Neurodevelopmental impairment is common in survivors of surgery for congenital heart disease (CHD) in early infancy.\textsuperscript{1,2} Recently, prospective magnetic resonance imaging (MRI) studies of young infants with CHD have provided important insights into the nature and timing of acquired brain injury in a cohort of young infants undergoing surgery for congenital heart disease both with and without cardiopulmonary bypass.

Methods and Results—A total of 153 infants undergoing surgery for congenital heart disease at <8 weeks of age underwent serial magnetic resonance imaging scans before and after surgery and at 3 months of age, as well as neurodevelopmental assessment at 2 years of age. White matter injury (WMI) was the commonest type of injury both before and after surgery. It occurred in 20\% of infants before surgery and was associated with a less mature brain. New WMI after surgery was present in 44\% of infants and at similar rates after surgery with or without cardiopulmonary bypass. The most important association was diagnostic group ($P<0.001$). In infants having arch reconstruction, the use and duration of circulatory arrest were significantly associated with new WMI. New WMI was also associated with the duration of cardiopulmonary bypass, postoperative lactate level, brain maturity, and WMI before surgery. Brain immaturity but not brain injury was associated with impaired neurodevelopment at 2 years of age.

Conclusions—New WMI is common after surgery for congenital heart disease and occurs at the same rate in infants undergoing surgery with and without cardiopulmonary bypass. New WMI is associated with diagnostic group and, in infants undergoing arch surgery, the use of circulatory arrest. (Circulation. 2013;127:971-979.)

Key Words: brain ■ cardiopulmonary bypass ■ heart defects, congenital ■ magnetic resonance imaging

New White Matter Brain Injury After Infant Heart Surgery Is Associated With Diagnostic Group and the Use of Circulatory Arrest

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Background—Abnormalities on magnetic resonance imaging scans are common both before and after surgery for congenital heart disease in early infancy. The aim of this study was to prospectively investigate the nature, timing, and consequences of brain injury on magnetic resonance imaging in a cohort of young infants undergoing surgery for congenital heart disease both with and without cardiopulmonary bypass.

Clinical Perspective on p 979

Although we now have an emerging impression of the spectrum of brain injury on MRI in young infants with CHD, the picture remains incomplete because of the inconsistency of classification and the limited longitudinal data. There is little information on infants with simpler CHD, and no data have been published on those undergoing surgery without cardiopulmonary bypass (CPB), making it difficult to assess whether CPB might contribute to brain injury. Furthermore, no studies have reported the relationship between perioperative MRI abnormalities and subsequent neurodevelopment.

The aim of this study was to prospectively investigate the nature, timing, and consequences of brain injury on MRI in reported rates of various abnormalities, especially stroke, in infants with CHD and the associated risk factors in the current literature.\textsuperscript{5,79}
Methods

The Hearts and Minds Study is a prospective longitudinal cohort study of 153 infants <8 weeks old undergoing cardiac surgery with or without CPB at the Starship Children’s Hospital (SCH), Auckland, New Zealand, and The Royal Children’s Hospital (RCH), Melbourne, Australia, between 2005 and 2008. Infants were excluded if they were <36 weeks’ gestational age, if they had a recognized genetic or malformation syndrome known to be associated with abnormal neurodevelopment, or if they required extracorporeal membrane oxygenation before surgery. The study was approved by the Institutional Review Boards of both hospitals.

MRI Scans

Three MRI scans were planned for all enrolled infants. The first was performed preoperatively; the second, 7 days after surgery. Infants who required a preoperative balloon atrial septostomy (BAS) underwent the preoperative scan after the BAS. The third scan was performed at 3 months of age and before any planned second-stage cardiac surgical operation. MRI scans were performed with a 1.5- or 3.0-T Magnetom Avanto scanner (Siemens, Erlangen, Germany). Standardized sequences were used for all studies, including coronal 3-dimensional fluid-attenuated inversion-recovery T1-weighted images (1-mm slice thickness), coronal and axial T2-weighted dual-echo, fast spin-echo images (2-mm slice thickness), and axial diffusion-weighted imaging (12–20 directions, 4-mm slice thickness). In addition, T2-gradient–weighted imaging (3-mm slice thickness) was performed on SCH infants, and susceptibility-weighted imaging (1.5-mm slice thickness) was performed in a subset of the RCH infants.

All scans were reported independently by 2 neuroradiologists (A.H., L.C.) who were blinded to all clinical information. Differences in classification were initially reviewed and either revised or averaged when differences persisted. Brain injury was classified as focal infarction (stroke), WMI, or hemorrhage (intraventricular or parenchymal). Stroke referred to discrete areas involving the cerebral cortical or deep nuclear grey matter of hyperintensity on diffusion-weighted imaging with hypointensity on the corresponding apparent diffusion coefficient scan and/or hyperintensity on T2-weighted images. WMI referred to discrete, usually punctate, foci of T1 hyperintensity and/or T2 hypointensity. This was classified as normal (no WMI), mild (≤3 foci and all ≤2 mm), moderate (>3 and ≤10 foci or any >2 mm), or severe (>10 foci). Subdural hemorrhage was recorded but was not considered brain injury, given its frequent occurrence in the healthy neonatal population.11 Cerebrospinal fluid (CSF) spaces were classified according to a system previously used in classification were initially reviewed and either revised or averaged when differences persisted. Brain injury was classified as focal infarction (stroke), WMI, or hemorrhage (intraventricular or parenchymal). Stroke referred to discrete areas involving the cerebral cortical or deep nuclear grey matter of hyperintensity on diffusion-weighted imaging with hypointensity on the corresponding apparent diffusion coefficient scan and/or hyperintensity on T2-weighted images. WMI referred to discrete, usually punctate, foci of T1 hyperintensity and/or T2 hypointensity. This was classified as normal (no WMI), mild (≤3 foci and all ≤2 mm), moderate (>3 and ≤10 foci or any >2 mm), or severe (>10 foci). Subdural hemorrhage was recorded but was not considered brain injury, given its frequent occurrence in the healthy neonatal population.11 Cerebrospinal fluid (CSF) spaces were classified according to a previously described classification: 2 ventricles without aortic arch obstruction, 2 ventricles with aortic arch obstruction, single ventricle without aortic arch obstruction, and single ventricle with aortic arch obstruction.

Operative Management

For the infants who required CPB, the perfusion strategy included continuous full-flow CPB at 150 mL·kg⁻¹·min⁻¹ with a procedure-specific target temperature of 15°C to 36°C. At RCH, venous cannulation was always bicaval; at SCH, single venous cannulation was used if there were no major intracardiac defects to be repaired. Alpha-stat acid-base management was used in both centers, with the use of pH-stat at temperatures <30°C in the SCH group. Antegrade cerebral perfusion was maintained by the use of a Gore-tex shunt to the innominate artery in all infants undergoing Norwood-type palliations in both centers and in infants with biventricular circulations requiring arch reconstruction in the RCH cohort. Deep hypothermic circulatory arrest (DHCA) was used in SCH infants with a biventricular circulation during arch reconstruction and during surgery to the atrial septum. When DHCA was used, this time was not included in the CPB time. Near-infrared spectroscopy was not used routinely in either center at the time of this study.

Neurodevelopmental Assessment

Survivors underwent a detailed neurodevelopmental assessment with the third edition of the Bayley Scales of Infant and Toddler Development within 6 weeks of their second birthday by a pediatrician and/or psychologist. The normative mean±SD for each domain (cognitive, language, or motor) equates to a score of 100±15.

Data and Statistics

The prospectively defined primary outcomes for this study were WMI on the first scan, new WMI on the second scan, and CSF spaces (as a reflection of cerebral atrophy) on the third scan. WMI was chosen because it was likely to be the most common abnormality and was more likely to have a homogeneous pathophysiology. Combined brain injury, including WMI, stroke, and hemorrhage, was also assessed as a secondary outcome. Cardiac lesions were divided into 4 diagnostic categories according to a previously described classification: 2 ventricles without aortic arch obstruction, 2 ventricles with aortic arch obstruction, single ventricle without aortic arch obstruction, and single ventricle with aortic arch obstruction.

Normally distributed data are presented as mean±SD; data that have an irregular or skewed distribution are presented as median with interquartile range. Proportions and odds ratios are presented with 95% confidence intervals. Clinical variables in infants with and without WMI and combined brain injury were compared by use of the t test, Wilcoxon rank-sum test, and either χ² or Fisher exact test as appropriate. We used ordinal logistic regression to identify significant associations in univariable analyses and then performed forward stepwise building of multivariable models to determine which associated variables independently contribute to the outcome. The multivariable models were developed first for all patients and then for 2 prespecified subgroups of infants undergoing surgery with CPB and infants having surgery involving the aortic arch. The relationship between neurodevelopment and MRI variables was investigated with linear regression or ANOVA as appropriate. Analysis was performed with Stata 10.1 (Stata Corp, College Station, TX). The nominal value of P<0.05 was used as a threshold of statistical significance, but all P values are presented.

Results

Details of surgical procedures are shown in Table 1. Demographic and operative data are shown in Table 2. DHCA was used in 30% of 2 ventricles, 74% of 2 ventricles with aortic arch obstruction, 9% of single ventricles without aortic arch obstruction, and 43% of single ventricles with aortic arch obstruction infants. Twenty-one infants (14%) died before 2 years of age: 8 (5%) in the pediatric intensive care unit (PICU), 2 (1%) on the ward after discharge from the PICU, and 11 (7%) after initial discharge from hospital. A preoperative MRI scan was undertaken in 147 participants; 138 underwent an early postoperative scan; and 120 had a scan at 3 months of age (86% of surviving infants at 3 months).

Preoperative MRI Findings

Thirty-eight infants (26%) had brain injury on the preoperative MRI scan. The commonest abnormality was WMI, which...
was present in 30 infants (20%). WMI was mild in 21 participants (70%), moderate in 8 (27%), and severe in 1 (3%). Seven infants (5%) had a preoperative stroke; 3 infants (2%) had small (<5 mm) cortical infarctions; and 5 infants (3%) had infarction involving the deep nuclear grey matter (2 caudate and 3 thalamic). One infant had both cortical and deep nuclear grey matter infarcts. Preoperative cerebral hemorrhage was present in 6 infants (4%), of which 4 were intraventricular hemorrhage (2 grade 1 and 2 grade 2) and 2 were small parenchymal hemorrhages (1 temporal and 1 cerebellar).

Characteristics of infants with and without WMI are shown in Table 3. Preoperative WMI was associated with brain immaturity (P=0.03). There was no significant association between WMI and gestational age at birth, diagnostic group, BAS before surgery, or any other preoperative physiological variables. Stroke occurred in 3 infants (8%) who underwent BAS and 4 (4%) who did not (P=0.38). There were no significant associations between combined brain injury and any other variables, including the brain maturity score.

**Early Postoperative MRI Findings**

Eighteen infants could not be assessed for the presence of new brain injury: 9 were on extracorporeal membrane oxygenation, 3 had not undergone a preoperative scan, and 6 for other reasons (ie, pacemakers, logistic issues such as MRI availability). Fifty-nine infants (44%) had new brain injury on their first postoperative scan. Fifty-seven infants (42%) had new WMI, which was mild in 38 (67%), moderate in 12 (21%), and severe in 7 (12%). Five infants (4%) had new strokes, which involved the deep nuclear grey matter alone in 4 infants (2 thalamic, 1 lentiform and thalamus, 1 lentiform and caudate) and involved both the cortex and basal ganglia in 1 infant (middle cerebral artery territory, caudate, and lenticulostriate nuclei). Four of the 5 infants with stroke also had WMI. Three infants (2%) had new intracranial hemorrhage (a grade 2 intraventricular hemorrhage in 2 infants and a small cerebellar hemorrhage in 1 infant), of whom 2 also had new WMI.

Preoperative stroke or hemorrhage was not significantly associated with new postoperative stroke or hemorrhage, respectively. There was no evidence of either hemorrhagic transformation or any increase in the size of preoperative WMI, stroke, or hemorrhage on the postoperative scans. Of the 27 infants with WMI before surgery who had both preoperative and early postoperative scans, 5 infants (19%) had resolution of some punctuate lesions. However, the WMI score for these preoperative lesions was unchanged in most: The 1 infant with severe WMI remained severe; 5 of the 7 (71%) with moderate WMI remained moderate whereas 2 infants (29%) became mild; and 17 of the 19 infants (89%) with mild WMI remained mild whereas 2 (11%) had no lesions.

Only 2 infants had either new stroke or hemorrhage and did not also have new WMI, so we did not repeat the analysis for combined brain injury. The postoperative characteristics of infants with and without WMI are shown in Table 4. Univariable ordinal logistic regression identified significant associations between postoperative new WMI and gestational age, birth weight, brain maturity score, diagnostic category, presence of preoperative WMI, use of DHCA, lactate on arrival in PICU and at 6 postoperative hours, and delayed sternal closure. There was no significant association between new
Table 2. Demographic and Surgical Data for All Infants

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>98 (64)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth, wk</td>
<td>38.8±1.6</td>
<td></td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.3±0.5</td>
<td></td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>34.5±1.8</td>
<td></td>
</tr>
<tr>
<td>Antenatal diagnosis, n (%)</td>
<td>90 (59)</td>
<td></td>
</tr>
<tr>
<td>Ventilated immediately before surgery, n (%)</td>
<td>30 (20)</td>
<td></td>
</tr>
<tr>
<td>Age at initial surgery, d</td>
<td>7 (4–11)</td>
<td></td>
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<tr>
<td>Diagnostic category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2V</td>
<td>57 (37)</td>
<td></td>
</tr>
<tr>
<td>2VA</td>
<td>24 (16)</td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>29 (19)</td>
<td></td>
</tr>
<tr>
<td>SVA</td>
<td>43 (28)</td>
<td></td>
</tr>
<tr>
<td>CPB used, n (%)</td>
<td>129 (84)</td>
<td></td>
</tr>
<tr>
<td>Duration of CPB when used, min</td>
<td>183±59</td>
<td></td>
</tr>
<tr>
<td>Circulatory arrest used, n (%)</td>
<td>50 (39)</td>
<td></td>
</tr>
<tr>
<td>Duration of circulatory arrest when used, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=50)</td>
<td>7 (5–17)</td>
<td></td>
</tr>
<tr>
<td>2V (n=17)</td>
<td>5 (4–5)</td>
<td></td>
</tr>
<tr>
<td>2VA (n=14)</td>
<td>22 (17–39)</td>
<td></td>
</tr>
<tr>
<td>SV (n=1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>SVA (n=18)</td>
<td>8 (5–13)</td>
<td></td>
</tr>
<tr>
<td>Delayed postoperative chest closure, n (%)</td>
<td>71 (46)</td>
<td></td>
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<tr>
<td>Postoperative ECMO, n (%)</td>
<td>10 (7)</td>
<td></td>
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<tr>
<td>CPR after surgery, n (%)</td>
<td>11 (7)</td>
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</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SV, single ventricle; SVA, single ventricle with aortic arch obstruction; 2V, 2 ventricle; and 2VA, 2 ventricle with aortic arch obstruction. Categorical data are shown as n (frequency) and continuous data as mean±SD or median (interquartile range) as appropriate.

WMI and the use of CPB, duration of postoperative vasoactive drug support, or PICU length of stay.

Associated factors on univariable analysis (P<0.10) were investigated for independent effects in multivariable analyses. Gestational age, birth weight, and brain maturity score are biologically and statistically (P<0.001) correlated to each other, and only brain maturity, the most strongly associated with new WMI (R²=0.03), was incorporated into the multivariable modeling. Table 5 presents the best multivariable model, resulting from a forward step-wise selection process, in which each covariable demonstrates an independent effect (P<0.05) on severity of new WMI. The multivariable ordinal logistic regression model for all infants has an R² of 0.12, of which the strongest component (R²=0.04–0.07) is attributable to the independent effect of diagnostic category. Other significant independent factors were the presence of WMI before surgery, higher serum lactate at 6 postoperative hours, and lower brain maturity score. For the subset of infants having surgery with CPB, significant independent factors were diagnostic category, longer duration of CPB, and the use of DHCA, with total R² of 0.15. The effect of DHCA was related to diagnostic group, specifically with arch surgery. There was no independent relationship between new WMI and DHCA in infants who did not require arch surgery (P=0.97). For infants having arch surgery (2 ventricles with aortic arch obstruction, single ventricle with aortic arch obstruction), independent predictors of postoperative WMI were longer duration of CPB, use of DHCA, the presence of WMI before surgery, and lower brain maturity score, with total R² of 0.20. Duration of DHCA was essentially interchangeable with use of DHCA as an independent factor in the multivariable model, but we chose use of DHCA because it is the simpler measure. Use of DHCA was associated with an odds ratio of 5.0 (95% confidence interval, 1.4–17.1) for increased severity of new WMI in infants having arch surgery. Odds ratios for the severity of new WMI for the factors in the models for the 3 patient groups are shown in Table 5. The model predictions of the probability of each grade of new WMI in infants in relation to the duration of CPB in all infants undergoing CPB and the duration of DHCA in infants having arch surgery are shown in Figures 1 and 2.

MRI at 3 Months

No infants had new WMI, stroke, or hemorrhage on their late postoperative scan. Of the 69 infants who had WMI present on their scan after surgery, WMI persisted at 3 months in 17 (25%), with 16 (94%) being mild and 1 (6%) being moderate. Of the 54 infants who had WMI after surgery and had early postoperative and 3-month scans, 1 of 5 (20%) with severe injury, 8 of 14 (57%) with moderate injury, and 4 of 35 (11%) with mild injury had mild WMI on the 3-month scan. The remainder in each group had no WMI. Eight infants (7%) had residual signs of stroke (1 cortical and 7 deep nuclear grey matter), and 6 (5%) had residual signs of hemorrhage.

Sixty-nine infants (58%) had normal CSF spaces on the late scan; 17 (14%) had mild, 24 (20%) had moderate, and 10 (9%) had substantial increases in the CSF spaces. Univariable ordinal logistic regression showed an association between increased CSF spaces and postoperative extracorporeal membrane oxygenation (P=0.009), increased duration of respiratory support (P=0.001), higher 6-hour lactate (P=0.014), and increased CSF spaces on a preceding scan (P=0.0001). Weaker associations were seen between increased CSF spaces and delayed sternal closure (P=0.053), WMI on the scan before surgery (P=0.068), and WMI present on the 3-month scan (P=0.067). On multivariable analysis, increased CSF spaces on a previous scan (odds ratio, 2.7; 95% confidence interval, 1.3–5.8; P=0.008) and increased duration of respiratory support (odds ratio, 1.07; 95% confidence interval, 1.02–1.12; P=0.006) were the only significant independent predictors of increased CSF spaces.

Survival and Neurodevelopment at 2 Years

Of the 8 infants who died in the PICU, 7 received extracorporeal membrane oxygenation and did not have a postoperative MRI. Seventy-five of the infants (96%) without postoperative WMI, 35 (92%) with mild WMI, 8 (67%) with moderate WMI, and 4 (57%) with severe WMI survived to the 2-year follow up. New postoperative WMI was associated with death after discharge from the PICU (P=0.02).

Mean composite cognitive, language, and motor scores on the third edition of the Bayley Scales of Infant and Toddler Development at 2 years of age were 94±15, 94±16, and 97±12, respectively. A delay in maturation of the posterior limb of the internal capsule on the first MRI scan was
associated with a lower motor score ($P=0.049$). Lower brain maturity score on the 3-month MRI scan was associated with reduced performance in all 3 neurodevelopmental domains: motor ($r=0.36$, $P<0.0001$), language ($r=0.21$, $P=0.024$), and cognitive ($r=0.25$, $P=0.007$). There was also no appreciable association between the Bayley Scales of Infant and Toddler Development scores and combined brain injury, WMI, or increased CSF spaces.

**Discussion**

This study reports the largest cohort to date of infants undergoing cardiac surgery in whom MRI scans have been performed before and after surgery. It is the first to include a group of infants having cardiac surgery without CPB and the first to investigate relationships between perioperative MRI and neurodevelopmental outcomes. Brain injury was present in 26% of infants before surgery, and new brain injury was observed after surgery in 44%. WMI was the commonest type of injury; WMI was present in 20% of infants before surgery, and new WMI was present in 42% after surgery. Stroke and hemorrhage were uncommon both before and after surgery.

There were 5 important associations between MRI abnormalities and perioperative factors. First, WMI occurred at the same rate in infants undergoing surgery without CPB as in those with CPB. However, in those who underwent CPB, increasing duration of CPB was associated with increased severity of new WMI after surgery. Second, preoperative WMI was associated with a lower brain maturity score. Third, the severity of new postoperative WMI was strongly associated with diagnostic group and occurred at the lowest rate in infants having 2-ventricle surgery compared with the other 3 groups. Fourth, DHCA was independently associated with the severity of new WMI in infants undergoing arch surgery. Fifth, the severity of new postoperative WMI was associated with both brain maturity score and the presence of WMI before surgery. This association was strongest in those infants having arch surgery.

In terms of outcome, new WMI after surgery was associated with increased risk of death after discharge from the PICU. Two-year neurodevelopmental outcome was associated with indexes of brain maturity—the posterior limb of the internal capsule on the preoperative MRI scan and the brain maturity score on the 3-month MRI scan—but not with WMI.

**The Nature of WMI**

The incidences of both preoperative and postoperative WMI in our cohort were similar to those in other reported series. WMI is the commonest type of injury in infants with CHD and is likely to have a more homogeneous pathophysiology than the less frequent stroke and hemorrhage. Some researchers have questioned whether larger punctate subcortical white matter lesions, especially when associated with restricted diffusion, might in fact represent embolic strokes rather than WMI and that this might also account for differences in reported rates of stroke before surgery. However, our findings would support a principally ischemic etiology. First, WMI was as common in infants having non-CPB surgery as in those with CPB. Second, preoperative WMI was strongly associated with diagnostic group and occurred at the lowest rate in infants having 2-ventricle surgery compared with the other 3 groups. Fourth, DHCA was independently associated with the severity of new WMI in infants undergoing arch surgery. Fifth, the severity of new postoperative WMI was associated with both brain maturity score and the presence of WMI before surgery. This association was strongest in those infants having arch surgery.

In terms of outcome, new WMI after surgery was associated with increased risk of death after discharge from the PICU. Two-year neurodevelopmental outcome was associated with indexes of brain maturity—the posterior limb of the internal capsule on the preoperative MRI scan and the brain maturity score on the 3-month MRI scan—but not with WMI.
surgery, embolic injury would be less likely. Second, the associations between the severity of new WMI and the use and duration of DHCA and the lactate level in the PICU also suggest an ischemic origin.

There is no standardized classification for WMI. The lesions are all hyperintense on T1-weighted imaging. Some authors have subclassified lesions according to whether there is T2 hypointensity or increased signal on gradient- or susceptibility-weighted imaging scans. We found that most lesions were associated with T2 hypointensity. We suggest that these lesions are ischemic rather than hemorrhagic because they do not go through the normal MRI evolution of blood on T1 and T2 images and were positive on T2 hypointensity and/or increased signal on either gradient- or susceptibility-weighted imaging. Microhemorrhage was rarely seen in the lesions and, when it occurred, these lesions then went through the normal evolution of blood and were positive on susceptibility-weighted imaging or gradient-weighted imaging.

**Preoperative Injury**

We found that the only association with preoperative WMI was with brain immaturity. Using the total maturity score, Licht et al.\(^\text{10}\) reported that infants with hypoplastic left heart syndrome or transposition of the great arteries had maturity scores \(\leq 1\) month less than expected for their gestational age. Andropoulos et al.\(^\text{11}\) reported that brain immaturity using the total maturity score was associated with WMI both before and after surgery. It has been suggested that relative brain immaturity in infants with CHD may relate to in utero hemodynamic factors that lead to a decline in brain growth and metabolism.\(^\text{15}\)

We found some relevant negatives relating to preoperative injury, including a lack of significant association with a prenatal diagnosis, time to surgery, lowest arterial oxygen tension, or BAS (which we previously reported).\(^\text{5}\) The lack of an association with preoperative BAS is in accordance with the findings of Petit et al.\(^\text{9}\) and Andropoulos et al.\(^\text{4}\) but not with those of McQuillen et al.\(^\text{7}\) However, it is possible that the marked differences with the McQuillen et al.\(^\text{7}\) findings may be related at least in part to the definition of stroke. Petit et al.\(^\text{9}\) found an association between preoperative injury and both hypoxemia and a longer time to surgery; we did not. However, the studies differ in that Petit et al.\(^\text{9}\) included infants with transposition of the great arteries and used data from continuous oximetry in all infants, whereas we included a heterogeneous group of lesions and used the lowest recorded PaO\(_2\) from arterial blood gases in those children who had arterial access. Finally, we also found that WMI present before surgery increased the severity of new WMI after surgery, an observation that was in keeping with the study of Andropoulos et al.\(^\text{11}\) but not McQuillen et al.\(^\text{7}\)

**Early Postoperative Injury**

The rate of new WMI in our cohort was similar to that in other studies. We observed that diagnostic category was the strongest predictive factor for the severity of new WMI, the lowest-risk group being infants with 2 ventricles without arch
White Matter Brain Injury and Infant Heart Surgery

The odds of increasing severity of new WMI were >4-fold in infants undergoing arch surgery with no difference between the categories of single ventricle without aortic arch obstruction and 2 ventricles. The risk of increased severity of new WMI in the single ventricle without aortic arch obstruction infants requiring bypass was very high. However, there were only 11 infants in this group, so the confidence intervals are wide for this estimate.

The use of CPB was not itself a risk factor for new WMI because it occurred at the same rate in infants having surgery without CPB. The incidence of postoperative WMI has never previously been reported in non-CPB patients. Two thirds of this subgroup of infants underwent a Blalock-Taussig shunt, and another 17% had a pulmonary artery band placed. Both of these operations may be associated with considerable perioperative hemodynamic instability with reduced systemic, and therefore cerebral, oxygen delivery.

In those infants who required CPB, the duration of CPB was independently an important factor for increased severity of new postoperative WMI. The mechanism for this association is unclear and could be related to an increased inflammatory response to CPB itself, or perhaps prolonged CPB might be a surrogate marker for other factors that increase WMI, for example, a more challenging operation with the potential for greater hemodynamic instability after surgery.

DHCA increased the odds of increased severity of postoperative WMI 5-fold in infants undergoing aortic arch surgery, and the duration of DHCA was positively associated with the severity of WMI. Moreover, severe WMI was present only in infants having DHCA. The application of DHCA in infant heart surgery represents a controversial area in current practice. Single-center studies cannot adequately address this because there are commonly strong biases about the application of DHCA within institutions. There is a paucity of data related to assessing the relationship between this aspect of perfusion practice and brain injury in the current era. Our findings support the need for a multicenter, randomized, controlled trial of DHCA compared with antegrade cerebral perfusion to resolve this issue.

**Table 5. Odds Ratios (95% Confidence Intervals) for Significant Factors in the Multivariate Models for Severity of New White Matter Injury After Surgery**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Infants (n=135)</th>
<th>CPB (n=113)</th>
<th>Arch Surgery (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Diagnostic category*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2VA</td>
<td>4.4 (1.5–13.1)</td>
<td>0.008</td>
<td>6.5 (1.8–23.5)</td>
</tr>
<tr>
<td>SV</td>
<td>2.6 (0.9–7.4)</td>
<td>0.080</td>
<td>18.5 (3.1–110)</td>
</tr>
<tr>
<td>SVA</td>
<td>4.4 (1.7–11.5)</td>
<td>0.002</td>
<td>5.2 (2.0–13.8)</td>
</tr>
<tr>
<td>Duration of CPB when used, min†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.02 (1.0–1.03)</td>
<td>0.005</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>DHCA used</td>
<td>2.7 (1.1–6.4)</td>
<td>0.029</td>
<td>5.0 (1.4–17)</td>
</tr>
<tr>
<td>WMI before surgery</td>
<td>2.4 (1.01–5.7)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Brain maturity score (postoperative)†</td>
<td>0.7 (0.5–1.0)</td>
<td>0.034</td>
<td>0.5 (0.2–0.9)</td>
</tr>
<tr>
<td>Lactate at 6 h in PICU</td>
<td>1.3 (1.05–1.7)</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; PICU, pediatric intensive care unit; SV, single ventricle; SVA, single ventricle with aortic arch obstruction; 2VA, 2 ventricle with aortic arch obstruction; and WMI, white matter injury.

*Odds ratios compared with the 2-ventricle group.
†Odds ratios are for a 1-unit increase.

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**Figure 1.** Calculated relation between the probability of each grade of new white matter injury after surgery and the duration of cardiopulmonary bypass (CPB).

**Figure 2.** Calculated relation between the probability of each grade of new white matter injury (WMI) after surgery and the duration of deep hypothermic circulatory arrest (DHCA) in infants having arch surgery. CPB indicates cardiopulmonary bypass.
We also confirmed the findings of Block et al\(^\text{17}\) that none of the preoperative MRI abnormalities, including WMI, strokes, and hemorrhages, showed signs of either extension or hemorrhagic transformation on the MRI after surgery.

**Brain Injury and Neurodevelopmental Outcome**

There are no published studies investigating the association between early postoperative WMI and outcome. In the Boston Circulatory Arrest Study (BCAS), infants undergoing the arterial switch operation with DHCA consistently demonstrated worse motor development than those undergoing surgery with low-flow CPB, but this was balanced against improvements in other measures of behavior.\(^\text{1,18}\) In contrast, other more recent studies of mixed cohorts have found no association between DHCA and neurodevelopmental outcome.\(^\text{19}\) Both groups in the BCAS performed below average in other domains, suggesting that factors apart from DHCA also play a role.

Although WMI was associated with mortality in our cohort, we did not find an association with 2-year neurodevelopmental performance. In our study, approximately two thirds of the WMIs were mild, and 7 of the 19 infants with moderate or severe injury died before follow-up. Therefore, three quarters of the survivors with WMI had only mild injury, raising the possibility that any consequences of this may not be discernible at 2 years of age. The BCAS study clearly demonstrated the importance of continued follow-up, with more than half of the children with low scores (<85) at 8 years of age having scores >84 at the 1-year assessment.\(^\text{20}\) Ongoing studies will further explore this question as our cohort approaches school age.

Motor, language, and cognitive scores at 2 years were all related to brain maturity on the third scan. In addition, delayed maturation of the posterior limb of the internal capsule on the first scan was related to worse motor development. These findings suggest that factors associated with brain development before surgery may have as much impact on neurodevelopmental outcome as perioperative factors. Although this is the first study to report the relationship between brain maturity and neurodevelopment in infants after cardiac surgery, MRI findings at term equivalent in very premature infants strongly predict adverse outcomes.\(^\text{12}\)

**Limitations**

This study has several limitations. Although it is the largest report in which serial MRI scanning has been performed, the sample size remains underpowered to determine which of multiple clinical factors are associated with MRI abnormalities. Most previous studies have emerged from single institutions with <100 infants. To delineate these issues further, a much larger sample is required, either from new studies or by combining existing data. Our multivariable models explained only 12% to 20% of the variance, suggesting that other unmeasured factors contribute significantly.

In terms of DHCA, which was used in only 1 center, it could be considered that this might be a contributor to the difference in WMI or potentially may be a surrogate for another center-related difference. However, there was no difference between centers in any of the factors in Table 2 apart from the use of DHCA. In addition, there was no independent effect of center, surgeon, pH strategy, or use of antegrade cerebral perfusion in the multivariable models.

We had only very limited measures of cardiorespiratory instability both before and after surgery. Continuous physiological data, including electroencephalogram and cerebral near-infrared spectroscopy, may help clarify the role that these factors might play. Finally, we believe that, although assessment of brain maturity will be an important component of future analyses, further work is needed to refine an appropriate score for high-risk cardiac cohorts such as ours who are born at or near term. The total maturity score was developed to assess infants from 23 through to 42 weeks’ gestation.\(^\text{13}\) The period of most interest for brain development in newborn infants with cardiac disease is likely the third trimester.\(^\text{16}\) Scores using more developmental detail related specifically to this period, for example, in gyral development, may offer more sensitivity in assessing the contribution of brain maturity to injury and later outcome.

**Conclusions**

WMI is the commonest type of brain injury in newborn infants undergoing surgery for CHD. It is present before surgery in 20% of infants, is associated with brain immaturity, is present early after surgery in 42% of infants, and occurs at similar rates after nonbypass and bypass surgery. The strongest associated clinical factor is diagnostic group, occurring at higher rates in infants having either single ventricle or arch surgery. It is also associated with the duration of CPB and with the use and duration of DHCA. WMI is associated with increased mortality after discharge from intensive care but was not associated with neurodevelopment at 2 years of age. Brain immaturity on MRI was associated with adverse neurodevelopmental outcomes in all domains. Future outcome studies of this cohort will further define the contribution of MRI injury to later development.

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**Disclosures**

None.

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CLINICAL PERSPECTIVE

This study investigates the nature, timing, and consequences of brain injury on magnetic resonance imaging scan in a cohort of young infants undergoing surgery both with and without cardiopulmonary bypass. We confirmed the findings of previous studies that white matter injury (WMI) is the most prevalent abnormality. WMI before surgery was significantly associated with a less mature brain but not with diagnostic group. The study has revealed some important new findings. First, new WMI after surgery occurred at the same rate in infants undergoing surgery without cardiopulmonary bypass as in those having cardiopulmonary bypass. Second, new WMI was significantly associated with diagnostic group and, in infants having arch surgery, the use of deep hypothermic circulatory arrest. Third, WMI was also associated with a less mature brain and the presence of WMI before surgery. Finally, impaired neurodevelopment at 2 years of age was significantly associated with a less mature brain but not with WMI. This is the first study to include infants having surgery without cardiopulmonary bypass and to investigate the relationship between neurodevelopment and both WMI and brain maturity. The results highlight the potential importance of impaired antenatal brain development on neurodevelopment and on WMI both before and after surgery. The findings suggest that avoiding the use of cardiopulmonary bypass, when that is an option, does not necessarily have benefits in terms of reduced brain injury. They also support the need for a randomized, controlled trial to investigate whether avoidance of deep hypothermic circulatory arrest might be associated with less WMI and improved neurodevelopment.
New White Matter Brain Injury After Infant Heart Surgery Is Associated With Diagnostic Group and the Use of Circulatory Arrest

John Beca, Julia K. Gunn, Lee Coleman, Ayton Hope, Peter W. Reed, Rodney W. Hunt, Kirsten Finucane, Christian Brizard, Brieana Dance and Lara S. Shekerdemian

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