Pediatr Cardiol (2015) 36:677–684
DOI 10.1007/s00246-014-1064-6

ORIGINAL ARTICLE

Oxygen Supply to the Fetal Cerebral Circulation in Hypoplastic Left Heart Syndrome: A Simulation Study Based on the Theoretical Models of Fetal Circulation

Sayaka Sakazaki · Satoshi Masutani · Masaya Sugimoto · Masanori Tamura · Seiko Kuwata · Clara Kurishima · Hirofumi Saiki · Yoichi Iwamoto · Hirotaka Ishido · Hideaki Senzaki

Received: 15 March 2014 / Accepted: 1 November 2014 / Published online: 15 November 2014

Abstract Hypoxia due to congenital heart diseases (CHDs) adversely affects brain development during the fetal period. Head circumference at birth is closely associated with neuropsychiatric development, and it is considerably smaller in newborns with hypoplastic left heart syndrome (HLHS) than in normal newborns. We performed simulation studies on newborns with CHD to evaluate the cerebral circulation during the fetal period. The oxygen saturation of cerebral blood flow in newborns with CHD was simulated according to a model for normal fetal circulation in late pregnancy. We compared the oxygen saturation of cerebral blood flow between newborns with tricuspid atresia (TA; a disease showing univentricular circulation and hypoplasia of the right ventricle), those with transposition of the great arteries (TGA; a disease showing abnormal mixing of arterial and venous blood), and those with HLHS. The oxygen saturation of cerebral blood flow in newborns with normal circulation was 75.7 %, whereas it was low (49.5 %) in both newborns with HLHS and those with TA. Although the oxygen level is affected by the blood flow through the foramen ovale, the oxygen saturation in newborns with TGA was even lower (43.2 %). These data, together with previous reports, suggest that the cerebral blood flow rate is decreased in newborns with HLHS, and the main cause was strongly suspected to be retrograde cerebral perfusion through a patent ductus arteriosus. This study provides important information about the neurodevelopmental prognosis of newborns with HLHS and suggests the need to identify strategies to resolve this unfavorable cerebral circulatory state in utero.

Keywords Cerebral circulation · Congenital heart disease · Fetus · Hypoplastic left heart syndrome

S. Sakazaki · S. Masutani · S. Kuwata · C. Kurishima · H. Saiki · Y. Iwamoto · H. Ishido · H. Senzaki (✉)
Division of Pediatric Cardiology, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama 350-8550, Japan
e-mail: hsenzaki@saitama-med.ac.jp

S. Sakazaki · M. Tamura
Division of Neonatology, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan

M. Sugimoto
Department of Pediatrics, Asahikawa Medical University, Asahikawa, Japan

Background

In recent years, neuropsychiatric developmental delay has been recognized in patients with congenital heart disease (CHD) who require surgery during the neonatal period [6]. Most notably, the impacts of surgical invasion, including cardiopulmonary bypass, and of the state of heart failure during the perioperative period on the neonatal brain, have been considered the major factors underlying this delay [2]. However, the importance of congenital factors, such as hypoxia due to congenital cardiovascular structural anomalies that adversely affect brain development during the fetal period, has recently been pointed out [1]. This is also suggested by reports showing that head circumference at birth, which is closely associated with the neuropsychiatric developmental prognosis, is significantly smaller in newborns with hypoplastic left heart syndrome (HLHS), characterized by anomalous hemodynamics from the fetal period, than in normal newborns [16]. Furthermore, reports on Doppler ultrasound measurements of cerebral blood flow in HLHS during the fetal period have also shown a brain-sparing effect, a finding indicating decreased oxygen supply

to the brain [8]. However, these findings are not consistently observed in many other forms of CHD showing hemodynamic derangement and hypoxia, and there are differences even in the descriptions of HLHS itself among reports [3]. In addition to the limited sample size of each study, one of the major reasons for this may be the difficulty in standardizing the effects of maternal factors including placental function and fetal factors affecting the cerebral circulation, such as developmental status, chromosomal abnormalities, and gestational age, in in vivo assessment. Thus, in this study, to eliminate potential confounding factors affecting the cerebral circulation and thereby assess the pure effects of hemodynamic factors due to cardiovascular structural anomalies in HLHS, we performed simulation studies of cerebral circulation in HLHS during the fetal period on the basis of the theoretical models of fetal circulation.

Methods

On the basis of a model of normal fetal circulation in late pregnancy that was introduced with preferential streaming of placental blood flow [18], the oxygen saturation of cerebral blood flow in HLHS fetuses was simulated. Moreover, with a model of Type Ia tricuspid atresia (TA, a disease showing univentricular circulation and hypoplasia of the right heart) and a model of type I transposition of the great arteries (TGA, a disease showing abnormal arteriovenous blood mixture), similar simulations were performed for comparison.

Model of Normal Fetal Circulation

Figure 1a shows the basic model of normal fetal circulation developed using the model proposed by Rudolph [18] on the basis of animal experiments. Data for blood flow distribution and oxygen saturations at each site used for calculating the oxygen saturation of cerebral blood flow are summarized in Table 1. Briefly, the oxygen saturation of umbilical venous blood ($S_{uv}O_2$) is 85 %, and the blood flow rate is 200 mL kg^{-1} min^{-1}, of which 130 mL kg^{-1} min^{-1} flows into the left atrium through the foramen ovale. The remaining umbilical venous blood of 70 mL kg^{-1} min^{-1} in combination with blood flow from the lower limbs ($S_{low\ IVC}O_2$, 35 %; blood flow rate, 100 mL kg^{-1} min^{-1}) and the upper limbs ($S_{SVC}O_2$, 35 %; blood flow rate, 170 mL kg^{-1} min^{-1}), a total of 340 mL kg^{-1} min^{-1}, flows into the right ventricle. Of the right ventricular output of 340 mL kg^{-1} min^{-1}, 300 mL kg^{-1} min^{-1} is distributed to the descending aorta through the arterial duct and 40 mL kg^{-1} min^{-1} is distributed to the pulmonary circulation. In total, 130 mL kg^{-1} min^{-1} of blood flow from the foramen ovale and 40 mL kg^{-1} min^{-1} of the pulmonary venous return without being oxygenated in the lungs flows into and out of the left ventricle. All of this left ventricular output circulates throughout the upper body, and all of the blood flow from the arterial duct to the descending aorta circulates throughout the lower body.

From the data listed in Table 1, we can calculate the oxygen saturation of the right and left ventricle where blood with different oxygen saturations is mixed according to the flow distribution as follows:

$$\begin{aligned}&\text{Oxygen saturation in the right ventricle}(S_{RV}O_2)\\&=([\text{inferior vena cava(IVC)flow from the placenta}\\&\quad\times\text{ oxygen saturation of the IVC flow from the placenta}]\\&\quad+[\text{IVC flow from other organs}\\&\quad\times\text{ oxygen saturation of the IVC flow from other organs}]\\&\quad+[\text{superior vena cava(SVC) flow}\\&\quad\times\text{ oxygen saturation of the SVC flow}])/\\&\quad(\text{IVC flow from the placenta}+\text{IVC flow from other organs}\\&\quad+\text{SVC flow})\end{aligned}$$

$$\begin{aligned}&\text{Oxygen saturation in the left ventricle}(S_{LV}O_2)\\&=([\text{foramen ovale (FO) flow from the placenta}\\&\quad\times\text{ oxygen saturation of FO flow}]+[\text{pulmonary artery(PA)flow}\\&\quad\times\text{ oxygen saturation of the PA flow}])/(\text{FO flow}+\text{PA flow})\end{aligned}$$

Similar calculations based on the flow and O_2 saturation were applied to fetal circulation with CHD.

Models of CHD

Data for blood flow distribution and oxygen saturations at each site used for calculating the oxygen saturation of cerebral blood flow in the models of CHD are also summarized in Table 1. Placental function was assumed to be normal, and thus the oxygen saturation of umbilical venous blood ($S_{uv}O_2$) was set at 85 %, and the blood flow rate was set at 200 mL kg^{-1} min^{-1}. The ventricular functions were presumed to be good enough to be capable of maintaining necessary systemic blood flow similar to the normal circulation. Furthermore, the blood flow rate from the upper limbs was hypothesized to be the same as the normal rate, 170 mL kg^{-1} min^{-1}. Because the pulmonary blood flow rates in HLHS (Fig. 1b) and TA (Fig. 1c) were expected to be slightly higher than the normal rate, the rates in both diseases were hypothesized to be 50 mL kg^{-1} min^{-1}. Because lower pulmonary vascular resistance and an even higher pulmonary blood flow rate were expected in TGA (Fig. 1d) [12], the rate was hypothesized to be 130 mL kg^{-1} min^{-1}. The blood flow rates from the lower

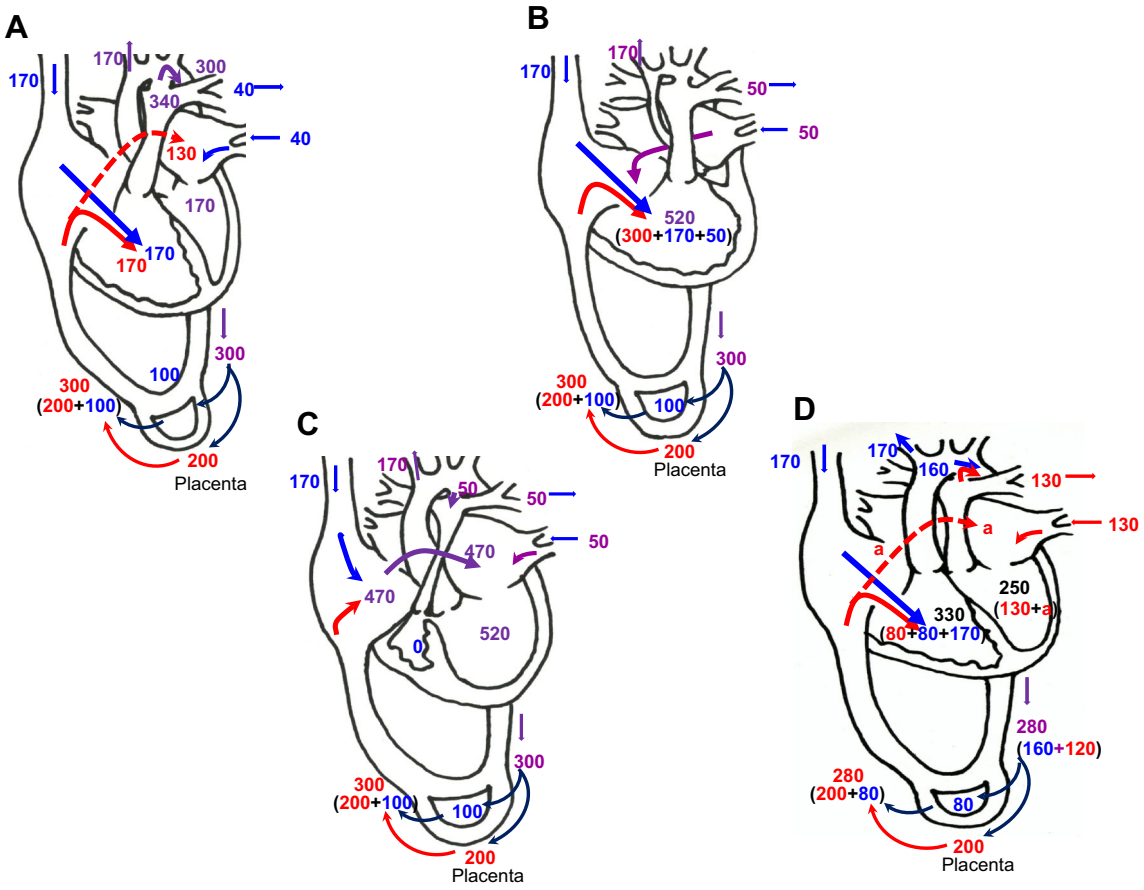

Fig. 1 Basic model of normal fetal circulation developed using the model proposed by Rudolph et al. (**a**). Model of fetal circulation in HLHS (**b**), TA (**c**), and TGA (**d**). The unit of blood flow is mL kg^{-1} min^{-1}

Table 1 Blood flow and the oxygen saturations in the main vessels used for simulation

	Normal	HLHS	TA	TGA
Blood flow (mL kg^{-1} min^{-1})				
UV	200	200	200	200
FO	130	50	470	[a]
IVC	100	100	100	80
SVC	170	170	170	170
PA	40	50	50	130
O_2 saturation (%)				
UV	85	85	85	85
FO	85			85
IVC[b]	35	35	35	35
SVC	35	35	35	35

UV umbilical vein, *FO* foramen ovale, *IVC* inferior vena cava, *SVC* superior vena cava, *PA* pulmonary artery

[a] The shunt flow rate from the right atrium to the left atrium through the foramen ovale was set as mL kg^{-1} min^{-1}

[b] IVC flow and O_2 saturation are those of blood from the lower limbs other than from the placenta

limbs in HLHS and TA were hypothesized to be similar to the normal rate of 100 mL kg^{-1} min^{-1}. Because high pulmonary blood flow was postulated in TGA, the blood flow rate from the lower limbs was hypothesized to be 80 mL kg^{-1} min^{-1}. The blood flow volume through the foramen ovale could be hypothesized to be the total volume of left atrial perfusion in HLHS and the total volume of right atrial perfusion in TA. Because the shunt volume varies substantially in TGA depending on the condition of the foramen ovale, the shunt flow rate was hypothesized to be (a) mL kg^{-1} min^{-1} only from the right atrium to the left atrium.

Furthermore, on the basis of the hypothesis that oxygen consumption in both the upper and the lower limbs was the same as that in the normal circulation, $S_{\text{low IVC}}O_2$, $S_{\text{SVC}}O_2$, and oxygen saturation in the right ventricle ($S_{\text{RV}}O_2$) (oxygen saturation in the left ventricle [$S_{\text{LV}}O_2$] in TA) were calculated. When this hypothesis did not fit the observations made, it was reexamined, and the analysis was attempted again.

Results

Oxygen Saturation at Each Site in the Normal Circulation

Oxygen saturation was calculated to be 45.3 % in the right ventricle and 75.7 % in the left ventricle, as follows:

$$S_{RV}O_2 = ([70 \times 85\,\%] + [100 \times 35\,\%] + [170 \times 35\,\%])/340 = 45.3\,\%$$

$$S_{LV}O_2 = ([130 \times 85\,\%] + [40 \times 45.3\,\%])/170 = 75.7\,\%$$

$$SVC = 35\,\%$$

Oxygen Saturation at Each Site in CHDs

HLHS

On the basis of the assumption that the blood flow rates and oxygen consumptions in the upper and the lower bodies were similar to those in the normal circulation, differences in arterial–venous oxygen saturation in both upper and lower bodies should be the same as in normal conditions:

$$S_{RV}O_2 - S_{SVC}O_2 = 41\,\%$$

$$S_{RV}O_2 - S_{low\,IVC}O_2 = 10\,\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the right ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{RV}O_2 = 45$ %, using the following equation:

$$S_{RV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\,\%] + [50 \times S_{RV}] + [170 \times S_{SVC}])/520.$$

Reexamination of the Hypothesis of HLHS

When the decrease in oxygen saturation was set at 41 % in the upper limbs and 10 % in the lower limbs, the equation in "HLHS" section yielded a nonphysiological value of $S_{SVC}O_2 = 4$ %. Because a portion of venous blood that had low oxygen saturation in simulation of the normal circulation passes through the foramen ovale, the actual oxygen saturation should be lower in the left ventricle and higher in the right ventricle than the values obtained in "HLHS" section. Thus, the decreases in oxygen saturation in the upper and lower limbs in the normal circulation were changed to 30 and 20 %, respectively, and simulations were then performed while the hypothesis that the blood flow rates and oxygen consumption in both the upper and lower limbs were similar to those in the normal circulation was maintained:

$$S_{RV}O_2 - S_{SVC}O_2 = 30\,\%$$

$$S_{RV}O_2 - S_{low\,IVC}O_2 = 20\,\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{LV}O_2 = 45$ %, using the following equation:

$$S_{RV} = ([100 \times S_{low\,IVC}] + [200 \times 85\,\%] + [50 \times S_{RV}] + [170 \times S_{SVC}])/520.$$

TA

On the basis of the assumption that the blood flow rates and oxygen consumptions in the upper and the lower bodies were similar to those in the normal circulation, differences in arterial–venous oxygen saturation in both the upper and lower bodies should be the same as in normal conditions:

$$S_{LV}O_2 - S_{SVC}O_2 = 41\,\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 10\,\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{LV}O_2 = 45$ %, using the following equation:

$$S_{LV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\,\%] + [50 \times S_{LV}] + [170 \times S_{SVC}])/520.$$

Reexamination of the Hypothesis of TA

When the decrease in oxygen saturation was set at 41 % in the upper limbs and 10 % in the lower limbs, the equation in "TA" section again yielded a nonphysiological value of $S_{SVC}O_2 = 4$ %. As is the case with "Reexamination of the Hypothesis of HLHS" section, the decreases in oxygen saturation in the upper and lower limbs in the normal circulation were changed to 30 and 20 %, respectively, and simulations were then performed while the hypothesis that blood flow rates and oxygen consumption in both the upper and the lower limbs were similar to those of the normal circulation was maintained:

$$S_{LV}O_2 - S_{SVC}O_2 = 30\,\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 20\,\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 19.5$ %, $S_{low\ IVC}O_2 = 29.5$ %, and $S_{LV}O_2 = 49.5$ %, using the following equation:

$$S_{LV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\,\%] + [50 \times S_{LV}] + [170 \times S_{SVC}])/520.$$

TGA

The blood flow rates and oxygen consumption in both the upper and the lower limbs were hypothesized to be similar

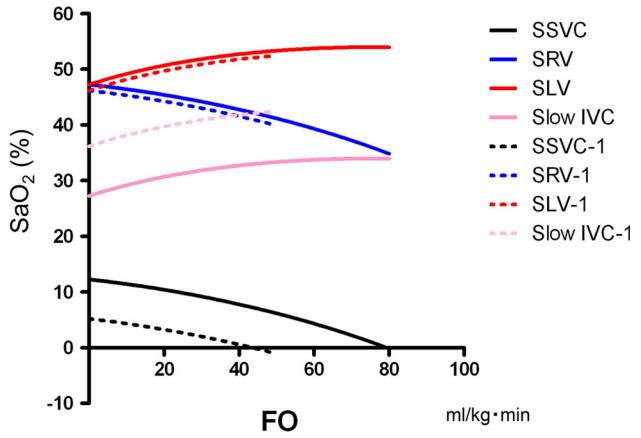

Fig. 2 Relation between the blood flow rate through the foramen ovale and oxygen saturation in the TGA model. *Dashed lines* indicates the results for oxygen saturation at each site in association with the blood flow rate at the foramen ovale (a). *Solid lines* indicate the changes at each site in association with the blood flow rate at the foramen ovale (a)

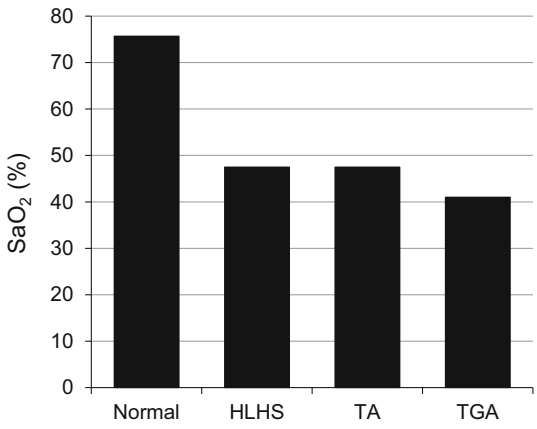

Fig. 3 Results of cerebral oxygen saturation for each CHD model

to those in the normal circulation, and oxygen saturation in the upper and lower limbs in TGA was equal to $S_{RV}O_2$ and $S_{LV}O_2$, respectively:

$$S_{RV}O_2 - S_{SVC}O_2 = 41\,\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 10\,\%.$$

Furthermore, the equation used for oxygen saturation of blood mixed in the right ventricle was

$$S_{RV}O_2 = ([80 \times S_{low\,IVC}] + [(200 - a) \times 85\,\%] + [170 \times S_{SVC}])/(450 - a).$$

The equation used for oxygen saturation of blood mixed in the left ventricle was

$$S_{LV}O_2 = ([130 \times S_{LV}] + [a \times 85\,\%])/(130 + a) \qquad (*)$$

On the basis of these equations, the following equation was derived:

$$S_{SVC}O_2 = ([44 \times a^2] + [1,170 \times a] - 133,900)/([a^2 - 150] \times [a - 26,000]).$$

Subsequently, oxygen saturation was calculated as follows:

$$S_{RV}O_2 = S_{SVC} + 41$$

$$S_{LV}O_2 = (*)$$

$$S_{low\,IVC}O_2 = S_{LV} - 10$$

Figure 2 (dashed lines) shows the results for oxygen saturation at each site in association with the blood flow rate at the foramen ovale (a).

Reexamination of the Hypothesis of TGA

When the blood flow rate at the foramen ovale was $a = 0$, the $S_{SVC}O_2$ obtained in "Reexamination of the hypothesis of TA" section was the highest at 5.15 %, a value that was too low physiologically. While the hypothesis that blood flow rates and oxygen consumption in both the upper and the lower limbs were similar to those in the normal circulation was maintained, the simulation of the normal circulation was changed as in "Reexamination of the hypothesis of HLHS" section. Furthermore, because the blood flow rate in the lower limbs was estimated to be low owing to high pulmonary blood flow in TGA, the decrease in oxygen saturation in the lower limbs was estimated to be slightly higher, in accordance with the following hypotheses:

$$S_{RV}O_2 - S_{SVC}O_2 = 30\,\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 25\,\%$$

Furthermore, as with the previous simulation, the equation used for the oxygen saturation of blood mixed in the right ventricle was

$$S_{RV}O_2 = ([80 \times S_{low\,IVC}] + [(200 - a) \times 85\,\%] + [170 \times S_{SVC}])/(450 - a).$$

The equation used for the oxygen saturation of blood mixed in the left ventricle was

$$S_{LV}O_2 = ([130 \times S_{LV}] + [a \times 85\,\%])/(130 + a) \qquad (*)$$

On the basis of these equations, the following equation was derived:

$$S_{SVC}O_2 = ([50 \times a^2] + [50 \times a] - 318,500)/([a^2 - 150] \times [a - 26,000]).$$

Subsequently, oxygen saturation was calculated as follows:

$$S_{RV}O_2 = S_{SVC} + 30$$

$$S_{LV}O_2 = (*)$$

$$S_{low\,IVC}O_2 = S_{LV} - 25$$

Figure 2 (solid lines) shows the changes at each site in association with the blood flow rate at the foramen ovale (a).

When the blood flow rate at the foramen ovale (a) was hypothesized to be 130 mL kg^{-1} min^{-1} as in the normal circulation, this simulation yielded $S_{SVC} = 13.3$ %, $S_{low\ IVC} = 20.7$ %, $S_{LV} = 45.7$ %, and $S_{RV} = 43.2$ %, which were lower than those obtained from the HLHS and TA simulations.

The results of cerebral oxygen saturation for each site in CHDs are summarized in Fig. 3.

Discussion

Although in recent years, ≥90 % of CHD patients have been saved owing to improved surgical outcomes, it has been widely recognized that there are many patients who develop various postoperative neuropsychiatric developmental abnormalities (affecting motor function, language, visuo-spatial perception, behavior, and learning) [11, 14]. Although the causes of these abnormalities may be multifactorial, the involvement of brain injury in utero is suggested by reports on decreased head circumference at birth [1, 10], delayed myelination detected by preoperative magnetic resonance imaging of newborns [9], and abnormal fetal cerebral blood flow waveforms demonstrated using the Doppler ultrasound [4, 5, 15]. Most notably, structural anomalies in CHD may be closely associated with decreased volume and oxygen saturation of cerebral blood flow, and abnormalities in oxygen supply to the brain may play a role in brain injury in utero. To address these issues, we performed a simulation study to obtain theoretical values of the oxygen saturation of cerebral blood flow using a mathematical model of fetal circulation, which allowed us to purely assess the effects of hemodynamic factors due to cardiovascular structural anomalies by eliminating potential confounding factors affecting the cerebral circulation.

Our mathematical model was based on the foundational study by Rudolph et al. [17–19]. By using the microsphere technique, those authors provided, for the first time, data for quantitative blood flow distribution in the fetus in utero. They found an important concept of preferential blood flow streaming to protect fetal cerebral circulation: well-oxygenated blood with an oxygen saturation of 85 % from the placenta passes through the ductus venosus and foramen ovale, and enters into the left ventricle, whereas blood from the SVC with a low oxygen saturation of about 35 % exclusively enters into the right ventricle. By using the information from the experiment of Rudolph's group, in the present study we constructed a model of fetal circulation with HLHS and contrasted it to other forms of CHD that may affect the fetal cerebral circulation. We found that the oxygen saturation of cerebral blood flow in a fetus with HLHS was markedly lower than that of a normal fetus; however, importantly, it was equally low as in a fetus with TA. Furthermore, cerebral oxygen saturation in TGA was even lower than that in HLHS. Although our model did not directly address changes in cerebral blood flow, it provided the oxygen content in blood with the condition of the blood flow being kept equal among the models. Thus, our model should help deduce the potential abnormality in blood flow as discussed below.

Kaltman et al. [8] divided CHD fetuses into those with pulmonary atresia/stenosis or a right-sided obstructive lesion and those with aortic atresia/stenosis including HLHS or a left-sided obstructive lesion, to examine differences in the Doppler patterns of cerebral blood flow using the pulsatility index and the resistance index. They reported that cerebrovascular resistance in the fetuses with a left-sided obstructive lesion was lower than that in the fetuses with a right-sided obstructive lesion, whereas cerebrovascular resistance in the latter fetuses was higher than the normal. Furthermore, decreased head circumference at birth, which is closely associated with neuropsychiatric developmental prognosis, is reported in HLHS at a remarkably higher frequency, as compared with TA [3]. Taking together these results with our present results showing the oxygen saturation of cerebral blood flow in TA (right-sided obstructive lesion) and HLHS to be equal, it is very likely that decreased blood flow or increased oxygen consumption in the brain is already present during the fetal period in HLHS. Because oxygen consumption in the brains of HLHS patients is unlikely to be markedly increased in comparison with that in the brains of TA patients, it is assumed that decreased cerebral blood flow is probably due to hemodynamics specific to HLHS, greatly affecting the cranial nerve development during the fetal period.

Decreased cerebral blood flow in HLHS fetuses is also suggested by a comparison between TGA and HLHS. While decreases in cerebrovascular resistance [7, 22] and head size at birth [4] in TGA fetuses have been reported by several investigators, many reports have shown that the decreases in TGA fetuses are smaller than those in HLHS fetuses. For example, Rosenthal reported that, although head circumference at birth is decreased in relation to body weight in both TGA and HLHS, the decrease is more

pronounced in HLHS [16]. Furthermore, Manzar et al., who directly compared head circumferences at birth adjusted for gestational age between TGA and HLHS, reported that, although the adjusted values were smaller in both TGA and HLHS than the normal value, the difference between the adjusted and normal values was significantly larger in HLHS [13]. These results, together with our present results showing that oxygen saturation of cerebral blood flow in TGA is lower than that in HLHS, strongly suggest that the cerebral blood flow rate is more highly decreased in HLHS than in TGA, as shown by the comparison with TA.

Broadly, there are two possible causes for the decreased cerebral blood flow in HLHS: one is retrograde cerebral perfusion from a patent ductus arteriosus (PDA), which is a characteristic of HLHS, and the other is that the right ventricle, which is the systemic ventricle in HLHS, cannot maintain adequate cardiac output. In this regard, Shillingford et al. reported the important observation that microcephaly in newborns with HLHS was associated with a small ascending aorta, but not a small transverse aortic arch, suggesting the importance of forward flow from the left ventricle for cerebral perfusion [21]. This notion was also supported by a report from Berg et al., who demonstrated that HLHS fetuses with aortic atresia have decreased cerebrovascular impedance and smaller heads, whereas fetuses with severe aortic stenosis and reversal of flow in the aortic arch do not [3]. Kaltman et al. also reported that a decrease in cerebrovascular resistance was more pronounced in HLHS, in which the cerebral blood flow is maintained only by reversal of flow from the arterial duct, than other left-sided obstructive lesions that have antegrade flow from the left ventricle [8]. When these results are considered together, we can reasonably assume, as the main cause, that the cerebral blood flow rate itself in HLHS fetuses is decreased by retrograde cerebral perfusion through a PDA. This is also supported by our recent report showing that cerebral blood flow after bilateral pulmonary artery banding in HLHS patients is more impaired than that after the Norwood procedure [20].

Because cerebrovascular insufficiency also means coronary vascular insufficiency, especially in HLHS patients with aortic atresia, cerebral perfusion is also considered to be possibly impaired by the synergistic effect of right ventricular dysfunction caused by coronary hypoperfusion. This condition results in insufficient uptake of oxygen and nutrients from the placenta and also adversely affects fetal development, which may lead to a vicious cycle resulting in developmental disorders of the brain. In fact, Berg et al. [3], who compared TGA and HLHS fetuses and observed decreased cerebrovascular resistance only in the latter, reported that, when fetuses with growth restriction and uteroplacental dysfunction were excluded, children born with HLHS had only slightly smaller head circumferences than controls, whereas the difference was more pronounced in newborns with TGA. This suggests that abnormalities of not only cerebral blood flow but also those of systemic perfusion may additively and synergistically be involved in developmental disorders of the brain in HLHS.

Conclusion

In this study, we performed simulations to assess the actual differences in the oxygen saturation of cerebral blood flow due to structural anomalies in CHD while excluding other factors that might affect the fetal cerebral circulation. We found the cerebral blood flow rate to be decreased in HLHS, and the main cause was strongly suggested to be retrograde cerebral perfusion through a PDA. These results provide important information about the neurodevelopmental prognosis in HLHS fetuses and simultaneously suggest the need to identify strategies to resolve this unfavorable cerebral circulatory state in utero. Also, future studies linking a mathematical simulation with more sophisticated blood flow modeling with fetal magnetic resonance imaging are needed to further improve our understanding and management of fetal circulation with CHD.

References

1. Barbu D, Mert I, Kruger M, Bahado-Singh RO (2009) Evidence of fetal central nervous system injury in isolated congenital heart defects: microcephaly at birth. Am J Obstet Gynecol 201(43):e1–e7
2. Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, Barnes PD, Holmes GL, Hickey PR, Strand RD et al (1995) Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 332:549–555
3. Berg C, Gembruch O, Gembruch U, Geipel A (2009) Doppler indices of the middle cerebral artery in fetuses with cardiac defects theoretically associated with impaired cerebral oxygen delivery in utero: is there a brain-sparing effect? Ultrasound Obstet Gynecol 34:666–672
4. Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, Cetta F, Falkensammer CB, Huhta JC, Kleinman CS (2003) Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. Pediatr Cardiol 24:436–443
5. Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A (1992) Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstetr Gynecol 79:416–420
6. Johnston MV (2007) Congenital heart disease and brain injury. N Engl J Med 357:1971–1973
7. Jouannic JM, Benachi A, Bonnet D, Fermont L, Le Bidois J, Dumez Y, Dommergues M (2002) Middle cerebral artery Doppler in fetuses with transposition of the great arteries. Ultrasound Obstet Gynecol 20:122–124

8. Kaltman JR, Di H, Tian Z, Rychik J (2005) Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. Ultrasound Obstet Gynecol 25:32–36
9. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, Vossough A (2009) Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg 137:529–536; discussion 536–527
10. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C (1999) Neurologic status of newborns with congenital heart defects before open heart surgery. Pediatrics 103:402–408
11. Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C, Darwish HZ (2002) Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. J Pediatr 141:51–58
12. Maeno YV, Kamenir SA, Sinclair B, van der Velde ME, Smallhorn JF, Hornberger LK (1999) Prenatal features of ductus arteriosus constriction and restrictive foramen ovale in d-transposition of the great arteries. Circulation 99:1209–1214
13. Manzar S, Nair AK, Pai MG, Al-Khusaiby SM (2005) Head size at birth in neonates with transposition of great arteries and hypoplastic left heart syndrome. Saudi Med J 26:453–456
14. Massaro AN, El-Dib M, Glass P, Aly H (2008) Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease. Brain Dev 30:437–446
15. Meise C, Germer U, Gembruch U (2001) Arterial Doppler ultrasound in 115 second- and third-trimester fetuses with congenital heart disease. Ultrasound Obstet Gynecol 17:398–402
16. Rosenthal GL (1996) Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. Am J Epidemiol 143:505–513
17. Rudolph AM (1985) Distribution and regulation of blood flow in the fetal and neonatal lamb. Circ Res 57:811–821
18. Rudolph AM (2007) Aortopulmonary transposition in the fetus: speculation on pathophysiology and therapy. Pediatr Res 61:375–380
19. Rudolph AM, Heymann MA (1967) The circulation of the fetus in utero: methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ Res 21:163–184
20. Saiki H, Kurishima C, Masutani S, Tamura M, Senzaki H (2013) Impaired cerebral perfusion after bilateral pulmonary arterial banding in patients with hypoplastic left heart syndrome. Ann Thor Surg 96:1382–1388
21. Shillingford AJ, Ittenbach RF, Marino BS, Rychik J, Clancy RR, Spray TL, Gaynor JW, Wernovsky G (2007) Aortic morphometry and microcephaly in hypoplastic left heart syndrome. Cardiol Young 17:189–195
22. van Houten JP, Rothman A, Bejar R (1996) High incidence of cranial ultrasound abnormalities in full-term infants with congenital heart disease. Am J Perinatol 13:47–53