fetuses of 34 weeks of gestational age. (c) At the top: schematic view of the anatomy visualized in (a) and (b) Doppler images. BCT = brachiocephalic trunk, CCA = common carotid artery and SC =subclavian artery. At the bottom: meaning of the profiles plotted below each Doopler image.

Mathematical models of the cardiovascular system are a powerful tool to recreate and understand the cardiovascular system. Several models of the cardiovascular system have been proposed [7]. However, only few models of the fetal circulation have been published [8–10], likely because the fetal cardiovascular system differs from the neonatal one (i.e. placental circulation and the three vascular shunts).

The aim of this study is to develop a simplified electric analog model of the fetal circulation and to investigate the "Brain-Sparing" effect in IUGR, in order to evaluate the influence of vascular resistance variation in the PI and IFI. The model

is composed of resistors, capacitors, and inductors, which model different physical features of the fetal circulation. Different degrees of severity in IUGR were modeled by varying the brain and peripheral resistances (mimicking vaso-dilation/-constriction), and in each case, the amount of reversed flow in AoI was quantified.

2 Materials and Methods

2.1 Anatomical Configuration

The simplified fetal cardiovascular system was modeled as a set of: 6 arterial segments, corresponding to: (1) ascending aorta (aAo), (2) upper body artery (ubA), (3) pulmonary trunk (pT), (4) ductus arteriosus (ductA), (5) aortic isthmus (AoI) and (6) descending aorta (dAo); 5 vascular beds: (1) lungs, (2) brain (3) upper body, (4) peripheral (per) and (5) heart. Flow velocity waves at the aortic (QLV) and pulmonary valves (QRV) were used as inputs of the circuit. A schematic representation of the simplified fetal circulation is shown in Fig.2A.

The physical dimensions of the different arterial segments depending on gestational age (GA) were extracted from the literature [11–15] except for the AoI, which was considered to be 20% of the total length of the ascending aorta and aortic arch, with a radius equal to the distal aortic arch.

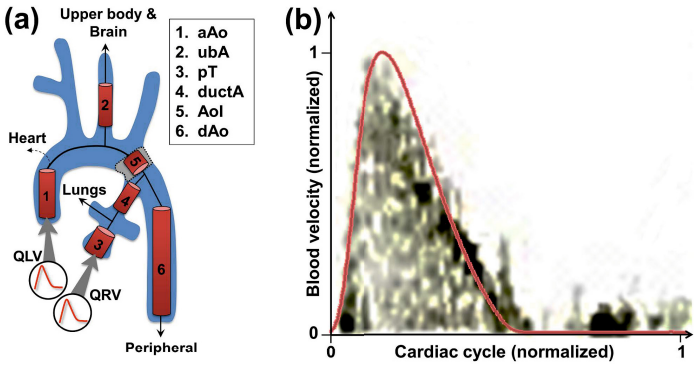

Fig. 2. (a) Simplified model of the fetal circulation composed of 6 arterial segments, 2 blood velocity profiles used as input: QLV (left) and QRV (right) and 5 vascular beds: brain, upper body, lungs, heart and peripheral. (b) Comparison between real (obtained from Doppler echocardiography of a healthy fetus) and modeled (red line) blood velocity waveform through the aortic valve.

2.2 Input Blood Flow Functions

Input blood flow waveforms were obtained from real echocardiographic data of a normal fetus 34 weeks' GA. Blood velocity profiles from the aortic and pulmonary valves were delineated using a custom program implemented in MATLAB (2007b, The MathWorks Inc., Natick, MA). Peak velocity (V_{peak}), heart rate (HR) and ejection time (ET) from echocardiographic data were also introduced to compute the blood velocity function (V). The final blood flow waveform

was calculated as: $Q = V * \pi r^2$, where r is the valve radius. Fig.2B shows an example of modeled and real blood flow velocity waveform.

2.3 Equivalent Electrical Lumped Model

The implemented 0-D lumped model of the simplified fetal circulation consisted of 2 different blocks. The block describing the arterial segments includes the local resistance of blood due to blood viscosity, modeled with a resistor (R), the arterial compliance modeled with a capacitor (C) and blood inertia modeled with an inductor (L), as previously described in other cardiovascular models [16]. The second block describes vascular beds and consisted of a resistor modeling the different peripheral resistances. A diagram of the developed 0-D lumped model is shown in Fig. 3.

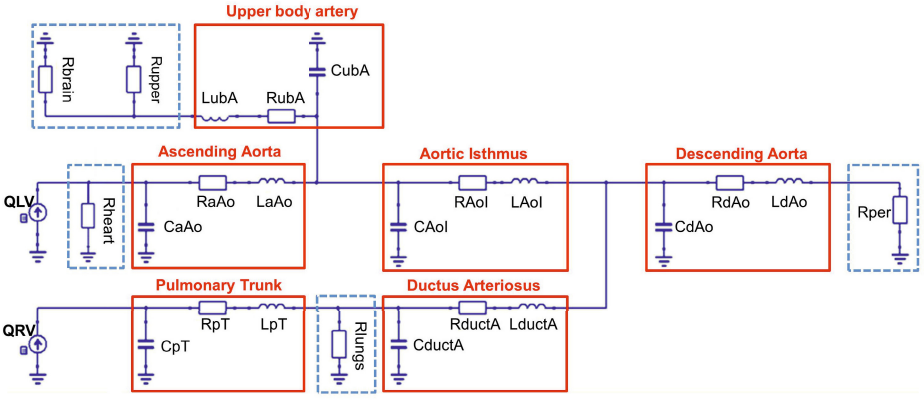

Fig. 3. Diagram of the equivalent electric 0-D model of a simplified fetal circulation. QLV and QRV are the left and right input blood flow respectively. The 6 blocks corresponding to the 6 arterial segments are highlighted in solid lines and the blocks corresponding to vascular beds in dashed lines.

The component values of the 0-D lumped model corresponding to the arterial segments were calculated according to their physical dimensions and properties, using the following equations: $R = 8\eta l/\pi r^4$, $L = \rho l/\pi r^2$ and $C = 3\pi r^3 l/2Eh$, where l is the arterial segment length, η is the fetal blood viscosity taken from [10], ρ is the blood density ($1.05\ g/cm^3$), h is the wall thickness and was assumed to be 15% of the arterial radius (r) [10] and E is the Young's Modulus estimated from [9] for the different arterial segments. Peripheral resistances were estimated from [8]. All the model component values are shown in Table 1.

The equivalent 0-D lumped model was implemented using Qucs, an integrated circuit simulator released under the GPL license [17].

2.4 Simulations

In order to simulate the brain sparing that occurs in IUGR fetuses, peripheral and upper body resistances were systematically increased to simulate an

Table 1. Model component values for a fetus of 34 weeks of GA

Arterial segment	R (mmHg·s/ml)	L (mmHg·s^2/ml)	C (ml/mmHg)	Vascular bed	R (mmHg·s/ml)
aAo	0.0100	0.0040	0.0182	Brain	19.4
pT	0.0047	0.0024	0.0139	Upper B	31.1
ductA	0.0157	0.0034	0.0020	Lungs	20.3
AoI	0.0154	0.0027	0.0017	Peripheral	6.8
ubA	0.4088	0.0403	0.0068	Heart	94.5
dAo	0.0957	0.0272	0.0068		

increased placental resistance and peripheral vasoconstriction. At the same time, brain resistance was systematically decreased to represent local vasodilatation. For each simulated case, IFI, PI and percentage of reversed flow in the AoI were calculated. In addition, the PI_{dAo}/PI_{brain} ratio was calculated to demonstrate the brain sparing effect. Finally, the percentage of blood flow towards the different peripheral parts was calculated to assess blood flow redistribution as a consequence of brain and peripheral resistance variation.

3 Results

3.1 Validation of the Equivalent Lumped Model

Firstly we checked if the combined cardiac output (CCO) distribution corresponded with reference values of a fetus 34 weeks' GA under normal physiological conditions. For this purpose, distributions of blood flow towards the different peripheral parts, measured or estimated clinically, were extracted from the literature [18, 19] and were compared with the blood distribution obtained from the equivalent 0-D lumped model. As shown in Table 2, the simulated values were in accordance to the reported blood flow distribution. For example, it can be observed that the right ventricular output is slightly larger than the left one, demonstrating the fetal right heart dominance. Also, most of the blood ejected by the left ventricle goes through the upper circulation and only a small portion passes through the AoI directed to the lower body and placental circulation. The mean aortic blood pressure was 40 mmHg which agreed with its corresponding

Table 2. Comparison between measured and modeled CCO distribution in a fetus of 34 weeks of GA

Fetal Area	Measured CCO %	Modeled CCO %
Left Output	40-43%	47.76%
Right Output	57-60%	52.24%
Brain	15%	16.92%
Upper body	13%	10.89%
Lungs	19%	18.46%
Peripheral	50%	49.90%
Heart	3%	3.83%

estimated value [20]. Finally, modeled flow waveforms in AoI (see Fig.4 and 5) were very similar to the measured ones (see 1).

3.2 Evaluation of Brain Sparing

Fig.4 shows 5 istmic flow waveforms with different degrees of severity and its corresponding IFI value, reproducing the clinical phenomena [5,6]. Fig.5 displays the modeled flow waveforms in the AoI and the amount of reversed flow. These two graphs show how AoI flow is reversed in late systole and in the whole diastole as a result of increased peripheral resistance and decreased brain resistance. The maximum percentage of reversed AoI flow (57%) was obtained when peripheral resistance was increased by a factor of 2, and, in turn, brain resistance decreased to 50% of its normal value. In this case, the percentage of CCO that enters to the brain increase up to 39.9%. These results suggest that the main factor for reversed flow in AoI seems to be an increase in peripheral resistance rather than decrease in brain resistance.

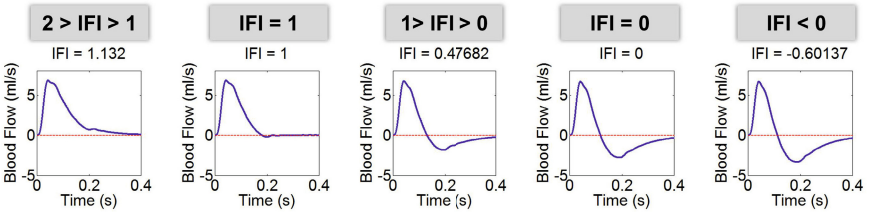

Fig. 4. Examples of modeled isthmic blood flow waveforms with various degrees of severity and their corresponding IFI values

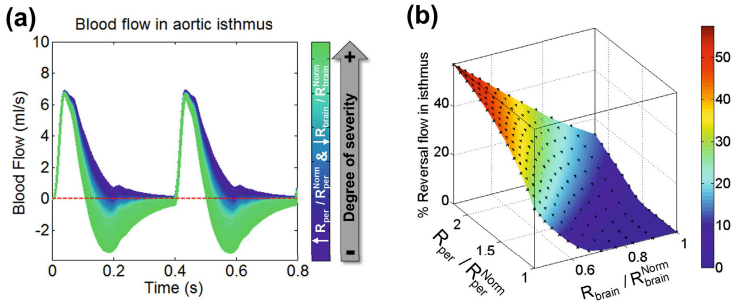

Fig. 5. (a) Modeled flow waveforms in the aortic isthmus (AoI) for varying degrees of peripheral/brain resistance changes. (b) The amount of reversal flow in AoI plotted as a function of normal R_{brain} and R_{per}. Dots indicate the modeled cases.

IFI and PI in the AoI, and the PI_{dAo}/PI_{brain} ratio are plotted as a function of simulated brain and peripheral resistances relative to their normal value in Fig.6. Regarding IFI, as the amount of reversed flow in the AoI increases, IFI decreases. When the amount of reversed flow equals anterograde flow, IFI is 0,

and it becomes negative when the reversed diastolic blood flow is dominant and net blood flow through the AoI is retrograde. Furthermore, the combined effect of an increase in peripheral resistance and a decrease in brain resistance showed an increased PI in the AoI. Also, the percentage of CCO flowing through the peripheral system is reduced and the percentage flowing through the brain is increased. This can be demonstrated with the PI_{dAo}/PI_{brain} ratio, which also increases. For this parameter, the increase in the peripheral resistance seems to have a greater effect.

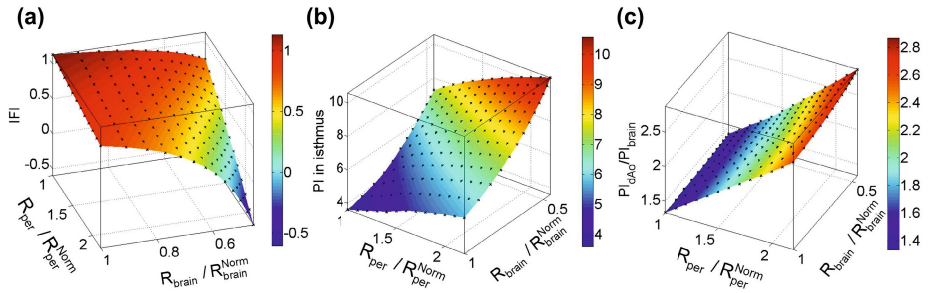

Fig. 6. (a) IFI, (b) pulsatilty index (PI) in AoI and (c) PI_{dAo}/PI_{brain} all of them plotted as a function of normal R_{brain} and R_{per}. Dots indicate the modeled cases.

4 Discussion and Conclusion

In this study we developed a simplified equivalent lumped model of the fetal arterial circulation to evaluate the blood flow and its reversal in the AoI. Arterial segments consisted of a capacitor, inductor and resistor, as previously described by Milisic et al. [16], and vascular beds were modeled with a resistor. We validated the physiological relevance of our simplified 0-D lumped model by computing the distribution of CCO through different cardiovascular parts. The calculated distribution of CCO was in good agreement with the range of measured values for a normal fetus of the same GA [18,19].

The aim of this study was to simulate the brain sparing effect which occurs in IUGR fetuses. Brain sparing is a compensatory mechanism, which causes a blood flow redistribution to maintain adequate cerebral oxygenation when blood oxygen availability decreases. Reversed diastolic and late-systolic flow in the AoI is a clinical marker for potential fetal problems. We simulated brain sparing by increasing peripheral resistance and decreasing brain resistance, and we could reproduce the clinical phenomenon. We studied the influence of the brain sparing effect on PI and IFI indexes. The simulated AoI PI showed an increase with the degree of severity. Also, the variation of IFI with the amount of reversed flow in the AoI agreed with those described clinically by Fouron et al. [5]. Finally, Mäkikallio et al. described that the PI_{dAo}/PI_{brain} ratio increased as the net flow in AoI became retrograde [6], and we described the same tendency.

In conclusion, the proposed equivalent 0-D lumped model seems to be a good approximation to assess blood flow in the fetal AoI and to quantify the effect

of brain sparing on the commonly used parameters in clinical practice for its evaluation, thus providing a tool to select the optimal parameters and link this to risk factors of the fetus.

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