Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion

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Objectives: Neurologic deficits are common after the Norwood procedure for hypoplastic left heart syndrome. Because of the association of deep hypothermic circulatory arrest with adverse neurologic outcome, regional low-flow cerebral perfusion has been used to limit the period of intraoperative brain ischemia. To evaluate the effect of this technique on brain ischemia, we performed serial brain magnetic resonance imaging in a cohort of infants before and after the Norwood operation using regional cerebral perfusion.

Methods: Twenty-two term neonates with hypoplastic left heart syndrome were studied with brain magnetic resonance imaging before and at a median of 9.5 days after the Norwood operation. Results were compared with preoperative, intraoperative, and postoperative risk factors to identify predictors of neurologic injury.

Results: Preoperative magnetic resonance imaging (n = 22) demonstrated ischemic lesions in 23% of patients. Postoperative magnetic resonance imaging (n = 15) demonstrated new or worsened ischemic lesions in 73% of patients, with periventricular leukomalacia and focal ischemic lesions occurring most commonly. Prolonged low postoperative cerebral oximetry (<45% for >180 minutes) was associated with the development of new or worsened ischemia on postoperative magnetic resonance imaging ($P = .029$).

Conclusions: Ischemic lesions occur commonly in neonates with hypoplastic left heart syndrome before surgical intervention. Despite the adoption of regional cerebral perfusion, postoperative cerebral ischemic lesions are frequent, occurring in the majority of infants after the Norwood operation. Long-term follow-up is necessary to assess the functional effect of these lesions.

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Neurologic and developmental abnormalities are common in children with hypoplastic left heart syndrome (HLHS) after the Norwood procedure.[1-5] Although the cause of brain injury in these infants is likely multifactorial, with contributions from preoperative, intraoperative and postoperative events, the use of deep hypothermic circulatory arrest (DHCA) appears to play a role in poor neurologic and developmental outcome.[6-10] Ischemic brain lesions have been documented on pathologic brain specimens[11] and on magnetic resonance imaging (MRI)[12] in neonates after surgical palliation with DHCA.

Because of these concerns, many centers have adopted the technique of regional low-flow cerebral perfusion (RLFP) during aortic arch reconstruction in lieu of DHCA. RLFP decreases the period of cerebral ischemia by limiting decreases in cerebral blood volume and oxygen saturation.[13] Although RLFP has been associated with better neurologic outcome in animal models,[14] such studies have not been performed in human subjects. In the present study we compare preoperative and postoperative brain MRI

Abbreviations and Acronyms

BT = Blalock-Taussig
CHD = congenital heart disease
CICU = cardiac intensive care unit
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
EEG = electroencephalography
HLHS = hypoplastic left heart syndrome
MRI = magnetic resonance imaging
NIRS = near-infrared spectroscopy
PVL = periventricular leukomalacia
RFLP = regional low-flow cerebral perfusion
rSO_2 = regional cerebral oxygen saturation
Sao_2 = arterial oxygen saturation
Svo_2 = venous oxygen saturation

findings in neonates undergoing the Norwood procedure with RLFP.

Methods

With institutional review board approval and informed consent, all infants with HLHS or its variants admitted to the cardiac intensive care unit (CICU) at Cincinnati Children's Hospital Medical Center between September 2003 and March 2005 were evaluated for study inclusion. Inclusion criteria included term gestational age ($\geq$36 weeks) and an intention to undergo surgical intervention (Norwood operation with aortic arch reconstruction) with RLFP. Infants were excluded if they had (1) a history of birth asphyxia (5-minute Apgar score $<$5), (2) a genetic anomaly associated with neurodevelopmental abnormalities, or (3) preoperative cardiac arrest.

MRI scans of the brain were performed preoperatively (day of the operation) and in the early postoperative period. The scans were performed on a Signa LX 1.5-T scanner (GE Medical, Milwaukee, Wis). The following sequences were performed: (1) sagittal T1-weighted spin-echo images, (2) axial T1-weighted inversion-recovery images, (3) axial and coronal T2-weighted fast spin-echo images, (4) axial diffusion-weighted images, and (5) short echo proton magnetic resonance spectroscopy in the basal ganglia. All MRI scans were reviewed by a single neuroradiologist blinded to the subjects' clinical status. MRI scans were reviewed for congenital and acquired lesions, including general or focal atrophy, periventricular leukomalacia (PVL), cerebral edema, delayed myelination, intraparenchymal hemorrhage, intraventricular hemorrhage, and infarction. All lesions were classified as mild, moderate, or severe. PVL, infarction, and intraparenchymal hemorrhage were considered to represent ischemia.

Clinical Management

Preoperative clinical management was provided in the CICU. Infants were maintained on a continuous prostaglandin infusion. Pulmonary overcirculation was managed with administration of subambient oxygen (fraction of inspired oxygen, 0.17-0.20) or addition of inhaled CO_2. Inotropic medication was administered at the discretion of the attending physician. As an assessment of overall status, a preoperative inotropic score was calculated as the sum of all inotrope doses, correcting for potency.[15,16] Preoperative neurologic evaluation included electroencephalography (EEG) and examination by a pediatric neurologist directed at level of consciousness, motor tone, response to stimuli, and deep tendon reflexes. Regional cerebral oxygen saturation (rSo_2) was monitored continuously by using near-infrared spectroscopy (NIRS; Somanetics INVOS 5100A, Troy, Mich), with the probe placed on the right side of the patient's forehead. Monitoring commenced 12 hours before the operation. Data were recorded at 1-minute intervals. An rSo_2 value of less than 45% was considered to represent cerebral desaturation. Cumulative time spent with rSo_2 values of less than 45% was recorded. Management was not altered on the basis of cerebral oximetry readings.

For the preoperative MRI, anesthesia was induced with fentanyl (5 μg/kg), midazolam (0.1 mg/kg), and vecuronium (0.2 mg/kg). In patients not already mechanically ventilated, nasotracheal intubation was performed. Patients were monitored during the MRI with continuous pulse oximetry, capnography, electrocardiography, and blood pressure measurements. After the MRI, patients were transported to the operating suite for cardiac surgery. Surgical repair consisted of aortic arch reconstruction, ascending aorta–to–pulmonary artery anastomosis, and creation of an unrestrictive atrial septal communication. Pulmonary blood flow was provided by either a systemic–to–pulmonary artery shunt or a right ventricle–to–pulmonary artery conduit.

Cardiopulmonary bypass (CPB) and surgical management followed our usual institutional practice. Whole blood was added to the primer to yield a goal hematocrit value of 28% to 30% during CPB. Arterial blood gas-pH management followed the alpha-stat strategy on CPB initiation, with switch to pH-stat strategy during cooling. The alpha-stat strategy was resumed during rewarming. All patients were cooled to deep hypothermia (18°C). During reconstruction of the aortic arch, continuous RLFP was provided through the innominate shunt at 30 $mL \cdot kg^{-1} \cdot min^{-1}$. Before separation from CPB, patients received a loading dose of milrinone (37.5 μg/kg). Dopamine and epinephrine infusions were instituted and titrated to achieve adequate blood pressure and systemic vascular resistance.

Postoperative management was provided in the CICU. Inotropic medication was adjusted at the discretion of the attending physician. Sodium nitroprusside was added as tolerated for afterload reduction and to improve cardiac output. Management targets included mean arterial pressure of 45 mm Hg or greater, mixed venous oxygen saturation (Svo_2) of 50% or greater, arterial oxygen saturation (Sao_2) of 70% or greater, and a hematocrit value of greater than 40%. Blood for Svo_2 measurement was sampled from a catheter placed intraoperatively in the superior vena cava. Svo_2 was measured on admission and every 4 hours. Cerebral rSo_2 monitoring continued for 48 hours after the operation. Postoperative inotrope scores were calculated every 6 hours.

The postoperative MRI was performed when the patients were deemed suitable for transport, generally between 5 and 14 days after the operation. Sedation was provided with oral pentobarbital (5 mg/kg) in spontaneously breathing patients and with inhaled anesthesia in intubated patients. Patients were monitored in similar fashion as the preoperative scan. Postoperative EEG and neuro-

TABLE 1. Patient demographics and cardiac diagnoses

Cohort size	22
Gender	
Male	15
Female	7
Race	
African American	3
White	19
Cardiac diagnoses	
HLHS	18
DORV/mitral atresia/aortic arch hypoplasia	1
Heterotaxy/DILV/aortic arch hypoplasia	1
TA/TGA/aortic arch hypoplasia	1
DORV/LV hypoplasia/aortic arch hypoplasia	1
Birth weight (kg)	2.94 (2.1–3.96)
Birth head circumference (cm)	33.5 (32.5–37.0)
Gestational age (wk)	39 (36–41)
Size for gestational age	
AGA	21
SGA	1
Apgar score, 5 min	9 (8–9)

Values are expressed as medians and ranges where appropriate. *HLHS*, Hypoplastic left heart syndrome; *DORV*, double-outlet right ventricle; *DILV*, double-inlet left ventricle; *TA*, tricuspid atresia; *TGA*, transposition of the great arteries; *LV*, left ventricle; *AGA*, appropriate for gestational age; *SGA*, small for gestational age.

logic examination by a pediatric neurologist were performed when the patient was no longer receiving sedation.

Data Collection and Statistical Analysis

Primary outcome measures were (1) ischemia on preoperative MRI and (2) development of new or worsened parenchymal lesions on postoperative MRI when compared with the preoperative study. Data collected preoperatively included patient demographics, birth history, Apgar scores, birth weight and head circumference, indirect measures of cardiac output (acid-base status [pH and base deficit], serum lactate level, mean arterial pressure, and Sao_2], inotropic score, and rSo_2 value. Operative events (including type of shunt placed for pulmonary blood flow and duration of CPB, RLFP, and DHCA) and intraoperative variables (acid-base status, serum lactate level, hematocrit value, and rSo_2 value) were included in the analysis. Postoperative variables analyzed included acid-base status (pH and base deficit), lactate level, mean arterial pressure, diastolic arterial pressure, urine output, inotropic scores, Sao_2, Svo_2, and rSo_2 value. Cerebral desaturation was assessed both as a continuous variable (cumulative minutes with rSO_2 $<45\%$) and a categoric variable (>180 or <180 cumulative minutes of cerebral desaturation).

Distributions of variables were examined for normality, and appropriate adjustments were done, either by using variance stabilizing transformations or nonparametric analyses when necessary. Associations between the outcome variables and various risk factors were analyzed with Fisher exact tests for categoric outcome and risk factor variables, Student *t* tests and logistic regression for binary outcomes, and linear regression for continuous variables.

TABLE 2. Patient preoperative variables

Variable	Mean ± SD	Median	Range
Preoperative inotrope score	3.6 ± 4.0	5	0–15
Preoperative hematocrit (%)	41.6 ± 3.7	41.0	33.4–48.2
Average preoperative Sao_2 (%)	89.4 ± 6.3	90.3	88.5–94.0
Average preoperative rSo_2 (%)	60.7 ± 8.2	59.0	44–79
Lowest preoperative pH	7.31 ± 0.06	7.30	7.20–7.43
Largest preoperative base deficit	4.2 ± 1.9	4	1–7.5
Highest serum lactate (mmol/L)	2.9 ± 1.2	2.7	1.0–5.6

SD, Standard deviation; Sao_2, arterial oxygen saturation; rSo_2, regional cerebral oxygen saturation.

Analysis was performed with SAS statistical software (SAS Institute, Cary, NC).

Results

Twenty-two of 30 eligible neonates were enrolled. Table 1 details patient demographic information. All infants were of term gestation and had normal 5-minute Apgar scores. One infant was small for gestational age. All infants had normal head circumference (between the 5th and 95th percentiles). The male predominance (68%) in our study is compatible with a known higher occurrence of HLHS in male subjects.[17] Prenatal diagnosis of congenital heart disease (CHD) had been made in 17 (77%) of the 22 patients.

Table 2 summarizes patient preoperative status. Subambient oxygen (fraction of inspired oxygen, 0.17-0.20) was used to manage preoperative pulmonary overcirculation in 12 of the 22 patients. One patient received inhaled CO_2. Nine of the 22 patients were mechanically ventilated before the day of the operation. Twelve patients received inotropic medication before the operation; 11 of the 12 received a single inotropic medication, and 1 received 2 inotropic medications. Average inotrope score before the operation was 3.6 ± 4.0. Average preoperative rSo_2 value was 60.7% ± 8.2%, and average preoperative Sao_2 value was 89.4% ± 6.3%. Significant low cardiac output was not observed in any patient before the operation.

Patients underwent the Norwood procedure at a median age of 4 days (range, 1-8 days). The procedure was accomplished with a brief period of DHCA followed by RLFP in 21 of the 22 patients. In 1 patient surgical intervention was accomplished with DHCA alone (rather than RLFP) because of complex strap vessel anatomy (cervical aortic arch with aberrant right subclavian artery and small right carotid artery). This patient was subsequently excluded from postoperative results and analysis. In the 21 patients with RLFP, mean duration of CPB was 186.4 ± 46.5 minutes, mean duration of DHCA was 5.5 ± 5.7 minutes, and mean duration of RLFP was 83.4 ± 15.2 minutes. Fifteen of the 21 patients had a modified Blalock-Taussig (BT) shunt (3.0-3.5 mm) placed, and 6 of the 21 patients had a 5-mm right ventricle–to–pulmonary artery conduit performed.

TABLE 3. Summary of preoperative studies

Patient no.	Preoperative neurologic examination	Preoperative EEG	Preoperative MRI	Preoperative MRS	Preoperative rSo_2 <45% (min)
1	Normal	ND	No ischemia; ↑ T1 basal ganglia-thalamus	Normal	0
2	ND	ND	No ischemia; ↑ T1 basal ganglia-thalamus	ND	0
3	ND	Normal	No ischemia	ND	0
4	↓ LOC	Normal	No ischemia; small extra-axial hemorrhage occipital lobes	Normal	0
5	↓ LOC	Normal	No ischemia; ↑ T1 basal ganglia-thalamus	Normal	0
6	↓ LOC	ND	No ischemia	Normal	0
7	Normal	Normal	No ischemia	Normal	0
8	Normal	Normal	No ischemia	Normal	0
9	ND	ND	No ischemia	Normal	0
10	↓ LOC	Normal	No ischemia	Normal	101
11	↓ LOC	Normal	No ischemia; ↑ T1 basal ganglia-thalamus	Normal	23
12	Normal	Normal	No ischemia	Normal	0
13	Normal	ND	No ischemia	Normal	392
14	ND	ND	No ischemia	Normal	18
15	Normal	Abnormal	No ischemia; ↑ T1 basal ganglia-thalamus	Normal	0
16	Normal	Abnormal	Small ischemic lesion L-frontal lobe	Normal	0
17	Normal	Normal	Small ischemic lesion R-frontal lobe; ↑ T1 basal ganglia-thalamus	Normal	0
18	Normal	Normal	No ischemia	Normal	0
19	Normal	Normal	Mild PVL	Normal	0
20	Normal	ND	Small ischemic lesion L-frontal lobe; small extra-axial hemorrhage posterior fossa; ↑ T1 basal ganglia-thalamus	Normal	0
21	↑ Muscle tone	Abnormal	Small ischemic lesion L-frontal lobe; ↑ T1 basal ganglia-thalamus	Normal	0
22	ND	No ischemia	Normal	Normal	0

EEG, Electroencephalography; *MRI*, magnetic resonance imaging; *MRS*, magnetic resonance spectroscopy; *rSO_2*, regional cerebral oxygen saturation; *ND*, not done; ↑ *T1 basal ganglia-thalamus*, increased T1 signal in basal ganglia and thalamus of unclear significance; *LOC*, level of consciousness; *PVL*, periventricular leukomalacia.

Neurologic Evaluation and MRI Results

Preoperative studies. Table 3 summarizes preoperative results. Preoperative neurologic examination was performed in 17 of the 22 patients. Eleven patients had normal examination result, 5 patients had diminished level of consciousness caused by sedative medications but had otherwise normal examination results, and 1 patient had increased muscle tone. Of the 15 patients with preoperative EEG, 12 (80%) had normal EEG pattern, and 3 (20%) had mild diffuse slowing. These 3 patients had all had normal neurologic examination results and were not receiving sedative medication. No seizures were observed clinically or by means of EEG before the operation. Preoperative MRI was performed on the day of the operation in all 22 patients. No congenital structural abnormalities were identified in any patient. Ischemic lesions were seen in 5 (23%) of 22 patients. One infant had multifocal diffusion abnormalities in the parietal white matter consistent with mild PVL, 1 had focal infarction in the right frontal lobe, and 3 had focal ischemic lesions in the left frontal lobe. Extra-axial hemorrhage was identified in 2 patients who had bilateral small hemorrhagic collections in the posterior cerebral and occipital regions. In 8 (36%) of the 22 patients, 5 of whom had otherwise normal studies, mild increases in T1 signal of unclear significance occurred in the basal ganglia–thalamic region. Ten patients had completely normal study results. Magnetic resonance spectroscopy was performed in 20 of the 22 patients, including the 5 with ischemic lesions, and demonstrated normal pattern without lactate increase in all patients.

Cerebral oximetry was performed in all 22 patients for 12 hours before the operation. In 18 of the 22 patients, rSo_2 values remained greater than 45% throughout the preoperative monitoring period. Two patients spent more than 60 cumulative minutes with rSo_2 values of less than 45%. Both of these patients had normal preoperative MRI results but died in the early postoperative period and did not have follow-up MRI studies performed.

TABLE 4. Summary of postoperative studies

Patient no.	Type of shunt	Postoperative neurologic examination	Postoperative EEG	Postoperative MRI	Postoperative MRS	Postoperative rSo_2 <45% (min)
1	BTS	Normal; clinical seizures	Abnormal (seizures)	Moderate PVL; moderate extra-axial blood; mild IVH	↑ Lactate	224
2	RV-PA	↑ DTR	Normal	Mild atrophy; no ischemia	Normal	58
3	BTS	Normal	Normal	Small hemorrhagic-ischemic lesion R-frontal lobe	Normal	298
4*	RV-PA	Normal	Normal	Excluded	Normal	1163
5	BTS	Normal	Normal	Small hemorrhagic-ischemic lesion R-frontal lobe; mild atrophy	Normal	13
6	BTS	↑ DTR	Normal	Mild PVL; mild extra-axial blood; mild IVH	Normal	359
7	BTS	Normal	Normal	Normal	Normal	170
8	BTS	Normal	Normal	ND (pacemaker)	ND	385
9	RV-PA	ND	ND	ND (early death)	ND	562
10	BTS	ND	ND	ND (early death)	ND	ND
11	BTS	Normal	Normal	Mild PVL	Normal	222
12	BTS	Normal	Normal	Mild atrophy; mild IVH; no ischemia	Normal	325
13	BTS	ND	ND	ND (early death)	ND	894
14	BTS	ND	ND	ND (early death)	ND	ND
15	BTS	Normal	Normal	Normal	Normal	56
16	RV-PA	Normal	Normal	Mild PVL; small ischemic lesion L-frontal lobe; mild IVH	Normal	367
17	RV-PA	Normal	Normal	Moderate PVL; moderate hemorrhagic-ischemic lesion L-frontal lobe; mild IVH; mild extra-axial blood	↑ Lactate	537
18	RV-PA	Normal	Normal	Mild PVL; mild IVH	Normal	458
19	BTS	Normal	Normal	Moderate PVL; small R-cerebellar infarction; mild IVH	Normal	0
20	BTS	Normal	Normal	Mild PVL; small ischemic lesion L-frontal lobe; mild extra-axial blood	Normal	749
21	BTS	↑ DTR; ↑ muscle tone; clinical seizures	Abnormal (seizures)	Moderate L-frontal hemorrhagic-ischemic lesion; large L-subdural hemorrhage	↑ Lactate	228
22	BTS	ND	ND	ND (early death)	ND	27

EEG, Electroencephalography; *MRI*, magnetic resonance imaging; *MRS*, magnetic resonance spectroscopy; *rSO_2*, regional cerebral oxygen saturation; *BTS*, Blalock-Taussig shunt; *PVL*, periventricular leukomalacia; *IVH*, intraventricular hemorrhage; *RV-PA*, right ventricle–to–pulmonary artery conduit; *DTR*, deep tendon reflexes; *ND*, not done. *Surgical intervention performed with deep hypothermic circulatory arrest; patient excluded from magnetic resonance imaging results and risk factor analysis.

Postoperative studies. Table 4 summarizes postoperative study results. Of the 21 patients who underwent surgical intervention with RLFP, postoperative MRI was performed in 15 patients. Five patients died early after the operation, and MRI was deferred in 1 patient because of the need for cardiac pacing. The median duration between surgical intervention and postoperative MRI was 9.5 days (range, 4-112 days). Two patients had follow-up MRI performed more than 3 weeks after the operation because of clinical instability.

Postoperative neurologic examination was performed in 17 of the 22 patients. One patient (with significant ischemia and subdural hemorrhage on MRI) demonstrated increased tone and deep tendon reflexes, and 2 patients (1 with mild PVL on MRI and 1 with normal MRI results) had increased deep tendon reflexes. The results of all other examinations were considered normal. Postoperative EEG was performed in 17 patients; 15 of the patients had normal results. Two patients (both with clinical seizures and with ischemia on postoperative MRI) had focal seizures on EEG. Clinical seizures were not observed in any other patient.

New or worsened ischemic lesions were observed in 11 (73%) of 15 patients. These lesions included PVL in 7 (47%) patients and focal ischemic or hemorrhagic-ischemic

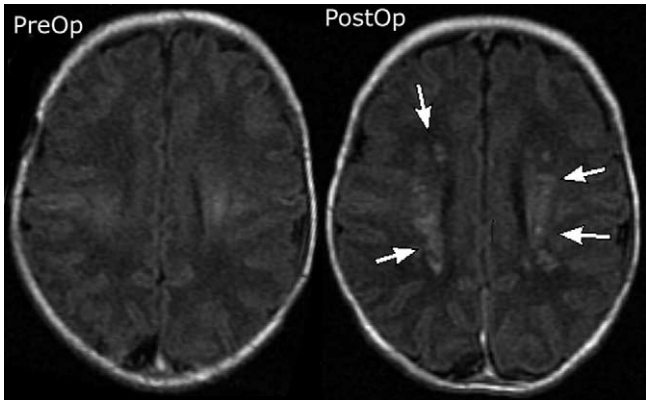

Figure 1. Axial T1 inversion recovery images on a patient before *(left)* and 7 days after *(right)* surgical intervention. The preoperative MRI result was normal. This infant had multiple foci of hemorrhagic staining within the periventricular white matter *(arrows)* characteristic of ischemia from hypoperfusion.

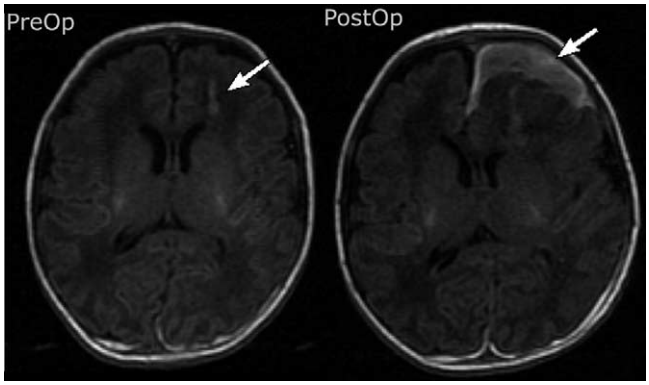

Figure 2. Axial T1 inversion recovery images on a patient before *(left)* and 4 days after *(right)* surgical intervention. The preoperative scan demonstrates increased signal intensity in the left frontal lobe *(arrow)* consistent with a small focal area of hemorrhage. There are also small bilateral extra-axial subdural blood collections in the occipital regions. The postoperative scan demonstrates signal abnormalities consistent with new ischemia in the left frontal lobe and a large left frontal subdural-subarchnoid hemorrhage with mass effect *(arrow)*. The extra-axial fluid collections have not changed.

lesions in 8 (53%) patients. The PVL occurred primarily in the frontoparietal region and occurred bilaterally in 6 of the 7 patients (Figure 1). All patients with preoperative ischemia had new or worsened lesions on postoperative study. Mild extra-axial (subdural or choroid plexus) or intraventricular hemorrhage not requiring intervention was observed in 7 (47%) patients. One patient had significant hemorrhage into an area of ischemia in the left frontal area (seen preoperatively), which was surgically drained (Figure 2). Magnetic resonance spectroscopy demonstrated lactate increase in 3 of the 15 patients, all with ischemic lesions on MRI. Eight (73%) of 11 patients with conventional BT shunts and 3 (75%) of 4 patients with right ventricle–to–pulmonary artery conduits had new or worsened ischemia on postoperative MRI.

Postoperative cerebral oximetry was performed on 20 of the total cohort of patients and in all of the 15 patients with postoperative MRI studies. Two patients died before postoperative monitoring. Ten of the 15 patients with MRI studies and 14 of the 20 patients monitored had prolonged (>180 cumulative minutes) cerebral desaturation (rSO_2 <45%) in the postoperative period. Nine of the 16 patients with modified BT shunts and 5 of the 6 patients with right ventricle–to–pulmonary artery conduits had prolonged cerebral desaturation.

Risk Factor Analysis

Analysis of preoperative variables demonstrated a significantly higher peak preoperative base deficit in patients with ischemic lesions on preoperative MRI compared with those not showing ischemic lesions on preoperative MRI (P = .024). No other preoperative variables, including other indirect measures of cardiac output, were associated with preoperative ischemia.

Analysis of risk factors for the presence of new or worsened area of ischemia on postoperative MRI demonstrated a significant association between prolonged postoperative low rSo_2 values (>180 cumulative minutes with an rSo_2 <45%) and the development of MRI lesions (P = .029, Fisher exact test). Sensitivity and specificity were calculated at 82% and 75%, respectively, with a positive predictive value of 90% and a negative predictive value of 60%. The nadir of rSo_2, indirect measures of cardiac output (eg, Svo_2), and inotrope scores in the postoperative period were not related to the development of lesions. Similarly, intraoperative variables, including type of pulmonary blood flow (BT shunt or right ventricle–to–pulmonary artery conduit) and durations of CPB and RLFP, did not relate to the development of MRI ischemic lesions. Patients with evidence of preoperative ischemia were more likely to have new postoperative ischemia (P = .08), but this did not reach statistical significance.

Discussion

Preoperative Findings

This study confirms that MRI abnormalities are common in infants with HLHS before surgical intervention. Despite normal clinical examination and EEG, 23% of infants had evidence of ischemic lesions on MRI, primarily in the form of PVL or focal infarction. This incidence is similar to that seen in other CHD populations.[12,18]

Risk factors for preoperative ischemia have not been well defined. In our study, although peak preoperative base deficit, one indicator of tissue perfusion, was associated with the presence of preoperative ischemia, other postnatal clinical indicators of overall cardiac output (eg, pH and serum lactate) were not associated with lesions on preoperative MRI. Our study also demonstrates that preoperative rSo_2 is not associated with preoperative MRI ischemic lesions. A possible explanation for this finding is that cerebral ischemia occurred before the time period of NIRS monitoring, either in utero or after birth but before the monitoring period. Although our NIRS monitoring did not encompass the entire preoperative time period, no patient had a significant change in hemodynamics or Sao_2 values during the preoperative period, and therefore the measurements obtained during our monitoring period are likely to be representative of the entire preoperative state. Nevertheless, because rSo_2 measurements are being performed in a small (regional) area of the brain, they might not be a global representation of cerebral perfusion or might miss areas of regional ischemia and could therefore be falsely reassuring. A recent study found that low cerebral blood flow is common in patients with CHD and is associated with MRI findings of PVL.[18] There is also evidence that ischemia might occur in these infants in utero. Abnormalities in cerebral vascular blood flow dynamics have been found in fetuses with HLHS, similar to those seen with other forms of fetal hypoxia.[19,20]

In contrast to a previous study[21] that demonstrated very low preoperative cerebral rSo_2 values in patients with HLHS, we found cerebral desaturation to be relatively uncommon in our preoperative patients, with only 4 of the 22 patients having any preoperative rSo_2 values of less than 45% and only 2 with more than 30 minutes at an rSo_2 value of less than 45%. Interestingly, all 4 of these patients had normal preoperative MRI results.

Postoperative Findings

Despite modification in surgical technique with RLFP, new or worsened ischemic brain lesions occurred in the majority (73%) of our patients after the Norwood procedure in a similar incidence to that seen with DHCA.[12] Prolonged low rSo_2 values (>180 minutes with $rSo_2 \leq 45\%$) were associated with the presence of lesions on postoperative MRI. Intraoperative factors, such as CPB and RLFP time, were not associated with MRI lesions nor were indirect measures of overall cardiac output, such as Svo_2 value, serum lactate level, or acid-base status. These data are interesting for 2 reasons. First, they suggest that the postoperative rather than intraoperative period might now be the critical period during which neurologic injury occurs or progresses. Second, they suggest that the usual clinical measurements followed in the CICU to assess global cardiac output might not reflect cerebral perfusion, particularly in the early postoperative period, perhaps as a result of loss of cerebral autoregulation.

The modification of the Norwood procedure to adopt the use of RLFP has been made in many centers to avoid longer periods of DHCA. The association of longer periods of DHCA with impaired neurologic outcome has been well documented,[1,7,8,22,23] but until recently, DHCA has been believed to be a necessary component of arch reconstruction. RLFP limits the period of cerebral ischemia, improves cerebral oxygenation, and has been shown to be associated with better neurologic outcome in piglets.[14] It is unknown, however, whether RLFP is associated with better neurologic outcome after the Norwood procedure. Our study demonstrates that ischemic lesions on MRI are no less frequent in patients who have had operations with RLFP versus those who underwent operations with DHCA.[12] Hoffman and colleagues[24] have noted that although RLFP provides consistent brain perfusion associated with high rSo_2 values, cerebral desaturation occurs rapidly on removal from CPB. Furthermore, they noted that cerebral rSo_2 values decreased to much lower levels after CPB than somatic rSo_2 values (measured in the splanchnic bed), suggesting that cerebral vascular resistance is higher than somatic resistance in this time period. We noted an identical rapid decrease in cerebral rSo_2 values in our patients after separation from CPB, which persisted in the early postoperative period.

Animal models of cerebral hypoxia-ischemia have demonstrated an association between low rSo_2 values and neuronal dysfunction, cell death, and poor neurologic outcome. In a piglet model of graded hypoxia-ischemia to determine thresholds for neurologic injury, brain tissue lactate accumulation began when rSo_2 values decreased to less than 45%.[25] Our findings suggest that the rSo_2 threshold for neuronal injury is similar in neonates and that maneuvers to improve cerebral perfusion during the postoperative period might lessen the incidence of postoperative ischemia. There are both animal and human data associating low rSo_2 values and neurologic outcome.[26,27]

The clinical relevance of our MRI findings is unknown. In the preterm neonate, however, MRI findings of PVL have been associated with long-term neurocognitive impairment, including visuospatial and visuomotor abnormalities, attention deficit disorders, and developmental delay.[28,29] Given the frequency of neurodevelopmental abnormalities in patients with HLHS, it seems likely that these lesions are clinically relevant as well.

Limitations

A limitation of this study is that neurodevelopmental evaluation of these children is not yet available. Although an association between MRI findings and neurodevelopmental outcome has been established in preterm infants, this association has not yet been found for infants with CHD. A

second limitation is the timing of the postoperative MRI, which was performed at a median of 9.5 days after surgical intervention. Although the patients were not clinically suitable for transport and MRI scanning until this time, we cannot definitively pinpoint the timing of the ischemia (operative vs postoperative). Third, our patients had just one postoperative MRI scan. In one study resolution of MRI lesions occurred on later MRI in some patients,[12] making clinical follow-up even more crucial. Lastly, we used previous studies in which DHCA was used for the Norwood procedure as a comparison group for our patients rather than a control DHCA group within our own institution, and therefore we cannot eliminate the possibility of institutional differences accounting for some of our findings.

Conclusions

MRI ischemic lesions occur in approximately 25% of infants with HLHS before surgical palliation. In addition, despite the use of RLFP during the Norwood operation, new or worsened MRI ischemic lesions occurred in 73% of infants after surgical intervention. Prolonged low postoperative rSo_2 values ($<45\%$) are associated with the development of ischemic lesions.

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