Temporal and Anatomic Risk Profile of Brain Injury With Neonatal Repair of Congenital Heart Defects

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Background and Purpose—Brain injury is common in newborns with congenital heart disease (CHD) requiring neonatal surgery. The purpose of this study is to define the risk factors for preoperative and postoperative brain injuries and their association with functional cardiac anatomic groups.

Methods—Sixty-two neonates with CHD were studied with preoperative MRI, and 53 received postoperative scans. Clinical and therapeutic characteristics were compared in newborns with and without newly acquired brain injuries. A subset of 16 consecutive patients was monitored with intraoperative cerebral near-infrared spectroscopy.

Results—Brain injury was observed in 56% of patients. Preoperative brain injury, seen in 39%, was most commonly stroke and was associated with balloon atrial septostomy (P=0.002). Postoperative brain injury, seen in 35%, was most commonly white matter injury and was particularly common in neonates with single-ventricle physiology and aortic arch obstruction (P=0.001). Risk factors associated with acquired postoperative brain injury included cardiopulmonary bypass (CPB) with regional cerebral perfusion (P=0.01) and lower intraoperative cerebral hemoglobin oxygen saturation during the myocardial ischemic period of CPB (P=0.008). In a multivariable model, new postoperative white matter injury was specifically associated with low mean blood pressure during the first postoperative day (P=0.04).

Conclusions—Specific modifiable risk factors can be identified for preoperative and postoperative white matter injury and stroke associated with neonatal surgery for CHD. The high incidence of postoperative injury observed despite new methodologies of CPB indicates the need for ongoing evaluation to optimize neurological outcome. (Stroke. 2007; 38[part 2]:736-741.)

Key Words: heart defects, congenital ■ magnetic resonance imaging ■ stroke ■ white matter injury

Congenital heart disease (CHD) is the most common birth defect, with moderate or severe forms occurring in 6 of 1000 live births.¹ Advances in cardiopulmonary bypass (CPB), surgical technique, and intensive care have lowered hospital mortality for most neonatal procedures to <3%.² Improvements in survival have stimulated an increasing focus on morbidity, especially neurological, which remains high. Depending on the severity of the lesion, the incidence of neurodevelopmental impairment may approach 70%, and the etiology is multifactorial.¹ Seminal studies of CPB established the association of deep hypothermic circulatory arrest with adverse early neurological events including postoperative seizures³ and later neurodevelopmental outcomes. Moreover, with repeated assessment of this cohort to school age, both the nature and severity of neurodevelopmental deficits evolved.⁴ As such, the rapid progression of clinical care may outpace the ability to accurately evaluate the neurological consequence of novel intervention strategies. In particular, new promising techniques may be adopted in advance of full assessment of the effects on neurological outcome. An example is regional cerebral perfusion (RCP) during CPB, a widely used technique to avoid circulatory arrest during aortic arch reconstruction.⁵ This highlights the need for appropriate surrogate measures of neurological well-being. Advanced MRI, applied in the perioperative period,⁷–¹¹ holds promise as one such surrogate measure.

The objectives of this prospective cohort study using serial MRI in term newborns with CHD are (1) to identify the spectrum of brain abnormalities on MRI before and after cardiac surgery and (2) to identify the clinical risk factors for these abnormalities.

Subjects and Methods

Patients

Since September 2001, of the 90 term newborns in our institution requiring surgery for CHD, 66 were enrolled (73%) in this prospective cohort study. Neonates were excluded if gestational age at birth was <36 weeks or if there was a congenital infection or genetic or

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malformation syndrome. Sixty-two of the enrolled newborns were studied with MRI before heart surgery, and 53 had repeat studies postoperatively. Four enrolled newborns were not studied preoperatively: 3 required urgent surgery, and 1 was discharged home with surgery deferred. Postoperative MRI was not acquired in 9 newborns: 4 newborns required a permanent pacemaker, and 5 newborns died. Preoperative MRI findings in the first 29 newborns with transposition of the great arteries were reported previously.10 Neonates were studied after voluntary, informed parental consent was obtained. The University of California at San Francisco Committee on Human Research approved the study protocol. Perioperative data were prospectively collected from the medical records, as reported previously (also see supplemental Methods, available online at http://stroke.ahajournals.org).

MRI Studies
Preoperatively, MR studies were performed as soon as the baby was stable enough to be safely transported to and from the MR scanner. Postoperative studies were performed after temporary pacemaker wires were removed. No adverse events occurred with this scanning protocol (see supplemental Methods). A neuroradiologist blinded to all clinical information beyond corrected gestational age and cardiac anatomic diagnosis scored each MRI scan for acquired focal, multifocal, or global changes, as reported previously.10 White matter injury (WMI) was scored as minimal (≤2 areas of abnormality, each ≤2 mm), moderate (>3 areas of abnormality or areas >2 mm), or severe (>5% of the hemisphere involved). The presence of newly acquired injury on the postoperative study was noted.

Intraoperative Cerebral
Near-Infrared Spectroscopy
Intraoperative near-infrared spectroscopy (NIRS) was recorded in a subset of 16 consecutive newborns with the use of a near-infrared spectrophotometer (NIRO-300, Hamamatsu, Japan) as described.12 Mean total oxygen index (a measure of percent hemoglobin oxygen saturation) was calculated for each bypass period.

Data Analysis
Clinical variables in neonates with and without preoperative brain injury were compared with Stata 8 (Stata Corp) with the use of the Mann-Whitney U test for continuous or ordinal data and the Fisher exact test for categorical variables. Multivariable logistic regression was used to determine the independent association of variables that were associated with acquired preoperative and postoperative brain injury on univariable analysis with P<0.1.

Results
Timing of Brain Injury in Newborns With CHD
The 62 newborns studied prospectively with MRI of the brain before and after surgery include a variety of cardiac diagnoses representing the spectrum of complex CHD requiring neonatal surgical intervention (supplemental Table I, available online at http://stroke.ahajournals.org). Transposition of the great arteries (TGA) (n=32) and hypoplastic left heart syndrome (HLHS) and variants requiring the Norwood procedure (see supplemental Methods) for surgical palliation (n=15) were the most frequent diagnoses.

Brain injury was observed on preoperative or postoperative MRI in 35 of 62 neonates (56%) (Table 1). Preoperative injury tended to be more common in patients with 2-ventricle physiology, whereas postoperative injury was significantly more frequent after the Norwood procedure for HLHS and variants (P=0.001).

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<th>Type of Injury Based on Timing</th>
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| The most common acquired injuries were noncystic WMI and stroke (Table 2 and Figure 1). On the preoperative MRI, WMI (11 of 62) was minimal in 7 infants, moderate in 3, and severe in 1. Postoperative WMI was more common (14 of 53) (Table 2) and more severe in that half of the patients had moderate (n=4) or severe (n=3) WMI. Lesions were located in both superficial and deep white matter and were variably associated with reduced diffusion. Focal stroke was more commonly observed on the preoperative study (Table 2 and Figure 1). Infarcts were evenly distributed by hemisphere and were most commonly observed in middle cerebral artery territory (n=15), although strokes also occurred in posterior (n=2) and anterior cerebral artery territory (n=1) areas. Five patients (8%) had subependymal or mild intraventricular hemorrhage (grade 2) on their preoperative studies. Subdural hemorrhage along the tentorium, without mass effect, was noted in 11 patients (18%) preoperatively, with new hemorrhage in 8 (15%) postoperatively. Despite risk factors for global hypoxic-ischemic brain injury in newborns with CHD, including cyanosis and cardiac arrest, the basal nuclei and watershed predominant patterns of injury were not observed in any newborn. However, in the preoperative study 1 newborn had delayed myelination with immature sulcation, and another had globally decreased parenchymal volume suggesting an in utero process. Developmental malformations were noted in 2 patients: venous anomaly (n=1) and bilateral germinolytic cysts (n=1).

Risk Factors for Preoperative Brain Injury
Newborns with and without brain injury were studied with MRI on similar postnatal days (median, 5 versus 5.5 days, respectively; P=0.8). Despite the broader representation of congenital heart diagnoses in the present cohort, risk factors for preoperative injury were similar to those identified in a

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<th>TABLE 2. Timing and Classification of Injury</th>
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<td>Preoperative (n=62)</td>
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<td>Postoperative (n=53)</td>
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*One newborn had both preoperative WMI and stroke.
cohort limited to TGA\textsuperscript{10} (Table 3). Specifically, the Apgar score at 5 minutes and need for balloon atrial septostomy (BAS) were significantly associated with injury on preoperative brain MRI. Neither the presence nor duration of umbilical artery or vein catheterization was associated with brain injury (all $P>0.3$). When BAS and 5-minute Apgar were placed in a multivariable logistic regression model, only BAS was significantly associated with brain injury on preoperative MRI ($\text{OR}=5.0; 95\% \ CI, 1.5$ to $16.5; P=0.01$), whereas Apgar score was not ($\text{OR}=1.0; 95\% \ CI, 0.7$ to $1.4; P=1.0$). As in our initial report, all TGA patients with stroke had undergone BAS ($11$ of $22$ requiring BAS; risk difference=$0.5; 95\% \ CI, 0.3$ to $0.7; P=0.005$). However, only $4$ of the $6$ newborns with TGA and WMI received BAS (risk difference=$0; P>0.9$).

Risk Factors for Postoperative Brain Injury
No acquired injury on preoperative MRI, including hemorrhagic lesions, was noted to be worse in the postoperative study, and the presence of preoperative brain injury did not predict new postoperative injury (Table 4). Newborns with and without brain injury had their MRI on similar postnatal days (median, $19$ versus $18.5$ days, respectively; $P=0.7$). Neither total length of support with CPB nor myocardial ischemic time (aortic clamping time) was associated with risk of postoperative injury. However, some factors were associated with injury, including lowest flow used during CPB and largest base deficit noted on arterial blood gas analysis during CPB. The majority of patients in this cohort were supported with either full-flow bypass ($n=34$) or RCP ($n=10$) during bypass, and a significant incidence of injury was observed.

Figure 1. A and B, Term newborn with TGA requiring preoperative BAS on day of life $1$, imaged $48$ hours later. On the T2-weighted image (A), a middle cerebral artery distribution infarct is seen as hyperintensity of the cortex (white arrow) in the left frontal lobe and reduced diffusivity (hypointensity, large arrowhead) on the average diffusivity ($D_{av}$) map (B). A smaller infarct is present in the right caudate (small arrowhead). C and D, Term newborn with unbalanced complete atrioventricular septal defect imaged postoperatively at day of life $18$, $7$ days after a modified Norwood procedure. A posterior cerebral artery distribution infarct is seen as cortical T2 hyperintensity (black arrows in C) and reduced diffusivity (white arrows in D) in the left medial occipital lobe. E and F, Term newborn with TGA imaged postoperatively at day of life $16$, $8$ days after an arterial switch procedure. Multiple foci of T1 hyperintensity are seen in the bilateral periventricular white matter on the coronal spoiled gradient echo sequence (E, arrows). Some foci have reduced water diffusivity on the $D_{av}$ map (F, arrow).
after RCP (8 of 10; \( P = 0.01 \), Fisher exact test). Conventional measures of postoperative illness severity, including measures of oxygen delivery and utilization, were not associated with new postoperative injury. Postoperative cardiac arrest and need for extracorporeal life support were uncommon in those with (1 newborn each) and without (2 and 3 newborns, respectively) brain injury. Of the clinical measures of low cardiac output state on postoperative day 1, decreased mean blood pressure was the strongest predictor of acquiring brain injury.

Because the intraoperative CPB variables were strongly associated with the specific CPB method, a single intraoperative variable (base deficit during CPB) was included in a multivariable model with mean blood pressure to explore the relative significance of intraoperative and postoperative risk factors. In this model, base deficit during CPB (OR \( = 0.8; 95\% \text{ CI, 0.6 to 0.98}; \ P = 0.04 \)) but not mean blood pressure (OR \( = 0.9; 95\% \text{ CI, 0.8 to 1.01}; \ P = 0.09 \)) independently predicted new postoperative injury (stroke or WMI). In light of recent reports that periventricular leukomalacia, a form of WMI, is associated with low postoperative diastolic blood pressure,\(^8\) this analysis was repeated to predict new postoperative WMI alone. In this model, new postoperative WMI was associated with lowest mean blood pressure on postoperative day 1 (OR \( = 0.9; 95\% \text{ CI, 0.6 to 1.03}; \ P = 0.04 \)), with a trend for pump base deficit (OR \( = 0.8; 95\% \text{ CI, 0.6 to 1.03}; \ P = 0.08 \)).

**Intraoperative NIRS**

The subset of 16 patients studied with NIRS, including 11 patients with TGA, 4 patients with HLHS, and 1 with aortic coarctation, was representative of the broader cohort with respect to gestational age, sex, birth weight, and frequency of preoperative injury (all \( P > 0.1 \)). Six patients, including 2 with TGA and all 4 with HLHS, developed new postoperative injury. Mean total oxygen index during aortic clamping was significantly lower in injured patients (\( P = 0.008 \), Bonferroni correction) and trended lower during the subsequent periods after clamp removal and after CPB (Figure 2).

**Discussion**

In the largest series of infants studied with MRI before and after neonatal surgical intervention reported to date, perioperative brain injury is identified in more than half of newborns with CHD. More than one third of newborns with CHD...
have brain injuries before cardiac surgery, with an additional third of newborns acquiring brain injuries during or shortly after cardiac surgery. The spectrum of brain injuries and their associated risk factors differ in the preoperative and postoperative periods. The findings of the study confirm and extend prior observations, including the high incidence of preoperative injury, the association of BAS with preoperative injury, and the high frequency of acquired WMI.

### Preoperative Brain Injury

The catheter-based intervention BAS remains the predominant risk factor for preoperative injury. Because this procedure was only applied to patients with TGA, the incidence of preoperative injury was higher for this group of patients. However, the association of BAS with preoperative brain injury in newborns with TGA is strongest for preoperative stroke. In this expanded cohort, we observe an incidence of preoperative WMI (18%) in neonates with TGA or other lesions that is similar to that reported in other series. Additional attention to preoperative WMI is needed to determine whether it relates to risk factors associated with postoperative WMI, such as hypoxemia and hypotension, because it appears to be unrelated to BAS.

### Postoperative Brain Injury

Although the overall risk of injury does not differ by cardiac anatomic classification, the risk of newly acquired postoperative injury is significantly greater for single-ventricle patients requiring the Norwood procedure and in those newborns with the greatest base deficit during CPB. With advances in the conduct of CPB and incumbent improvements in neurological morbidity, combined with evidence for both preoperative and early postoperative risks, attention has been diverted from the operative period. Assuming that some cerebral blood flow will be better than circulatory arrest, new CPB methods, including RCP, have been adopted (by us and others) in advance of detailed evaluation of associated intermediate and long-term neurological morbidity. Intraoperative monitoring with cerebral NIRS in the present study suggests the possibility of inadequate oxygen delivery during all CPB techniques and an association with newly acquired postoperative injury.

In the subset of patients monitored with NIRS, 4 of the 6 injured patients were supported with RCP. Although monitoring cerebral oxygenation with NIRS has been used to “titrate” the amount of flow during RCP, there are upper limits to how much flow can actually be achieved, based on cannulation technique and other factors. The safe or preferred range is largely empirical and is not supported with a large body of evidence. It is therefore possible that the amount of flow delivered was insufficient. An alternate hypothesis is suggested by observations of relative cerebral desaturation after CPB with RCP in another study. These authors suggested that cerebral vascular resistance was increased after bypass with RCP. In the present study, although cerebral NIRS was significantly lower during aortic clamp, after aortic clamp, and after bypass, cerebral saturation remained low in injured patients.

All 5 postoperative strokes occurred after RCP in single-ventricle patients undergoing the Norwood procedure. Imaging characteristics of the strokes suggest embolism as a possible mechanism. However, the observation of lesions in both hemispheres, despite the fact that RCP is always delivered to the right innominate artery, indicates that the etiology of these strokes is complex. After the Norwood procedure, there is complete intraventricular mixing, and postoperative embolism is a well-described risk.

Prior studies have identified low postoperative blood pressure as a significant risk factor for new injury. In the present cohort, only a trend toward lower blood pressure was observed in patients with new postoperative injury. However, this trend became significant when mean blood pressure was analyzed for association with WMI in a multivariable model with blood gas base deficit on bypass. Acquired WMI has been linked to hypoxemia and hypotension in the early postoperative period and specifically to low postoperative cerebral NIRS in newborns with HLHS. However, a prediction for WMI in these term infants is highly unusual. The typical result of global injury in a term infant is predominantly damage localized to the basal nuclei (basal ganglia and thalamus) or intervascular boundary watershed regions. WMI is more commonly observed after impaired oxygen delivery or infection in the premature infant. These patterns of brain damage are thought to result from differences in selectively vulnerable cell populations between premature and term infants’ brains (reviewed by McQuillen and Ferriero). The continued susceptibility of the white matter in newborns with CHD suggests a relative immaturity of brain development, supported by the observation of elevated lactate on preoperative MR spectroscopy in newborns with TGA and other heart lesions, a finding more typical of premature newborns. Additionally, the presence of focal preoperative brain injury in newborns with CHD is associated with widespread impairments in subsequent brain development in functionally significant white matter pathways, highlighting an important interplay between brain injury and abnormal brain development.

These data emphasize the need to distinguish the pattern of brain injury in order to separate specific and potentially modifiable risk factors. With the potential overlap in imaging characteristics of solitary white matter injuries and focal strokes, specific imaging markers for each of these findings are needed to optimally distinguish their independent risk factors. This cohort is being monitored to determine the specific neurodevelopmental significance of these lesions. In identifying risk factors for preoperative and postoperative brain injuries in this cohort, a significant but inevitable limitation of this nonrandomized study is the potential for confounding by indication. For example, just as the neonates with TGA who require a BAS by definition have more hypoxemia, newborns receiving RCP are those with single-ventricle physiology and aortic arch obstruction, who have a greater risk for embolism and low cardiac output postoperatively. The limited number of single-ventricle patients receiving CPB without RCP precludes a direct comparison of RCP with alternate CPB strategies. However, the high incidence of injury is similar to those
in published studies of single-ventricle patients and consistent with the overall worse neurodevelopmental outcome in this group, suggesting that RCP as currently conducted has not decreased neurological morbidity.

Taken together, these observations begin to suggest models in which intraoperative risk factors interact with postoperative risk factors, eg, the conduct of CPB may predispose to elevated cerebrovascular resistance, which in turn increases the risk of injury during episodes of postoperative hypotension. Accurate models of the specific pathophysiology of acquired and preventable perioperative brain injury provide the foundation for optimizing current therapies and proposing specific neuroprotective strategies to be evaluated in randomized trials.

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Disclosures

None.

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